

**BIOAVAILABILITY ENHANCEMENT OF DRUGS  
THROUGH STRATUM CORNEUM BY USING  
NATURAL PENETRATION ENHANCERS VIZ. *B.*  
*LANZAN* AND *S. CHINESIS***

**A  
Thesis**

**Submitted for the Award of the Ph.D. degree of  
PACIFIC ACADEMY OF HIGHER EDUCATION AND  
RESEARCH UNIVERSITY**

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**2024**

# DECLARATION

I, **Mr. SURYAVANSHI KIRAN ARUN S/o Mr. ARUN KAUTIK SURYAVANSHI** resident of Audumbar, Bungalow No. D-1, Sai Shraddha Bungalows, Opp. Sai Simaran Row Houses, Narhari Nagar, Pathardi Phata, Nashik - 422010, Maharashtra, hereby declare that the research work incorporated in the present thesis entitled **“BIOAVAILABILITY ENHANCEMENT OF DRUGS THROUGH STRATUM CORNEUM BY USING NATURAL PENETRATION ENHANCERS VIZ. B. LANZAN AND S. CHINESIS”** is our original work. This work (in part or in full) has not been submitted to any University for the award of a Degree or a Diploma. I have properly acknowledged the material collected from secondary sources wherever required. I solely own the responsibility for the originality of the entire content.

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(**SURYAVANSHI KIRAN ARUN**)

Signature of the Candidate

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It gives me immense pleasure in certifying that the thesis entitled **“BIOAVAILABILITY ENHANCEMENT OF DRUGS THROUGH STRATUM CORNEUM BY USING NATURAL PENETRATION ENHANCERS VIZ. *B. LANZAN AND S. CHINESIS*”** and submitted by **Mr. SURYAVANSHI KIRAN ARUN** is based on the work research carried out under my guidance. He has completed the following requirements as per Ph.D. regulations of the University;

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**SURYAVANSHI KIRAN ARUN**

Place: Udaipur

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**SURYAVANSHI KIRAN ARUN**

# PREFACE

The thesis entitled “**Bioavailability enhancement of drug molecule through stratum corneum by using natural penetration enhancers viz. *B.Lanzan* and *S. Chinesis***”

Philosophy (Ph.D.) contains the research work carried out during the period of March 2016 to July 2024, at the Department of Pharmaceutics, Pacific University of Higher Education and Research, Rajasthan, India under the supervision of Prof. A. Venkatachalam and Dr Yogesh V Ushir. This thesis contains introduction, literature review, the detailed procedures for extraction of oil, its evaluation, the formulation of gel, its evaluation and characterization by physico-chemical and spectroscopic methods and finally pharmacokinetic evaluation in animal.

The formulated of colchicine were subjected to the physicochemical parameters. The gel contains colchicine as API along with IPA, TEA, PEG, methyl paraben, propyl paraben mixed with water. Before preparing formulation, the ingredients were evaluated for their compatibility which was found negative and hence ingredients used in final formulation.

- The formulated gel was evaluated for *in-vitro* permeation studies by using snake and goat skin. The obtained data was compared with standard permeation enhancer i.e. capsaicin. The data shown the ability of drug molecule to get into the blood through the skin. The selected formulation in the *in-vitro* studies were subjected to drug release kinetics in the rat. The area where gel was to be applied was shaved and cleaned. The selected formulations were applied on the skin of rat. The sampling was done by retro-orbital. The acute toxicity was performed on albino mice. Acute toxicity studies reveled that, no any abnormalities were shown by the mice throughout the study. Prepared gel formulations were subjected to skin irritation test and allotted score depending on the reaction shown on the skin of volunteers the score below 2 shows acceptability of gel formulations to be applied on skin. The optimized gel showed acceptable physical properties, pH, viscosity, spreadability, and extrudability.

The release of Phytoconstituents would in controlled manner at the site of action thereby decrease the possible side effects Mathematical models play a vital role in the interpretation of mechanism of drug release from a dosage form. It is an important tool to understand the

drug release kinetics of a dosage form. The drug release was found to be best fitted by Higuchi square root model  $r^2 = 0.865$  for BL4 and SCO4 and  $r^2 = 0.865$  for BL5 and SCO5 and  $r^2 = 0.865$  for BL6 and SCO6 which implies that release of drug as a square root of time dependent process and diffusion controlled. The dissolution data was also plotted according to Hixson – Crowell  $r^2 = 0.9182$  for BL4 and SCO4 and  $r^2 = 0.9182$  for BL5 and SCO5 and  $r^2 = 0.9182$  for BL6 and SCO6 which describes that change in surface area and diameter of the formulation with the progressive dissolution as a function of time. Also, the model Korsmeyer-Peppas power law equation states the type of diffusion, which was evaluated by value,  $n$  (Release exponent) which is higher than 0.8751 which implies that the drug release from the system follow Super case II transport

In the end relevant references are included along with list of papers presented & published and reprint of publications from the present study is also included. The contents of this thesis may be useful for to work on natural penetration enhancers and open new vista in firmament of designing and developing topical gel for any DDS. The whole thesis was divided into nine chapters as follows:

### **Chapter 1: Introduction**

Represented the detailed introduction about transdermal patch, NSAID's and *Simmondsia chinensis* family of Simmondsiaceae and the *B. Lanza* family of Anacardiaceae.

### **Chapter 2: Need for study** Explained about necessity of study **Chapter 3: Aim and Objectives**

The aim of the study is to make transdermal formulations of a few anti-inflammatory agents like extracts of seeds of *B.lanza* family Anacardiaceae and extracts of seeds of *Simmondsia chinensis* family Simmondsiaceae.

#### **Objectives:**

A vast summary of literature survey gives some views, which hypothesized as follows,

- To Collect and identify, authenticate of plants materials and seeds.
- To study Morphology and microscopy of plant material.
- To study Isolation methodology
- To perform Qualitative analysis for isolated oil
- To study Toxicity of isolated penetration enhancers.

- To perform preformulation study of isolated components (oil)
- To prepare formulation using isolated oil.
- To evaluate formulated product (Medicated gel)
- To perform comparative drug release studies (*in vivo and ex vivo*)
- To establish of Pharmacokinetics in rat
- To establish of release kinetics.
- Accelerated stability studies

#### **Chapter 4: Review of literature**

Seeds of *B.lanzan* family Anacardiaceae and extracts of seeds of *Simmondsia chinensis* are a miracle herb widely used by Indian tribes for treating various diseases. Literature review reference for the pharmacological properties, pharmacognostic studies and phytochemical investigation of these two seeds extracts.

#### **Chapter 5: Materials and methods**

The Phytochemical investigation of a plant involves authentication and extraction of plant material; qualitative and quantitative evaluations; separation and Parallel to this may be the assessment of pharmacological activity.

#### **Chapter 6: Results and discussion**

The study comprises standardizing seed extracts from the *Simmondsia chinensis* family of *Simmondsiaceae* and the *B. Lanzan* family of *Anacardiaceae* using a variety of characteristics, such as ash value, extractive value, and loss on drying, preliminary phytochemical screening, and fluorescence analysis. After standardization, the chemical components and % yield were extracted for additional screening. Following drug characterization, pre-formulation experiments were conducted to determine the drug's organoleptic properties.

#### **Chapter 7: Conclusion**

#### **Chapter 8: Summary**

#### **Chapter 9: Bibliography**

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<b>84.</b>	<b>6.72</b>	Time vs Cube root drug remaining	<b>153</b>
<b>85.</b>	<b>6.73</b>	Time vs cumulative % drug remaining	<b>153</b>
<b>86.</b>	<b>6.74</b>	Log time vs Log cumulative % drug released	<b>154</b>
<b>87.</b>	<b>6.75</b>	Time vs Cumulative % drug released	<b>156</b>
<b>88.</b>	<b>6.76</b>	Sq root time vs Cumulative %drug released	<b>156</b>
<b>89.</b>	<b>6.77</b>	Time vs Cube root of drug remain	<b>157</b>
<b>90.</b>	<b>6.78</b>	Time vs cumulative % drug released	<b>158</b>
<b>91.</b>	<b>6.79</b>	Time vs log cumulative % drug remaining.	<b>159</b>

<b>92.</b>	<b>6.80</b>	Sq root time vs cumulative % drug released	<b>160</b>
<b>93.</b>	<b>6.81</b>	Log time vs log cumulative % drug released	<b>161</b>
<b>94.</b>	<b>6.82</b>	Log time vs log cumulative % drug release	<b>163</b>
<b>95.</b>	<b>6.83</b>	Time vs cumulative % drug release	<b>163</b>
<b>96.</b>	<b>6.84</b>	Sq root time vs cumulative % drug released	<b>164</b>
<b>97.</b>	<b>6.85</b>	Time vs Log cumulative % drug remaining	<b>164</b>
<b>98.</b>	<b>6.86</b>	Time vs cube root drug remained	<b>165</b>
<b>99.</b>	<b>6.87</b>	Time vs log cumulative % drug remaining	<b>167</b>
<b>100.</b>	<b>6.88</b>	Log time vs <Log cumulative % drug released	<b>167</b>
<b>101.</b>	<b>6.89</b>	Time vs cumulative % drug released	<b>168</b>
<b>102.</b>	<b>6.90</b>	Sq root time vs cumulative % drug released	<b>168</b>
<b>103.</b>	<b>6.91</b>	Time vs cube root of drug remain	<b>169</b>
<b>104.</b>	<b>6.92</b>	Log time vs log cumulative % drug release	<b>171</b>
<b>105.</b>	<b>6.93</b>	Time vs cumulative % drug release	<b>171</b>
<b>106.</b>	<b>6.94</b>	Sq root time vs cumulative % drug released	<b>172</b>
<b>107.</b>	<b>6.95</b>	Time vs Log cumulative %drug remaining	<b>172</b>
<b>108.</b>	<b>6.96</b>	Time vs Cube root drug remain	<b>173</b>
<b>109.</b>	<b>6.97</b>	Time vs cube root drug remain.	<b>175</b>
<b>110.</b>	<b>6.98</b>	Log time vs Log cumulative % drug release	<b>177</b>
<b>111.</b>	<b>6.99</b>	Time vs Cumulative % drug release	<b>177</b>
<b>112.</b>	<b>6.100</b>	Sq root time vs cumulative % drug released	<b>178</b>
<b>113.</b>	<b>6.101</b>	Time vs log cumulative % drug remaining	<b>178</b>
<b>114.</b>	<b>6.102</b>	Time vs cube root drug remain	<b>179</b>
<b>115.</b>	<b>6.103</b>	Time vs cube root of drug remain	<b>181</b>
<b>116.</b>	<b>6.104</b>	Time vs cumulative % drug released	<b>183</b>
<b>117.</b>	<b>6.105</b>	Time vs log cumulative % drug remaining	<b>184</b>



<b>118.</b>	<b>6.106</b>	Sq root time vs cumulative % drug released	<b>185</b>
<b>119.</b>	<b>6.107</b>	Log time vs log cumulative % drug released	<b>186</b>
<b>120.</b>	<b>6.108</b>	Log time vs Log cumulative % drug release	<b>188</b>
<b>121.</b>	<b>6.109</b>	Time vs cumulative % drug release	<b>188</b>
<b>122.</b>	<b>6.110</b>	Sq root time vs cumulative % drug released	<b>189</b>
<b>123.</b>	<b>6.111</b>	Time vs log cumulative % drug remaining	<b>189</b>
<b>124.</b>	<b>6.112</b>	Time vs Cube root of drug remain	<b>190</b>
<b>125.</b>	<b>6.113</b>	Time vs Cube root of drug remain	<b>192</b>
<b>126.</b>	<b>6.114</b>	Log time vs log cumulative % drug release	<b>194</b>
<b>127.</b>	<b>6.115</b>	Time vs cumulative % drug release	<b>194</b>
<b>128.</b>	<b>6.116</b>	Sq root time vs cumulative % drug releasesd	<b>195</b>
<b>129.</b>	<b>6.117</b>	Time vs log cumulative % drug remaining	<b>195</b>
<b>130.</b>	<b>6.118</b>	Time vs cube root of drug remain	<b>196</b>
<b>131.</b>	<b>6.119</b>	Time vs cube root of drug release	<b>198</b>
<b>132.</b>	<b>6.120</b>	Log time vs log cumulative % drug release	<b>200</b>
<b>133.</b>	<b>6.121</b>	Time vs cumulative % drug release	<b>200</b>
<b>134.</b>	<b>6.122</b>	Sq root time vs cumulative % drug released	<b>201</b>
<b>135.</b>	<b>6.123</b>	Time vs log cumulative % drug remaining	<b>201</b>
<b>136.</b>	<b>6.124</b>	Time vs Cube root drug remain	<b>202</b>
<b>137.</b>	<b>6.125</b>	Time vs Cube root of drug remain	<b>204</b>
<b>138.</b>	<b>6.126</b>	Time vs cumulative % drug released	<b>205</b>
<b>139.</b>	<b>6.127</b>	Time vs log cumulative % drug remaining	<b>206</b>
<b>140.</b>	<b>6.128</b>	Sq root time vs cumulative % drug released	<b>207</b>
<b>141.</b>	<b>6.129</b>	Log time vs log cumulative % drug released	<b>208</b>
<b>142.</b>	<b>6.130</b>	Log time vs log cumulative % drug release	<b>210</b>
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147.	6.135	Time vs cube root of drug remain	214
148.	6.136	Log time vs log cumulative % drug release	216
149.	6.137	Time vs cumulative % drug release	216
150.	6.138	Sq root time vs Cumulative % drug released	217
151.	6.139	Time vs log cumulative % drug remaining	217
152.	6.140	Time vs cube root of drug remain	218
153.	6.141	Time vs cube root of drug remain	220
154.	6.142	Log time vs Log cumulative % drug release	222
155.	6.143	Time vs cumulative % drug release	222
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# INTRODUCTION



**TRANSDERMAL DRUG DELIVERY**

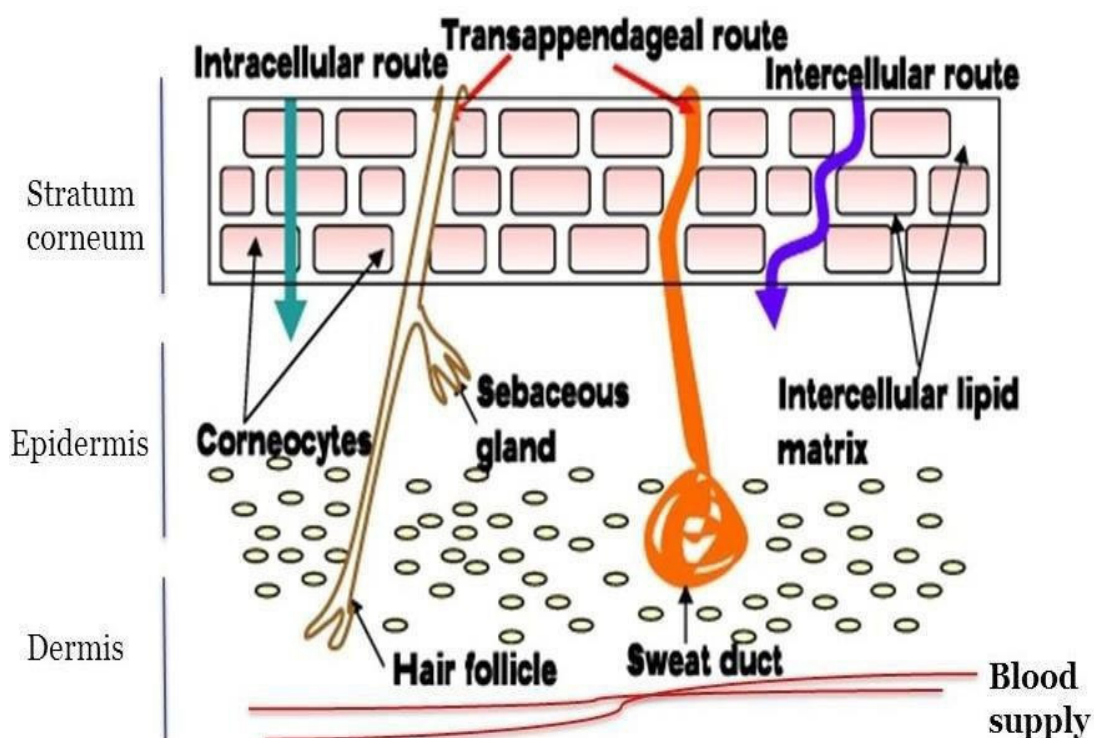
The advantages of percutaneous distribution over swallowing include avoiding hepatocytes breaking down impacts along with digestive discomfort. Additionally demonstrated control as well as a maintained distribution that fits along with is simple to apply and remove. Although the non-invasive method of medication delivery offers multiple benefits, its effectiveness is restricted by the strata corneum's barrier-like properties and minimal skin penetration. Therefore, several penetrating boosts, pharmaceuticals, redundant vehicles, ionizing radiation procedures, and electroplating have been utilized to maximize the proportion of penetrated skin. Using diffusion garnishes is one of the maximum effective approaches to increase the amount of penetration into the skin, and its results have been commendable. A process called which involves the application of an electric current is a commonly used cutaneous penetration treatment. However, there is a risk of irritation to the skin as a result of the pH shift. Therefore, the drug in a water-based solution will be used only.<sup>6-8</sup>

Synthesis medications currently serve an important therapeutic character in the management of autoimmune syndromes. In the treatment of arthritis, pain relievers, NSAIDs and cortisone have proven beneficial. Those drugs affect different parts of the pathologic pathway schemas. One major downside of the medication treatment is lower cooperation in people over 50 with Arthritis. Subcutaneous distribution of medication is a more effective means of administering drugs since it is associated with excellent adherence among patients.<sup>9-13</sup>

**Advantages**

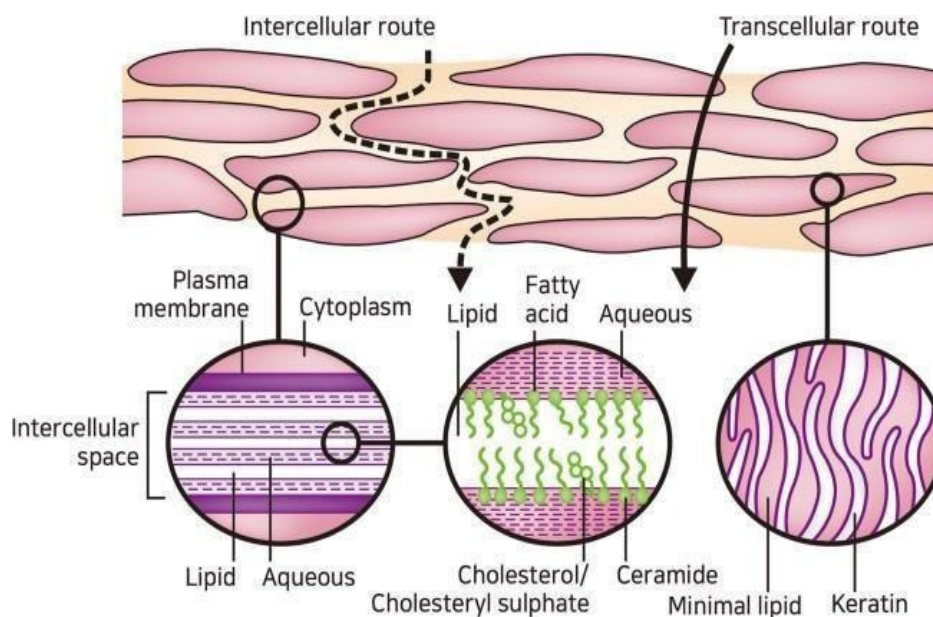
- Avoids hepatic first-pass metabolism.
- Keeps up steady blood levels for longer timeframe.
- Promote bioavailability.
- Decreases in administration of dose.
- Adverse effects are decreased.
- Simple to discontinue if there is an occurrence of harmful effects
- Increased patient compliance<sup>14</sup>

## Routes of skin permeation



**Figure No 1.1. Illustration of macroroutes of drug permeation across intact skin**

The Macro route transports substances through perspiration organs and the follicles of hair with their subordinate sebaceous organs. In the trans-epidermal route, the corneum transport is through intracellular and intercellular areas. Diffusement of Polar along with inert materials through interstitial and transcellular pathways is seen by unique mechanisms. Hydrous corneum which has a Tropical Lane containing free aquatic helps to diffuse the polar particles, while the layer corneum macromolecule framework non-polar particles diffuse through it. Figure 2 describes potential micro routes for the permeation of the drug. The transappendageal route is taken into account to be of minor importance due to its comparatively little space. Yet, this route is significant for large polar compounds. Several mathematical models to explain the porousness across the stratum are reported. These models can be comprehensively grouped into homogeneous and heterogeneous models<sup>15-16</sup>.



**Figure 2: Conceivable micro ways for medicine infiltration crossways human membrane intracellular or Trans cellular**

### Transmembrane diffusion process

Drugs are considered to move from the skin by passive diffusion, it is described by Fick's Law and the drug release rate. Diffusion of drugs in the corneum layer having low molecular weight is consistent. Hair follicles in association with sebaceous glands, by sweat ducts, or over the stratum corneum are three possibilities by which drug can reach from skin. The availability of the surface for the intention of diffusion from the skin tissues is almost very small, up to 1%. This route might be significant to particles and enormous charged molecules. The drug reaches systemic circulation by the plexus of the capillary after diffusing from the corneum layer. The molecules travel a convoluted path and need to intersect, successively and over and over, various aqueous and lipid layers. Around ten times the elongated duration is required to attain  $C_{max}$  when the proportion is given by the most common route of administration. Drugs that have extreme affinity or extreme repelling properties towards water are absorbed poorly. Along with the pH of the vehicle, molecular size of the drugs is important in the infiltration of the skin. The solubility, melting point, and ionization state of the drug molecule is also considered.<sup>17-18</sup>

Molecular weight and flux permeation have an inverse relationship between them. So faster rate of diffusion is observed with smaller molecules and diffusion slows down with molecules of larger size. Medication formulations used for topical application are always in

aqueous form to reduce the consumption of the permeant from the formulation. Drugs that are used are mostly feeble acid or feeble bases depending upon the pH of the used formulation and the pH of the layer through which medication has to diffuse<sup>19</sup>.

Factors like age, presence of disease, the occurrence of skin structure, and physiochemical properties of corneum are responsible for influencing skin permeability. Corneum hydration also plays an important role. The permeability of hydrophilic drugs through the corneum is boosted by the quantity of water available in the corneum layer<sup>19</sup>.

Transdermal therapeutic systems (TTS) are independent, distinct medicinal devices that govern the penetration of medication into circulation through epidermal application<sup>19</sup>. Drugstore products with chemical compound that are adaptable and can come in numerous shapes are called percutaneous devices. Creation of the TDDS to avoid the first pass metabolism by delivering the medication particles enter the bloodstream through the outermost dermis. It is beneficial for achieving rate-controlled circulatory medication distribution as well as for giving medications via IV<sup>20</sup>.<sup>20</sup>.

The epidermal layer serves to act as slowing hurdle with the penetration of the majority of medications. Potential a result, some improvements in fluid modification have come out as methods to enhance the scope of cutaneous medicine. One such method is iontophoresis, which lets medication molecules get past all the layers of skin by applying the use of direct current (DC) as a physical mean. This method works on the premise of the saying, like draws away kind.<sup>21</sup>.

### **Enhancement Techniques for Skin Penetration Physical Concept Iontophoresis**

The Physical mean Iontophoresis is technique for improving the immersion of transdermally applied medication specialists from the layers of skin by utilizing direct electric current. The therapeutic agent is applied to a terminal having similar charge as the therapeutic agent, and a uninterested cathode is located anywhere on body. Active molecules repelled from active anode are forced in skin. Below mechanism would be responsible for Enhanced penetration of drug through iontophoresis:

- i) A primary technique indicated that drugs are limited by straight forward electronic revulsion of competitive charges in the skin. By using an oppositely charged working electrode terminal, anionic drugs will cross the skin. When a specifically

charged anode is used, cationic drugs may also cross the skin.

- ii) The subsequent technique proposes whereas the electric flow upgarde the pervasion through skins hindering capacity to make defensive hindrance work
- iii) Finally, due to iontophoresis, successful permeation enhancer water emerged, helping to penetrate the corneum layer (SC) through electrosmosis. Transdermal iontophoresis is particularly important for the transport of hydrophilic drug molecules (peptides and oligonucleotides). Iontophoretic drug transmission may be helpful in the treatment of skin problems, such as it has been used widely in such dermatological states<sup>22-23</sup>.

### **Electroporation**

It is one more electrical improvement strategy that can incorporates utilization of less time, large voltage (50-1000 volts) towards skin. Transport pores are developed as entering gate by electric pulses that in these way macromolecules are permitted into intracellular space outside from the cell methods for blending of electrophoresis. Molecules larger in size have been transported by this method, which includes insulin, immunizations, oligonucleotides, and nanoparticles. A couple of pattern mixes, for example, calcein and LHRH agents likewise continue to read for expanded transdermal assimilation by electroporation<sup>24</sup>.

### **Microporation**

In this microneedles are used for the microporation to the skin by applying it. Considering that after application they simply fracture the structure of skin and increases permeability. Microneedles having height of 10 to 200  $\mu\text{m}$  and having width min 10 to 50  $\mu\text{m}$  width Microneedles can't animate the nerve, that's why a patient doesn't come across any adverse effects. Microneedles are generally drug filled hollow metal needles, with masked spine or rigid silicon<sup>25</sup>.

### **Heat**

Warmth improves the stratum corneum pervasion by drug molecules by rising liquid circulation in the body, porousness, rate-controlling film permeability, and solvency of drug, consequently improves shifting of drug to the systemic circulation. On application of heat active drug molecules, sugars, lipids and protein is increased in the cellular layer. Additionally, drug solvency of drug in the patch also inside the corneum layer will increase



in presence of temperature. Estimation of flux values were done for *in vitro* transdermal delivery of fentanyl on application of temperature 32° to 37°C. In between this 5°C approximately drug permeation flux was found double. Further investigations demonstrated change of 5°C temperature roughly is important to produce quantifiable modification in cell film porosity. Application of heat changes patch physiochemical properties and causes hydration of skin, which facilitates the drug permeation<sup>26</sup>.

### **Needleless injection**

It includes a technique free from pain for administering drugs into the skin layers. This method includes forcing the fluid and rigid particles at higher velocities into the skin layer. This system contains transport of He or N<sub>2</sub> gas through the spout with drug molecule entered in small stream, which moves at sufficient speed for cellular infiltration. Drawback of this strategy is its high cost of its kit and measurement structure also failure to control delivery of drug to makeup skin penetrability<sup>27</sup>.

### **Medicated tattoos**

These are transformation of brief tattoos which are containing active drug for delivering it transdermally. Application of tattoos are done by wetting them in water and Rubbing on skin which feels extremely appealing, enjoyable to wear It contains two layers one contains drug and other layer is of glue which holds the skin. The maker gives a shading diagram that can be contrasted with shade of the treating individuals tattoo for deciding when the applied tattoo should evacuate. It shows clear sign of drug retained into the corneum. After absorption of drug the tattoo blurs away slowly and can be removed easily washing with isopropyl alcohol. The sedated tattoo contains the drugs like acetaminophen, vitamin C and so forth<sup>28</sup>.

### **Pressure wave**

Extreme radiation laser creates pressure waves that can make the corneum more permeable like as cell film. Application of pressure wave is for an extremely brief timeframe i.e into nano seconds. It is believed that pathway created over the corneum due to extension of lacunae spaces into corneum layer by applied pressure waves. To make the layer corneum permeable single wave is sufficient and permit vehicle containing large drug molecules in the corneum. Likewise, delivery of drug through skin could enter the blood stream and produce a therapeutic effect. For instance; delivery of insulin using this method showed decrease in level of blood glucose after hours. Pressure wave doesn't harm or feels

uneasiness and the hindrance capacity of corneum layer consistently recoups. Permeation of caffeine is reported by enhancing the pressure of waves<sup>29</sup>.

### **Sonophoresis**

Sonophoresis method is used to allow the dynamic drug particles to enter into skin which uses ultrasonic vitality. Transdermal delivery of drugs is critical at lower frequency ultrasound ( $20 \text{ KHz} < f < 100 \text{ KHz}$ ) as compared with higher frequency. Frequency duration, force, length of beat is known as significant for influencing percutaneous assimilation. The component of skin saturation includes interruption of layer corneum lipids with arrangement of vaporous depressions; with this it permits drug substances across the skin layers. In treatment of ophthalmic disorders sonophoresis is utilized to deliver the drugs. Sonophoretically skin diseases are treated with administration of few anti-toxins including antibiotics<sup>30</sup>.

### **Magnetophoresis**

Magnetophoresis shows the use of an attractive field which acts as peripheral driving force to increase delivery of drug across skin layer. It incites modification in structure of skin that can facilitate expansion of skin porousness. Magnetoliposomes consist of phospholip bilayer covered attractive nanoparticles that can effectively deliver the drugs from various formulations; It is applied in the treatment of malignant growth analysis, and thermal cancer treatment<sup>31</sup>.

### **Radiofrequency**

In this 100 KHz high frequency current is applied to skin that results in changes in skin structure by heat actuated microchannels at the cellular level. The rate of drug delivery is lowered because of various number of microchannels present, it also depend on to the microelectrodes properties which is in contact with to skin at the time of treatment.<sup>32</sup>

### **Chemical Concept**

#### **Utilization of permeation enhancers**

Including permeation enhancers will help to promote permeation of drugs with modifying corneum hindrance property. Penetration enhancer should not show any pharmacological activity, should be free from toxic effect, free from irritation and without odour, stable within the drugs and added excipients. Must be cheap, and better dissolving properties. Penetration enhancers of different classes comprise of alcohols and polyols,

surfactants, unsaturated fats, amines and amides, terpenes, sulfoxides, esters. Penetration enhancers will improve penetrability of skin with various number of systems, incorporating communication with intercellular macrobiomolecule prompting disturbance of its association which will improve its smoothness, removal of macrobiomolecules from corneum layer, dislodging of tissue water, slackening of harsh cells, separation of corneum layer, upgrading solvency also expanding parceling within corneum layer<sup>33</sup>.

### **Prodrug approach**

Prodrugs are restoratively dormant subsidiaries remedially dynamic medications. It experiences digestion to create the restoratively dynamic medication. It is more lipid soluble than its parent molecule with diverse physicochemical properties. Estradiol prodrugs and "Transdermal Bioactive Hormone Delivery" systems were created dependent upon its outcomes. Delivery of Transdermal Bioactive Hormone is subject to chain elongation of ester bunch on the seventeenth position. Ketorolac prodrugs having alkyl ester gains ideal lipophilicity can improve delivery of drugs transdermally. Likewise, one can deliver the drug by using this approach through skin layers<sup>34</sup>.

### **Other enhancement Concept Supersaturation**

It is the method in which drugs can be delivered without changing the structure of corneum. The movement of drug in this process relies on expanded thermodynamics<sup>35</sup>. This builds the fixation inclination (Co-Ci) in Ficks law:

$\{(J = KD/h (Co-Ci))\}$  also subsequently powers the dynamic guideline away from layer of corneum.

Supersaturation can be created by utilizing below techniques:

- Heating and resulting cooling
- Elimination of dissolvable
- Creating less dissolvable compound by reacting two different solutes.
- Adding substance to decrease solute dissolvability.

### **Water as an infiltration enhancer**

Corneum hydration is essential criteria in enhancing the infiltration of permeants with hydrophilic properties and lipophilic properties. Unbound water in tissue can adjust

dissolving rate of a permeant in the corneum layer. Enhanced hydration of skin can grow also help to open reduced skin layer structure which promotes infiltration<sup>36</sup>.

### **Formulation approaches**

Improvement in infiltration along uncommon formulation is fundamentally founded upon utilizing colloidal transporters. Nanomolecules are expected to move the dynamic atoms into the layers of skin. Such vehicles contain all novel nano particles. Liposomes are considered as advanced methods for improving delivery of drugs by transdermal route. It is composed of bilayer one is phospholipid and other cholesterol. It contains hydrophilic as well as lipophilic bits which can work like transporters to polar and nonpolar drug substances. When Liposomes enters the corneum layers it gets associated with lipids of skin to discharge their drug substances. Changed liposome which has property to increase the skin tissue infiltration is known as Transferosomes<sup>37</sup>.

It contains phospholipids, cholesterol also some surface acting agents like sodium cholate. The surface acting agents are "edge activators", presenting most vascularity on the transferosomes that permits barely through corneum layer pores which is short of their distance across. Transferosomes are utilized like bearer to some proteins, immunomodulators, corticosteroids, NSAIDS, anticancer medications, and so on<sup>38</sup>.

Ethosomes are liposomes made essentially of phospholipids, sometime glycols and water in generally high concentrations<sup>39</sup>. They are fit to enhance entrance to superficial tissues and their fundamental discharge. Alcohol is considered that it will fluidize the lipids layer of ethosomes and intercellular lipids in layer corneum, hence it permeates delicate, adaptable ethosome that infiltrate the layer corneum. It shows improved corneum penetrability to different mixes and have been accounted for to successfully convey Antiviral, Antihypertensive drugs and hormones transdermally<sup>40</sup>.

### **Selection of drug candidates**

Wise decision of the medication substance is the most significant choice in the fruitful advancement of the transdermal system. The drug candidate should have the accompanying ideal qualities<sup>41</sup>.

**1 . Satisfactory skin porosity:**

- 1 Lesser small molecular mass remedy
- 2 Lesser medications with melting points.
- 3 Minimize oil and water solubility while taking medic
- 4 Effective drugs

**2. Satisfactory skin applicability:**

1. Non-Toxic drugs
2. Non sensitizing drugs
3. Non metabolizing drugs

**3. Satisfactory clinical necessity:**

1. Necessity of prolonged administration
2. Required to rise enduring obedience
3. Required to decrease adverse belongings on target tissue.

**Ultrasound**

Therapeutic uses of ultrasound exists utilization as imaging procedure. It almost perceived in year 1927 ultrasound (ULTS) should deliver enduring alteration in natural frameworks, and it was beginning of wellbeing examines and ultrasound treatment. Ultrasonic vitality ingestion prompts warming of tissue, and it is used with proper goals in various conditions. Ultrasound treatments are divided into "high" and "low" force treatments. Centered ULTS and lithotripsy are categorized under high force. Were as, sonophoresis, sonoporation are categorized under low force. Aside from physiotherapy utilizes ULTS treatments at present nowhere across the board. Utilization of ULTS in clinical field was done for long period.

Sound is a kind of mechanical essentialness which is proliferation beginning with single point then following with the correspondence within neighboring influencing particles. The heading of spread is relating to the direction of faltering and, from this time forward. Since expansion of itrelies upon creation of turning sub-nuclear pressure and rarefaction regions, sound can't exist into the void space. The pressure variety has a

similar generation speed and recurrence as the motions of atoms close to those harmony positions. Frequencies of sound waves within 20 Hz and ~20 KHz falls in limit of hearable sound. >20 KHz sound frequency meant as Ultrasonic. The force (I, denoted as W/cm<sup>2</sup>), either grouping the intensity inside particular territory in the beam of ULTS, which is relative to the square of the sufficiency, p, that is most extraordinary augmentation those decreasing weight near with encompassing conditions without the wave of sound. Thus total interrelation is:

$$I = p^2 / 2\rho c$$

Therefore,  $\rho$  stand for medium relative density and c stand for sound velocity (within human soft tissue, 1540 m/s is their velocity).

High recurrence sound (<20 kHz) is generally made when electrical vitality is generated this is changed into mechanical vitality along disfigurement of the electromechanical material into transducer. The transmission of delivered waves with propagation through atomic wavering, have a dynamic sound loss across organic tissue because of assimilation or dissipating waves of sound. At certain point association of ultrasound with human tissue changes are observed due to warming the tissues and cavitation with acoustic spilling. Phonophoresis is used to carry ultrasound vitality into the body in various therapies.

Especially investigations and clinical usefulness are inside these extents. Specifically, restorative recurrence phonophoresis from early days utilized clinically for pervasion of different drug substances, for example, lidocaine, hydrocortisone and prednisolone. Remedial ultrasound frequency helps to increase topical pervasion of drugs with low sub-molecular weight. Be that as it may, the improving impact of transdermal penetration diminishes with expanding atomic weight for example fluocinolone acetonide, benzydamine, nicotinate, salicylate, and so forth. Then again, ultrasound of 0.02 ~ 0.2 MHz low frequency ultrasound was accounted to produce critical vitality which permits profound percutaneous penetration of medications which are not easy to permeate at the remedial frequency<sup>42-44</sup>.

### **Iontophoresis**

Iontophoresis is an energizing innovation that was at first researched 250 years prior.

Essentially characterized, it is the use of a DC electric current which will keep the constant flow of electric current into layer of skin or obstruction which improves permeation of unionized drug molecules. In early years, several kinds of iontophoresis have been represented like transdermal, ophthalmic etc. Iontophoresis is one of the most interesting and testing has a go at standing up to the pharmaceutical analyst. The foundational tranquilize conveyance frameworks often require gigantic part and are connected with gastrointestinal responses, while treatment effective use of courses of action shows variance in patterns of absorption. Iontophoresis strategy fits for developing extent of exasperates that will pass on various courses.

Use of DC electric current in iontophoresis for transdermal application will maintain steady flow of electric current through the corneum and improves delivery of ionized and unionized molecules. It offers different preferences, for example, simpler end of treatment, better control of medication conveyance, improving conveyance of polar medications having high molecular weight, which gain advantage by bypassing the hepatic first pass also decreasing impressively variability in individuals and used capacity of delivering the drugs systemically or locally<sup>46-47</sup>.

### **Iontophoresis mechanism and devices**

Iontophoresis devise comprise of Direct current voltage deliver system and electrodes to which wires are connected within unit and electrodes, the whole unit is placed for current and time. In procedure of iontophoresis, current passed from device through anode into ionized solution of drug know as ionic stream. The particles of drug are moved towards skin where the revultion continues moving the therapeutically active agents from structures of trans-appendageal and pores of corneum layer. Greater the anode surface, more essential is the current that should effortlessly give a current for movement of drug substances. Iontophoresis upgrades delivery of drugs by transdermal route using three components<sup>48-49</sup>.

- Particle electric field connection gives an extra power to move the substances through layer of the skin.
- Increase in applied electric current enhances skin permeability.
- Electric current causes mass movement which leads to deliver the drugs into blood stream.

**Polymers in electro-responsive transdermal drug delivery**

Polymers gain importance in foundation of a transdermal drug delivery system. These systems are prepared by using multiple layers of polymer. These layers have reservoir of drug or else network of drug and polymer which is placed between layers of polymer: back surface of system have an external impenetrable layer that supports and prevents drug loss and inner surface of system lined with layer of polymer acts as adhesive and/or rate-controlling membrane. TDDS are classified broadly into the three types<sup>50</sup>

- Reservoir systems
- Matrix systems
- Micro reservoir systems

Polymers utilized for preparing transdermal delivery systems ought to be biocompatible and compound similar to drug and different components of prepared system, for example, skin permeants and PSAs. Systems additionally provide reliable, compelling delivery of a medication all through item's planned time span of usability or conveyance period and have by and large perceived as-safe status<sup>51</sup>.

It is hard to get new polymers and have explicit properties. Improving the properties of common polymers is hugely essential to address the different difficulties like upgraded warm soundness, multiphase physical reactions, similarity, sway reaction, adaptability, and unbending nature. In prior days, polymers were utilized as parts of the careful gadgets; today polymers have a significant job in the drug delivery. Change of natural polymers has gotten more prominent consideration in the light of the shortage of beginning materials required for the blend of new monomers to give better polymeric materials. The cutting edge anticipates polymer adjustments as it opens up additional opportunities. Surface and mass properties can be improved viably by changing customary polymers. In some cases, adjusting of properties is fundamental, and this is conceivable just through change of polymers<sup>52</sup>. There are a few different ways to change the polymer properties. Mixing is the physical blend, at least two polymers to acquire imperative Characters. In Grafting technique monomers are reinforced upon host polymer back.<sup>53</sup>

Electrically sensitive polymers would set up through polyelectrolyte<sup>54-57</sup>. Pulsatile release of drug through electrically sensitive polymers is noticed after turning electrical



current on/off. Release of drug after electrical stimulation occurs via migration of charged drugs toward the opposite electrode and usually, electric current regulates the release of drug from the polymer matrix. On application of electric stimulus, the drug release is due to shrinking and electroosmosis in polymer matrix<sup>58</sup>. Electrically sensitive polymers contact close to the anode, so water oozes near cathode and vice-versa observed with polycationic polymers. Electrically tweaked drug delivery offers remarkable points of interest for giving on-request drug discharge from transdermal dosage form<sup>59</sup>.

### **Graft copolymerization**

Grafting strengthens the features of natural polymers and also yields another property. Normal polymers are frequently favored for graft polymers over manufactured polymers because of their non-harmful, minimal effort, free accessibility, and biodegradability. An extra advantage of this implant copolymer incorporates transformation to ionics structure through method of hydrolysis of the amino group to get a pH-responsive copolymers. Certain copolymers can be utilized aimed at focusing to the lesser portion of the GIT like Colon.<sup>60</sup>

The most likely approach for changing polymers is to transplant the designed monomer upon organic polyethylene, as the framed copolymer will have additional characteristics than its base material. Organic polysaccharides have several beneficial qualities, such as their water-based accessibility and breakdown, which makes it conceivable that they could be used as the foundation for a mixture of copolymers composed of grafts. A web-like that supports distinct distinctive polysaccharides is used to graft vinyl or acryl monomers for short, which serve as the primary source for combined polyvinyl or polymers. Synthesis uniting of vinyl/acryl monomers differs from that of non-vinyl/acryl polymers. The method for grafting non-vinyl/acryl polymers is called polycondensation, although the harsh conditions of typical at elevated temperatures, a process called poly actions are inappropriate for the polysaccharide spine. The union of graft copolymers of polysaccharides is no longer accomplished by the use of the polycondensation process. There are two methods for synthesizing bonded polymers as follows: a) electromagnetic approach and b) traditional methodology. The traditional method is not conducive to the synthesis of block copolymers and may cause carbohydrate breakdown. On the other hand, a microwave-aided process is greener, highly repeatable, easier to use, plus healthier.

Graft polymerization is very encouraging procedure to alter the properties of a polymer also alteration in characteristic polymer materials offers the chance to modify its physical and compound characteristic properties and consolidate both common and the manufactured polymers. The grafted copolymers could be utilized to control the delivery of drug in transdermal administration, buccal administration and in network tablets<sup>61-63</sup>.

To have the desired properties of sustained or targeted drug release in polymer, the chemical modification of available polymers is the promising way. Generally, all molecular responses known from low atomic natural science might be conveyed out. However, till now not very many such synthetically adjusted items are created and utilized economically for the detailing of medication conveyance frameworks. Below various methods are mentioned how natural polymers are chemically modify:

- Grafting copolymerization
- Carboxymethylation
- Oxidation reaction
- Esterification

### **Graft copolymerization**

Graft copolymerization is the strategy that improves the characteristic features held by natural polymers. The regular polymers are frequently favored at the joining than the engineered polymers were due to their non-harmful, minimal effort, accessibility, and biodegradable. Another benefit position of this join copolymers is they could be effortlessly changed within the ionic structure by removing amide groups bringing about electrically responsive copolymers.<sup>64</sup>

### **Synthesis of cellulose graft copolymers**

The most intriguing technique for modifying polymers is transplanting synthetic polymers onto natural polymers, as the resulting monomer is going to possess features not found in the substrate. Owing to several advantageous characteristics such as their water-based availability and being biodegradable organic polysaccharides appear to represent a good choice for usage as a basis for the the synthesis of grafted polymers. A large portion of grafted polymers are synthesized by vinyl or acryl monomers grafting upon a network of different characteristic polysaccharides. Grafting of vinyl/acryl monomers artificially varies according to the nature of the monomer process a process called poly may be

employed to attach non-vinyl/acryl subunits; however, the polysaccharide framework is not compatible with the severe circumstances of conventional polycondensation responses such as excessive temperatures. Because of this reason, grafted copolymers of polysaccharides are not synthesized via the poly condensing process.<sup>65</sup>

Grafting forms branched structure copolymer, where the backbone of main polymer or substrate is covalently bonded by the side chains of synthetic monomer. Graft copolymers have a wide variety of valuable belongings not the same as those which each have alone. Grafting techniques can be arranged by grafting medium (homogeneous or heterogeneous) and the kind of commencement mechanisms.

### **Facilitator utilized for the purpose of Grafting cellulose copolymers**

It is realized that grafting is affected by type of initiator used. Which regulates the grafting rate upon monomer which to be grafted. In the process of vinyl monomers grafting on cellulose or its subsidiaries is done by synthetic initiators or by using light. Non-vinyl monomers and its subsidiaries are grafted by response of monomer with the receptive useful gatherings of the cellulose. As synthetic initiators, redox initiators, for example: ceric ammonium nitrate, acetylacetonate complex salts, ammonium persulfate, and free extreme generators, for example, ammonium persulfate can be utilized. Radiation/ microwave light is utilized to perform grafting<sup>66</sup>.

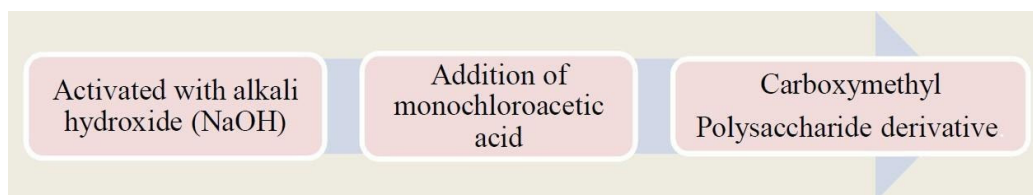
### **Vinyl/acrylic graft copolymerization**

Grafting of materials made with vinyl and acrylic upon polysaccharides is the most part accomplished by radical polymerization procedure. Graft copolymers set up first by creating free radicals upon biopolymer spine. For Grafting of monomers on polysaccharides radiation beginning systems are used.

### **Carboxymethylation**

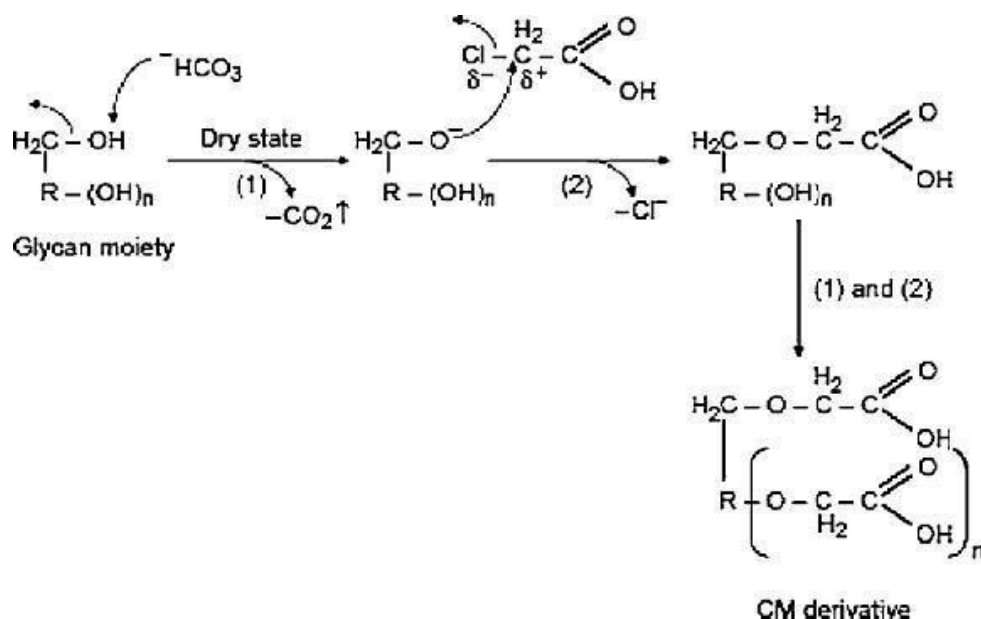
Many researches were carried out on the conversion of polysaccharides by carboxymethylation reaction, as it is the simple and easiest method of modification. In this method, fluid soluble base hydroxide for the most part sodium hydroxide is utilized for the actuation of polysaccharide and changed over monochloroacetic acid either the sodium salt as indicated by Williamson ether blend resulting carboxymethyl (CM) polysaccharide

subsidiary.



**Figure No 1.3: Williamson ether synthesis process**

In the process, the natural polysaccharide was made to dissolve in an aqueous solution of NaOH, under constant stirring. The temperature of the reaction was maintained at 70°C with constant stirring for 30 min, after the addition of monochloroacetic acid resolution. After cooling the response combination was added with 80% (v/v) methanol to get the swift which was then sieved and wash away. Glacial acetic acid was added to neutralize the solution (pH-7). The product was again filtered and further washed with the 80% (v/v) methanol 3 times. After sufficient washing the product was filtered and dried.



**Figure No 1.4: Carboxymethylation of natural gums**

The etherification method containing carboxymethylated groups is also known as carboxymethylation. Many natural polysaccharides including cellulose and starch can be chemically modified by this method. In the transdermal delivery system Carboxymethyl locust bean, guar & Xanthan gum is used<sup>65</sup>.

**Oxidation reaction**

Presence of primary hydroxyl groups in the natural polysaccharides is the site for the oxidation reaction and its chemical modification. Nature of the oxidants decides the oxidation reaction due to which it is difficult to get both selective as well as complete modification of any intended place. Majority of the oxidants having low molecular weight produces both carbonyl and carboxyl function groups unto large extent relying on experimental circumstances. This reaction can give more useful products with promising properties if the reaction is made more specific for the oxidation of desired positions.

**Esterification**

In this method of chemical modification, various esterifying agents can be used for the esterification of –OH groups of cellulose. Modification by esterification of different positions includes.

- Sodium tripolyphosphate Phosphate.
- Sulfurization by sulfuric acid.
- Reaction with derivatives of carboxylic.
- Nucleophilic reactions of displacement.<sup>67</sup>

The use of natural remedies as the main kind of treatment has existed since the dawn of time. Natural remedies stay in high demand in developed as well as developing countries these days, despite the high level of technological advancement. This is because they are organic and have fewer negative consequences. In addition to being used as therapeutic items in underdeveloped nations, herbal substances are quickly finding their way into the alternative and complementary medical facilities that make up the integrated medical centers in developed nations. Many botanical conventional therapies have emerged and are currently the mainstay of complementary treatment. This includes the Chinese and Thai medicinal herbs, the Indian Ayurvedic system, and the Western herbal tradition derived from Greek and Roman roots. In nations that are developing, where they have long been an essential part of their past and civilization, herbs, or herbal remedies, have long played a significant role in conventional systems. Ayurveda and Siddha are two such systems that originated from the past of India.

Plants are a rich source of numerous compounds having medicinal qualities, as has been widely accepted in the past. Medicines and seedlings are part of the broader biological family and also include many other types of plant compounds that are commonly employed as seasonings or in medicinal. Nuts can be consumed entire or, on occasion, extracts of them utilized to make medications. A medication or substance derived from one or more species and utilized for any of these is more widely recognized as a medicine made from plants. There is a lengthy history of using modern medications such as quinine, also digitalis, which is aspirin, and morphine as alternative therapies. Alternative medicines are likely to contain deeper chemistry and occasionally provide the ability to use medications or mixtures of medications that the healthcare sector has not yet fully utilized. Techniques like purification and quantification of these plant or part of plant extracts make them less unpredictable, and chemical preparation may at times beneficially modify the results.

Demands for natural treatments to be governed as drugs to guarantee excellent quality and to demonstrate their scientific basis have risen due to the extensive usage of plants or their parts in traditional medicine. Herbal medications offer to treat a wide range of illnesses in addition to preventing them. There are more than 760,000 florae in the world, yet just a few have been studied and researched for medical purposes. The majority of herbal medicine research focuses on locating and separating the active components. Although botanical remedies are naturally derived and have no or few adverse effects, both conventional physicians and researchers are turning to them these days to treat conditions including inflammation, rheumatoid arthritis, cancer, diabetes, healing from wounds, and a host of others. To make these extracts easier to administer, different mixes have been created. Compared to traditional forms of plant actives and gathers, the new mixtures are said to offer several benefits, the most desirable of which being increased dissolution, bioavailability lack of toxicity, increased pharmacological action, higher stability, experienced shipment, and resistance to chemicals as well as physical degeneration.

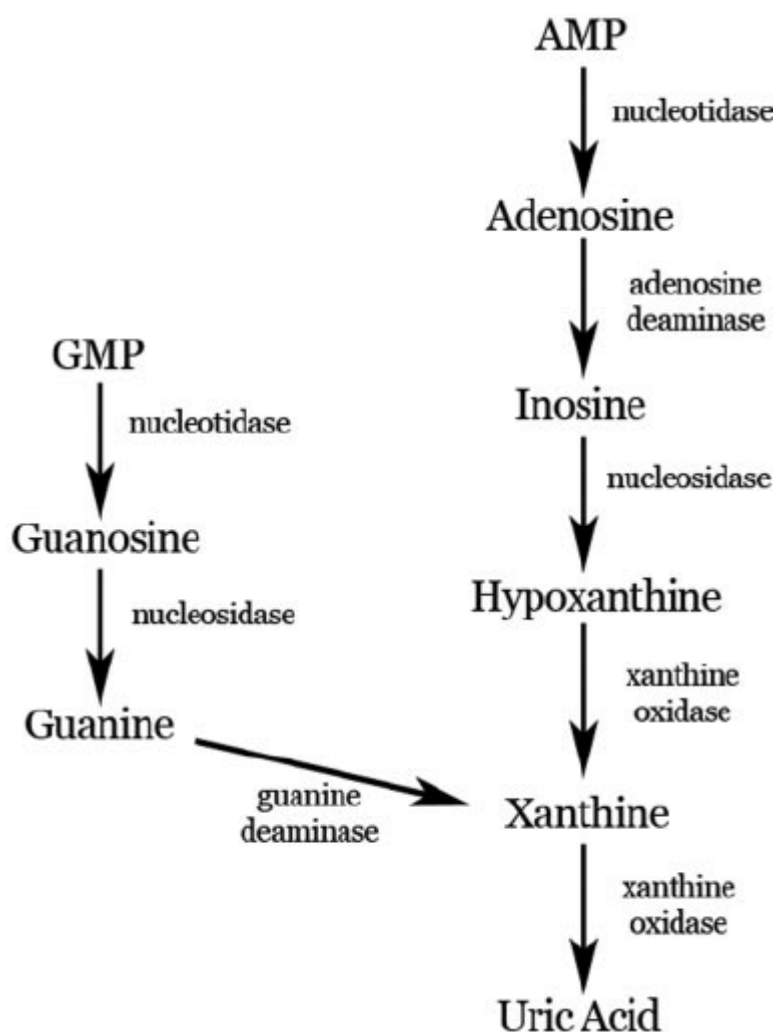
### **Rheumatology and its management with extracts of plants**

It is a prevalent form of arthritis that results in severe joint discomfort, edema, and tightness. Typically, this impacts the larger toe tendon. Infections with rheumatism can occur suddenly and often over time. It gradually damages tissue around the inflammatory area. Despite it primarily affects men, women are more vulnerable to it after puberty. It is

the most frequent type of inflammatory arthritis in men. According to information from the US Agency for Health Promotion and Control, 8.3 million people Individuals suffer from rheumatism.

**Here are a couple of important gout-related facts.**

1. A kind of rheumatism called gastritis is brought on by an overabundance of urinary acids in blood vessels.
2. A buildup of urinary acid particles in cartilage combined with the immune system's reaction to them causes symptoms associated with gout.
3. The socket at the base of the big toe is typically especially affected by rheumatism.
4. Symptoms with arthritis frequently happen suddenly in the latter part of the day.
5. The majority of those suffering from gout undergo treatment with particular drugs.

**Uric Acid Metabolism****Biosynthesis of Urate:****Figure No. 1.5: Uric acid metabolism**

(Hypoxanthine-guanosine phosphoribosyl transferase)

The last byproduct of the digestion of purines in the livers of people is a compound called uric acid. (Figure 1.6).



**The elimination of acid urea.**

The uric acid is broken down by human uricase to produce extremely water-soluble allantoin. It is anticipated that the renal system will eliminate around two-thirds of the uric acid. The primary mechanism for the filtration reabsorbing of urate is Reabsorbing after secretion via the S3 region of the basic nephron tubules. It was successfully determined which are the main genes that express the ion transporters involved in urate renal transfer. The electron exchanger URAT1, which is produced by the protein SLC 22 A 12 (solute transporter domestic 22 [carbon-based negative ion/urate transporters] members 12), is perhaps the most significant of them at all times. The gene responsible for uric acid anion reabsorption and genome 11q13. Voltage-dependent urea retention in the tubule's proximal section is facilitated by the hexose importer SLC2A9, also known to be the prosocco importer expressed by a mutation on chromosomes glucose transporter 9, GLUT9, or fructose transporter. SLC2A9 genetic variants may provide insight into the pathways connecting high levels of fructose and glucose to the condition and arthritis.

The primary transmitter or urea output in the tubules resides in the single nucleotide polymorphism (SNP) of ABCG2 (ATP-binding cassette subfamily G member 2), which is closely linked to a high level of in men, postmenopausal women, and estrogen patients.

**Different Gout Types such as**

- **Undiagnosed hyperuricemia**

Elevated uric acid levels can occur in people who don't exhibit signs. Therapy is not as important at this point, even if urate crystals are beginning to accumulate in tissue and cause little harm. Individuals with undiagnosed an elevated uric are recommended to follow specific measures to address potential causes of uric acid accumulation.

- **Aggressive gout**

The process is brought on by the abrupt development of crystals of uric acid, which can result in extreme discomfort and serious swelling. The term "flare" describes this abrupt outbreak, which usually goes away in three to ten days. Alcohol is narcotics, adverse circumstances, and freezing temperatures can all contribute to flare-ups.

- **Gastro interval or inter-critical**

This phase is recognized as the intermission amid acute episodes of gout. Even while they might not happen for months or years, additional flare-ups have the potential to become more common and persist lengthier if left untreated. More urate crystals are being deposited in the cells at this time.

- **Arthritis tophaceous persistent:**

The weakest kind of rheumatism is continuous tophaceous gout. There could have been irreversible harm to the heart and hips. Generate tophi, large masses of urate crystals, in colder parts of one's body, with the same value as the bones in your fingers, if you have persistent arthritis. The stage of chronic tophaceous gout typically requires an additional amount of time without therapy (may extend for roughly 10 years). Since this is the most crippling kind of gout, recovery from this condition is uncommon.

- **Falsedogout:**

Pseudogout is one illness that is frequently mistaken for gout. Pseudogout and signs of gout are extremely similar. The main distinction between flair and pseudogout lies in the fact that the calcium phosphate particles, as opposed to urate crystals, are what agitate the cartilage in the joint. Treatments for pseudogout differ from those for gout.

### **Phases of Gout**

- 1) **Unnoticed hyperuricemia:** This is the state that exists before the initial onset of gout. This stage is characterized by elevated levels of blood uric acid and the formation of crystallization in the joint disorder but without any symptoms.
- 2) **Severe gout**, often known as a gall strike, is caused by elevated uric acid levels that cause crystals to grow in a joint to surge, ultimately causing the attack to occur. Usually starting late at night, the subsequent swelling and pain worsen over the following eight to ten hours. The symptoms usually go gone in a week to ten days, however, it starts to fade after a few days. A subsequent gout incident may never happen to some others, but over 60% of those who suffer an incident will get another one before twelve months.

- 3) **Intermittent gout:** This refers to the duration of bouts. Not only there's no pain, but it appears that gout is not fully cured. Joint injury may result from low levels of uric acid irritation. Now is the time to start gout care to avoid more incidents of gout.
- 4) **Recurrent gout:** This condition arises in those whose uric acid levels don't go down for a long time. Triggers occur more frequently, and the agony does not subside as it formerly did. There could be injury to joints, which could result in less flexibility. This point can be avoided with the right care and attention.

<https://www.arthritis.org/about-arthritis/types/gout/what-is-gout.php>

### **Transdermal Drug Delivery:**

Pharmaceuticals might be administered to the localized target region or to the systemic blood circulation to treat disorders. There are several ways to conduct systemically their delivery, with oral administration being one of the most frequently used. The hepatic first-pass effect is a drawback of the oral path, though. As a result, alternate administrative channels are highly desirable. Transdermal, or is probably the most ideal of those. Chemicals could be continually delivered by injection through the skin into the bloodstream, blocking first-pass metabolism. Nevertheless, treatment of the medicine on its outermost layer also can raise the amount of the medicine at the site of action when targeting the administration of drugs to areas of the human body such hair follicles, perspiration, and oil glands. Furthermore, there may be a decrease in the transport into the systemic circulation, which would lessen the likelihood of adverse consequences. Since the pilosebaceous system is the source of many skin conditions, including alopecia malignancies, and breakouts, the rationale behind topical distribution may be especially relevant in these cases.

Additionally, it is interesting for products used to enhance certain conditions, like hair. Two strategies can be used to enhance local delivery. The first strategy involves choosing a suitable structure, which may include chemicals like propylene glycol, alcohol, and lubricants as well as particle carriers. Choosing a potential medication candidate is an extra strategy. The degree of delivery and targeting may be influenced by the medication's corporeal and biochemical features such as size, charge, and lipophilicity. When it is not possible to modify the manufacturing process, the only way to boost transport and focus is to modify the physical and chemical features of the permeation enhancers themselves.

It is now acknowledged that surface distribution is one of the possible non-intrusive dosage

routes. Its benefits include longer therapeutic action, fewer side effects, ease of usage, and better compliance among patients. Nevertheless, the skin's limited barrier has principally hindered the advancement of topical medications. To solve this issue, a variety of pharmaceutical enhancers for penetration have been developed recently for direct medication delivery, facilitating the drug's simple transit via the skin. It has been suggested that these synthetic boosters promote solubility within the stratum corneum or increase the lipid permeability of the internal bilayer, which aids in the uptake of taken medications.

**Skin:** The layer of skin serves as the primary interface between the human body and its ever-changing surroundings. As a result, it aids in controlling what passes through the skin and into the tissues of the body. Whereas additional organs, such as the permeable epithelia of the GI tract and pulmonary serve the main route of regulating entrance into the human system, the skin often permits entry for extremely few particles. The cortex, or the thin outer layer of the skin, is largely responsible for the complexion's extraordinary barricade. Unlike the rest of the body, the corneum layer is made up of corneal cells, which are mostly made of aggregating fibers of keratin wrapped in a cornified sheath. An extracellular milieu of lipids arranged as numerous laminated bilayers of surrounds the corneocytes in except medications that are lipid soluble and have low molecular weights, these organized well lipids stop the body from losing too much fluids and also stop the majority of pharmaceuticals from entering the body when administered externally. This presents a major obstacle to the application of skin-based medication, whether for topical application or as systemic therapies after penetration of shallow dermal vasculature.

#### **Skin's structural makeup: Different layers of skin**

The twofold purpose of skin is to act as a barrier between ourselves and our external surroundings. Both the epidermis and dermis are the two outermost layers of flesh.;

**The epidermis:** Horne layer stratum lucidum

Stratum granulosum

**Dermis:**

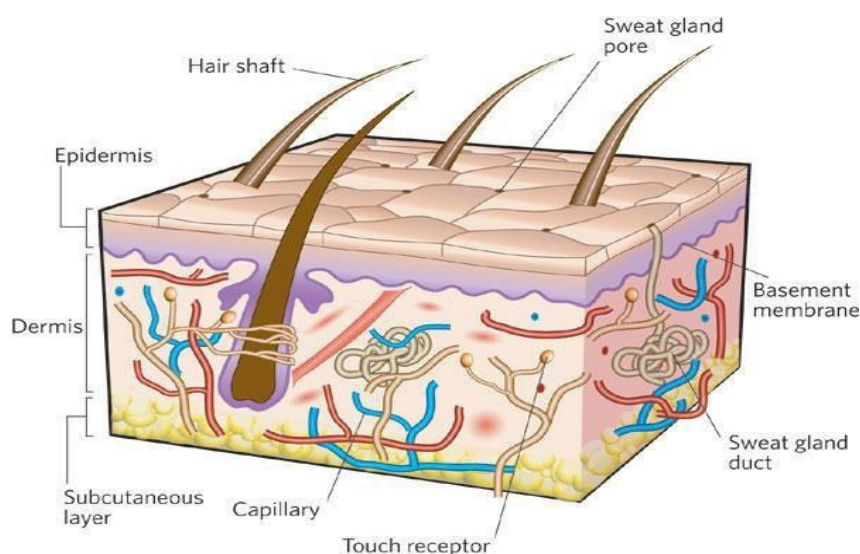
- 1) Malphagian layer
- 2) Papillary Layer
- 3) Reticular layer

**Epidermis: -**

According to its position on the human physique, the skin's epidermis, which is the outermost layer, has an overall thickness ranging from 0.1 to 0.6 mm.<sup>7</sup> Keratinocytes make up ninety-five per cent of the living tissue of the skin's outer layer. Indistinguishable skin cells that are close to the tissue make up the bottommost layers of the epidermis. These cellular rows are continuously dividing, creating new cells. Stratum corneum, the topmost layer of skin, is expanded further like stone.

**The Dermis: -**

The middle layer of flesh lies above the innermost and a further layer of cells, such as muscle, fat, etc. It is 0.3 to 0.4 mm thick. The dermis contains vessels of blood that deliver nutrition to all layers of the skin. The skin's outer layer is home to antibodies and external substances.



**Figure No. 1.6: Different Parts of the Skin**

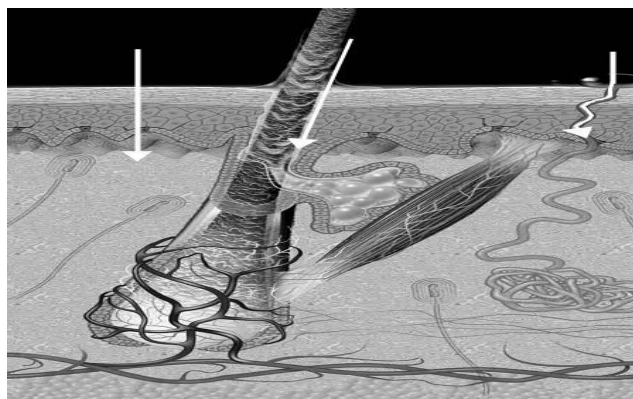
**Pharmaceutical Intake through Subcutaneous Techniques**

The outermost coating of functioning covering, and the stratum corneum layer are the multiple layers that make up the skin. It has extensions such as sebaceous glands, hair follicles, and glands for sweating. The outermost "horny" coating of the covering, known as the corneum layer, is made up of 15–20 rows of flat, partially dried, dead, keratinized epidermal cells.

This layer has a thickness of 10–20  $\mu$ m, based on the area of the body. The palms of the hands and the arch of the legs contain. When it comes to blocking chemical transportation, the corneal layer is noticeably stronger than the epithelial obstacles seen in the modes of administration: digestive tract, breathing, oral, genital tract, or colorectal. Because of the stratum corneum's tiny water quantity and lipid-rich composition—roughly 40% fats, 40% proteins, and 20% water—transport of hydrophilic compounds is particularly challenging. These hydrophilic medication compounds dissolve into the extracellular triglycerides surrounding the outermost layer of cells, which normally facilitates their transport. Hydrophilic substances can enter the skin via "pores," which are the holes in the glands that produce sebum and hair follicles. Therefore, this hole's relative dimension is only 1% of the skin's overall surface area. This tiny area of surface restricts how much of the medication is absorbed. In the circumstance of transdermic medication distribution systems, the transdermal permeation of drug compounds is crucial for the medication to be absorbed to a sufficient degree and velocity to reach and sustain consistent, widespread, beneficial doses for the entire course of therapy. Stated differently, the medication molecule enters deeper tissue the moment it passes through the skin's outer border.

Passive dissemination is the process by which drugs enter through the skin. Rendering to Fick's Theory of diffusion, the amount of drug transport across the stratum corneum is constant. In addition to aqueous solubility, the medicine's rate of transportation is directly correlated with its oil/water partition value, concentration in the formulation vehicle, and the exposed skin appearance area; it has an inverse correlation with the stratum corneum's size. The skin's post-auricular, axillary, and forehead regions have the smallest skin layer, whereas the plantar (soles) and palmar regions have the largest layer of skin. Comprehending the way medications move through the body is crucial for creating a topical or transdermal product that works effectively and it is also important for assessing and forecasting how the drug will behave in different combinations. The second is crucial from a practical standpoint for pharmacists, who must advise consumers on the appropriate handling and application of external and dermal treatments, or recommend one or more efficacious pharmacological items from among the numerous commercialized preparations accessible.

Two distinct pathways can be identified for entry into the stratum corneum: (i) a transcellular journey that alternates between penetrating via the lipid the lamellae and corneocytes and (ii) an interstitial pattern that follows the tortuous pathway along the lipid lamellae. It is widely acknowledged that the extracellular pathway is the primary means of entry into the corneum stratum. The thickly linked together cornified membrane that covers these cells is the primary source of this. It is not possible to fully rule out transcellular transfer for tiny molecules with hydrophilic qualities like freshwater. Whereas a follicular duct's substance is lipophilic in nature the intrinsic water cells' contents are primarily aqueous. The primary cause of this is the sebum released into the sebaceous duct aperture. Through the skin without active stimulation.



**Figure 1.7: Transportation pathways enter the skin via the trans epidermal (A) and trans appendageal routes. Distribution through hair shafts and the sweat glands is part of the trans-appendageal pathway (B).**

#### **External Remedies:**

For the best possible clinical results, efficient drug administration in addition to the appropriate choice of drugs is necessary. Throughout the past several years, the chemical sector has placed a greater emphasis on establishing a good drug transport system because skin provides the best and largest available space for drug administration. A drug's needed chemical reaction and unwanted effects are mostly determined by its concentration at the site of behavior, which is influenced by its dose type and rate of digestion. Although it has been known for a while that the whole layer of skin may serve as a pharmaceutical administering sanctuary in the human body, skin acts as a very tough barrier to substance entry, permitting only very minute amounts of drugs to pass past over time. It is among the entire human physique's easiest tissues to access.



**Drug Substance for Interesting Treatment Distribution Organization:**

A medication's composition is crucial to the effective development of a topical medication.

**Table No. 1.1: Optimal medication characteristics and a few things to think about when preparing an oral drug delivery device**

Parameters	Properties
Dose	Should be low (less than 20mg/day)
Half life	10/less(hrs)
Molecular weight	<400da
Skin permeability coefficient	$>0.5 \times 10^{-3} \text{cm/h}$
Skin reaction	Non irritating non sensitizing
Oral bioavailability	low

**Enhancements for biological entry:****These compounds, which are terpenoids are crucial fluids:**

MathurV, Satrawala, Rajput s, physical and chemical penetration enhancers in TDDS Asia pharmaceutics, 2010, Vol 4,173-183.

Terpenes and terpenoids are classified by their chemical makeup, which comprises several repeating synthetic rubber components.

**Monoterpenes:** Hold a pair of isoprene. **Sesquiterpenes:** consist of a trio of molecules.

**Diterpenes:** Consists of four isoprene molecules. **The two types of terpenes:** are made of flammable fuel. Terpenes are substances that only include three elements: hydrogen, oxygen, and carbon. Enhancements of permeation that work well include camphor and chenopodium species.

Terpenes' ability to enhance penetration is largely dependent on their chemistry as well as the physicochemical characteristics of the medications. According to findings from experiments utilizing skin from people, the penetration coefficient of different compounds



is greater in those with higher Logp. Additionally, it was noted that fluid terpenes have the potential to create additional hydrogen bonds in the stratum corneum's interfacial lipids and have stronger boosting effects than solid terpenes. In comparison to other aromatic compounds, triterpenes, and tetraterpenes often exhibited a lower penetrating impact; nevertheless, the addition of an alcohol or carbonyl functional category enhances their effectiveness.

**Fatty Acids:**

An aliphatic hydrocarbon chain and a terminal carboxylic acid group make up fat acids. The amount, status, and arrangement of two bonds, as well as the possibility of branches and other substitutes, determine the aromatic strand length of a sentence, which varies between them and can be either saturated or unsaturated.

Due to their high skin flux, lack of allergic reactions, and compliance using a wide range of medications, fatty acids as a cutaneous absorption enhancer seem to be therapeutically appropriate. Numerous long-chain fatty acids may be useful as modifiers of penetration into the skin.

**Saponin are:**

These are a very diverse class of carbohydrates found in vegetation. These substances are linked to multiple sugar chains by an aglycone that is either steroid or triterpenoid. They have a wide range of applications as epidermal penetration-improving agents because they are also categorized as natural cleansers.

The micelle-like collection caused by the combination of saponin particles organized in a circle with their hydrophobic moieties and cholesterol around the outer parameter causes ulcers in the membrane planes.

**Extracts of herbs:**

The extracts of herbs can quickly enter the epidermis. The tea flavone apigenin is luteolin, and a compound called 7-o-beta-glucoside was found to undergo in vivo skin penetration studies, which revealed that the compounds are taken in not just at the epidermal level but also permeate deeper than the epidermis. It is a crucial component for their topical utilization.

**New Organic Permeation Enhancement Applications**

- **THE BASIL OIL:**

Serves as the booster for organic penetrating. It is used to improve a medication's penetration via the skin. It has a diuretic antioxidants and antimicrobial effects. The procedure involves the collection of fats from the surface of the cornea and the polyamide hydrogen bonds being loosened, which causes the lipid layer of the skin to become looser.

- **OIL OF CLOVES:**

It improves permeation naturally. It is used to improve the medication's permeation through the skin. It is suitable for use in dental floss, drinks, and foods. It is also utilized as a painkiller and antibacterial.

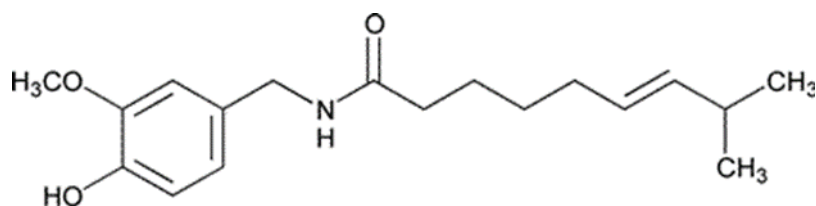
**CHILI POWDER:**

It is applied as a way to improve penetration to make drugs more permeable through the skin.

Designs containing topical jalapeño are employed to treat inflammation.

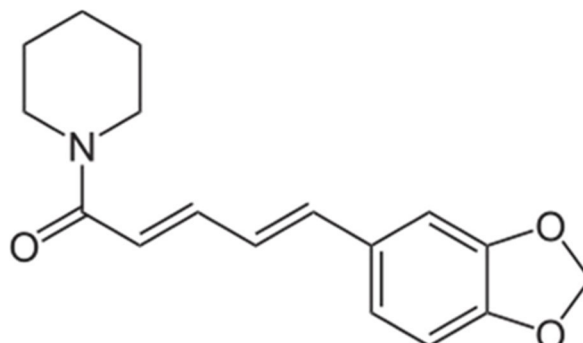
The mechanism: There are several factors at play. These involve the disablement of receptors, the blocking of voltage-activated channels containing calcium, the build-up of ions inside cells that alter the osmotic balance, and the activation of proteolytic enzyme systems.

**Dray A:** The way a chemical similar to capsaicin affects neurons in the senses. Pub Med.

**Capsaicin****PIPERINE:**

Acetate was utilized as a specimen pharmaceutical in a lab experiment to examine the percutaneous promoter action of piperine, an amide alkaloid found in black pepper, on humans' dead tissue. Moreover, FT-IR imaging investigations were carried out to

comprehend a potential enhancing process. These findings suggest that piperine is a increases aceclofenac's penetration into the skin through an intermittent strategy that involves interactions with SC keratin and partial release of the corneal layer (SC) fatty.



### Gels:

A material form exhibiting characteristics halfway above the two categories of fluids and solids is referred to as a "a gel." But it's frequently applied incorrectly on every liquid system. The structure created by the interlinking of the adhesive nanoparticles gives a gel its stiffness. The links, whose determine the organization of the network plus gel's characteristics, are caused by the nature of these particles and the kind of pull that acts upon them. The term hydrophilic colloid's parts might be solitary biomolecules or sphere or isometric aggregates of minuscule molecules. conceivable configurations for such particles within a liquid structure. Gels are swelling systems that have watery dispersion characteristics as well as rigid coercive features. Particles are often soft and extremely responsive somatically because of their flexible nature.

That are categorized as semisolid at higher temperatures because they contain perhaps big organic compounds interspersed throughout fluid or a suspension of small organic particles. Gels are semi-solids that range from translucent to transparent and have a high solvent to gelling agent ratio. Gel-forming reagent combines with solvent on dispersing to generate three-dimensional in nature capillary structures of networks. This arrangement of pores traps and immobilizes the chemical solvent particles limiting the rate of flow of liquids. Additionally, the interconnected structure gives the gel its viscous qualities.

Gels can be administered orally, topically, vaginally, or rectally in a fluid form. If every single one of the parts totally disintegrate in the dispersion solvent, the gel product can be considered transparent. However, not all gels exhibit this, and as a result, most are hazy. People like clear gel better. Gels that include discrete, small-sized molecules in them are referred to as two-phase

systems. A liquid is referred to as a one-phase structure if it doesn't seem to contain distinct particle. Because two-phase phenomena are thixotropic, they dissolve after shook yet remain somewhat solid while undisturbed. In a dual-phase arrangement, the gel is called volcanic if its particle size is big.

Devices in three stages incorporate the elements aluminum oxide, bentonite powder magnesium, and gel. Polymer proteins in systems with just one phase are straight or branching, melt in water-based, and do not appear to have a boundary with the dispensing media. Such macromolecules fall into one of three categories: synthetic compounds like carbomers, semi-synthetic substitutes for cellulose (like methylcellulose as), and polymers made from nature like the plant. Mucilage is the term for one phase gels composed of natural or synthetic polysaccharides.

**Division:**

These substances are categorized based on physical features, rheological qualities, liquid type, and particle stages:

**1. According to the colloid stages:**

Those can be separated under dual-phase systems or chemical types. The relationships among these dictate the characteristics of the gelatin and the structure of the network.

**i. Mechanism in one stage:**

Those are made up of big organic compounds that are continuously broken on twisting strands. These bigger molecules of organic material, which can be artificial or natural polymers, are known as gel precursors because they tend to become caught or be attracted to one another by the principles of those are made up of big organic compounds that are continuously broken on twisting strands. These bigger molecules of organic material, which can be artificial or natural polymers, are known as gel precursors because they tend to become caught or be attracted to one another by the principles of van der Waals. van der Waals.

**ii. Dual-phase setup:**

Enormous scattered dispersion particulates that create a structure in three dimensions in the gel constitute a chaotic system because they are made up of floc of minor elements rather than greater particles and lotion architecture.

They have to produce semisolid at higher temperatures upon resting that thixotropic ally develops into liquids upon agitating.

## 2. Hydrogels that are based on the composition of the fluid (water is related)

These include clay lava, and gelatin, which results in viscose instruments such as derivatives carpooler, and poloxamer that connect, all of which include water as their persistent fluid phase.

- **Gels are biological substances (using a non-aqueous fluid)**

These have a permanent phase made of a non-aqueous liquid. For instance, aluminum lubricant dissolves in liquids along with low molecular mass polypropylene soluble in minerals.

- **Electro gels:**

Xerogels is hard hydrogel that have a minimal liquid content. This are made by freezing or evaporated solvents, which leaves the gel structure behind. When they come into contact with new fluid, they swell and rehydrate. For instance, the presence of - from gum tears, polyester, drying a substance called and the herb streamers.

## 1. Considering the rheological features:

Martyn's Physical pharmacy and pharmaceutical science, Petric J. Sinko, 6<sup>th</sup> edition, Pg. No. 849-888.

Generally, lotions exhibit non-Newtonian movement belongings. Depending on these gels are classified into,

- a) Polymer gel
- b) Artificial plastic gels
- c) Gels with thixotropy

a) **Polymer gels** for instance, flocculated solutions of aluminium hydroxide found in Lawson banks show a flexible movement, and the rheogram plot indicates the gels' yields worth when the stretchy liquid deforms and initiates flowing.

- b) **Artificial plastic gels** for instance, pseudo-plastic it is seen in the fluid spreading of tragacanth, Na alginate, Na the CMC, etc. They have no yields worth and their viscosity falls as the rate of shear increases. A shearing action on the straight monomers' molecular chains produces the rheogram. Following the escape of water in the structure of the gel, the disorganized particles start to bring into line with their long axes in the way of the stream as the strain from shearing increases.
- c) **Gels with thixotropy** They have very fragile molecule connections that are easily disrupted by vibration. Because of the molecules' collisions and subsequent connecting, the solution that results is going to return to gel (the rescindable isothermal gel-sol-gel conversion). This takes place in nonspherical nanoparticles in a liquid fluid to create a scaffold-like architecture. For example, agar, is bentonite as and potash.

## 2. In accordance with physical characteristics

- a) **Gels are substances** that with elasticity agar, pectin, gum of guar, and alginates, or gels behave elastically. At this location of intersection, or the fibrous molecules are joined by fairly weak connections such dipole pull and hydrogen bonding are examples. Further interaction occurs by a bridge of salts of form  $\text{COO-X-COO}$  that links two neighboring strands systems if the molecules has a free the form of  $\text{COOH}$  group. Such as carbapol and chitosan.
- b) **Sticky gels** This could be created from a molecule with a fundamental valence bond linking its structure. For instance, the  $\text{Si-O-Si-O}$  link that holds silic acid particles together in a gel form creates a type of polymer form with an array of pores.

## Typical Gel Formation Substances

A plethora of substances that gel exist. Acacia's alginic acid bentonite clay methylcellulose, are alginate from sodium, the use of x gelatin, hydroxyethylcellulose, a type of cellulose, a the mineral aluminum silicate (Veegum), poloxamers that (Pluronics), the carboxymethylcellulose, ethylcellulose, or the mineral sodium alginate are a few of the most most popular.

**Emulgels in**

Emulgels are oils that, when a substance that gels are added, is transformed into a gel, either a water-in-oil or oil-in-water variety. Oil-in-water and water-in-oil blends are widely utilized because of their medicinal qualities and as a means of delivering different medications to the skin. Emulsions were easily washable anytime desired and have aesthetic qualities. Additionally, they have a high degree of skin penetration. Furthermore, the viscosity, appearance, and greasiness of diagnostic or decorative emulsion can be regulated by the formulator. Water-in-oil emulsions are used more frequently for restorative lotions and for the management of dryness of the skin, whereas emulsions composed of oil and water are best suited as medication bases that can be cleaned in water and for general cosmetic uses.

**Gels thixotropic**, greasiness-free, readily spreadable, easily removable, moisturizer, non-staining, compatible with several excipients, and water-soluble or miscible are only a few of the desirable qualities for dermatology treatment. Because emulgels contain the benefits of both fluids or liquids, as previously indicated, they have a high patient compliance rate. As a result, they are currently utilized to apply different medications topically. There are two emulates on the market:

Miconaz-H emulgel (Medical Union Pharmaceuticals, Egypt), which contains miconazole treatment salt and hydrocortisone, and Voveranemulgel (the company Novartis Pharma, Basle, Switzerland), which contains diclofenac a mixture of die, Nucoxia (Ziduscadila), which contains etoricoxib. Gels' primary drawback is their inability to distribute drugs that are hydrophobic.

**Essential ingredients** in the creation of gel Water-Based Polymer this creates the emulsion's water phase. Alcohols and water are often used agents.

**Agent for Gelling:**

Here constitute the thickeners that may be employed to improve the consistency of any dosage form. Gel-forming chemicals like HPMC and carbohydrates are frequently utilized.

**Enhancing agents of Penetration:**

These chemicals cause a transient and irreversible boost to pores in the skin by partitioning through and interacting with skin components. To improve penetration, you can add fatty acids, alcohol, and some essential oil blends.

**Medicine**

The external method of delivery is not suitable to all medication kinds. It is dependent on the drug's ideal thermodynamic and biological characteristics. Furthermore, it is imperative to take into account the drug's pharmacokinetics and pharmacologic properties.

**The following are the fundamental characteristics:**

- Your medication's molecules should be under or equal to 10,000 Daltons in size.
- The medicinal product needs to be affinities for both aqueous and a lipophilic phases.
- Severe partitioning properties make it difficult to successfully administer medication via the layer of skin.
- The medication should not melt at a temperature lower than 200°C.
- As the pH of the skin ranges from 4.2 through 5.6. Hair injury is prevented by using solutions with this pH range. At pH values where the unionized form of the medication predominates, there could be substantial dermal administration for an array of medicines.
- The medicine must possess significant biological attributes, but an average daily dosage comprising a few milligrams or less.
- The drug's the half-life ( $t_{1/2}$ ) ought to be brief.
- The medication must not cause irritation or allergies.
- Drugs that are inactive through their liver first-pass action or that break down in the GI tract make good transdermal administration options.
- Penetration boosters: a challenge in creating topical drug delivery systems is getting past the human body's innate transporter barriers. Your skin's outermost layer is easily penetrated by fats chemical agents.



The Latin phrase "herba" and the prehistoric French word "herbe" are the sources of the English term "herb." These days, a "herb" can be any portion of a plant, including plants other than woody ones and seeds, fruits, stems, growl, flowers, leaves, stigmas, and roots. Before, only plants that were not woody, such as those derived from plants like shrubs and trees, were referred to as "herbs." In addition to being utilized in specific spiritual practices, these plants for medicinal purposes can be utilized as meals, flavonoids, medication, or fragrance. From before the prehistoric era, people utilized plants for health care. According to recent estimates from the World Health Organization, eighty per cent of people globally depend on herbal remedies for some part of the main medical need. The WHO estimates that some 21,000 plant species have.

***Spreng, Buchanania Lanza.***

It's a great multifunctional kind of tree that comes from the Indian subcontinent and belongs to the Anacardiaceae group. According to old indigenous wisdom, practically every part of the plant—including the leaves, stems, roots, fruits, seeds, and gum—has enormous therapeutic worth applications. The seeds that are edible of the evergreen Buchanania Lanza tree are produced. It is called Charoli, or Chironji. In India, these seeds with an almond flavor are typically employed as a spice in culinary.



**Figure No. 1.8: Buchanania lanzan shrub and seed**

Studies show that over 75% of the total global population receives their health services mainly through plants and botanical extracts. More than thirty percent of all plant species have been used traditionally for medical purposes. Trees were the source of as many as 25% of medicinal products in developed countries like the United States of America, but up to 80% of drugs in fast-developing countries like China and India are plant-based. As a result, nations like India place a significantly larger financial stake in medicinal products than do other nations. Two thirds of the plants employed in modern therapies come from these nations, and the healthcare systems of rural populations rely on these native medical practices. Because there are little or no negative effects, using medicinal plants for treatment is seen to be extremely safe. The main benefit is that these medicines are in harmony with nature. The great thing about medicinal plants is that they're effective for all sexes and of all eras. The medicinal plants that treat various widespread illnesses include aloe, tulsi, neem, garlic, and curcumin. It is widely recognized as many customers use basil, sometimes called tulsi, in their daily routines for puja, black tea, and other purposes.

Several plants have been used as a sign of good fortune to honor the monarchs in various places of the globe. Many customers have begun planting tulsi and other beneficial plants in their backyard vegetable gardens since learning about the potential benefits of herbs for medical conditions. Medicinal plants may be used more often in India than in Western

nations. Echinacea, kava, Valerian, Ginkgo Biloba, the root of gins, and St. John's Wort are a few examples of medicinal herbs.

**Science categorisation**

Domain : Plantae

The phylum : Tracheophyta

Mangnoliopsida class Sequence : Sapindales The Anacardiaceae gen

The Anacardioideae subgroup Buchanania is the Genus. B. lanzan is a type.

Buchanania Lanzan, botanical name

Buchanania latifolia is a synonym. Cuddapah almonds, cheronjee, and almondette ROXB.

**Overview**

Almondette, cheronjee, cuddapah almond are the English names. Name in Hindi: chiraunji, chironji, achar, char, charoli, charoli-kernel, Kannada Name: char, charoli, chaara pappu, chaaruvaala, chalaali, Sanskrit Name: dhanu, dhanushpatta, cara, chara, charaka, akhatta, bahulavalkala, Names in Tamil: mudaikkai, mudaima, morala, moraimaram, and modama Utilize Sections: vegetables, seeds, the roots, and branches.

**Morphology**

Plant anatomy Subdeciduous trees that grow up to 18 meters tall, with bark that is 10 to 12 millimeters thick, tough, and has a top layer that is black or dark brown with deep, tiny holes that resemble croc skin. The outer layer of bark is flaming crimson. Clear, alternating, estipulate foliage; long, robust, translucent petiole (12–22 mm); broadly oblong lamina (10–23.5 x 5–12 cm), base round or acute, apex obtuse or emarginate, margin entire, glabrous above and densely tomentose beneath, coriaceous; 10–20 pairs of pinnate in shape visible, shiny added sides; intercostae reticulate and obvious. Bisexual, a greenish- blooms.

**Customary applications**

According to conventional cultural wisdom, practically every component of the plant—including the roots, leaves, fruits, seeds, and gum—has enormous therapeutic worth. Indigenous medicine uses the tree's gum to treat tuberculosis. 1. Both the Unani and Ayurvedic medical traditions employ charoli seeds. The roots have cooling, astringent, depurative, acrid, and constipating properties. They can be applied to treat diarrhea. 2.

Coughs and asthma are treated with the fruits. The seeds have tonic and expectorant properties. The oil that is derived from walnut kernels is used to treat skin condition three as well as to get rid of spots or imperfections on the face. The leaf juice has purgative, sexual stimulant, stimulant, and gastric properties. 4 The gum is formed following its combination using goat milk as an analgesic use

Methyl silk patches for the body containing the medication were used to test the diffusion improvement characteristics of *Buchanania lanzan* spreng seed oil, with particular essential oils serving as absorption modifiers. The impact of penetration-enhancing agents and drug loading on the in vitro delivery of drugs into the flesh of rats was studied. The use of pure oils improved Glipizide's moisture level, and ability to absorb water, thereby along with its capacity to pass through epidermal barriers. When compared with alternative seed oils,

*Buchanania lanzan* spreng seed oil is shown to be the most efficient. Additionally, it emerged that seed oil might be employed to improve the penetration of different kinds of tropical preparations.

### **Chinensis Simmondsia**

Tolerant of drought Jojoba *Simmondsia Chinensis* (Link) Miller is a valuable plant. Jojoba is primarily a woody, evergreen, perennial plant which yields tiny seeds with waxy substance that has a value comparable to the worth of whale eggs. The drug industry is the primary user of the oil. Native Jojoba grows in regions with Sonoran desert climates, which see 80–450 mm of precipitation annually and 9–54 °C ranges. Pistachio develops itself on marginally fertile soils; adding fertilizer and phosphorus to field plots increased plant growth and seed yield. The jojoba plant is resistant to drought, and it can be used as well to make ovarian personal care products, reduce animal weight, and make biodegradable lubricants for the automotive sector. Additionally, the oil extracted from jojoba seeds can be utilized to produce biofuel, which is a novel option.

Incredibly drought-tolerant plants provide nutrient-rich fodder for sheep, goats, and cattle, as well as for small ruminants like rabbit and nomadic ungulates that there are only very few crops planted in dry and marginal areas, and they are mostly grown for subsistence. Resistant to drought crops for money are absent from these places.

The use of versatile crops like flaxseed (*Simmondsia chinensis*), who can withstand stressful circumstances, has drawn a lot attention lately centuries.



**Figure No 1.9: Jojoba *Simmondsia chinensis***

### Applications

Jojoba is considered an agricultural product that has both promise as a commercial commodity and agricultural crop. Jojoba was utilized to fight and stop erosion in the Thar Desert, which is in India and the 6 October Desert in Egypt, and providing a source of cash to the underprivileged populations. The oil from jojoba trees has several uses in the fields of medicine and cosmetics. It can be employed in a variety of processes, including halogenation to sulfuration, and hydrogenation, to produce molecules with significant additional value. The oil of jojoba trees is utilized in numerous skin-care items in the skincare sector, mostly as a moisturizer but also as an emollient and in hair conditioners.

Apricot oil, waxy substance, and derivatives have shown promise in medicine as skin emollients, anti-acne, anti-psoriasis, and anti-inflammatory remedies for a variety of conditions affecting the skin and hairline.

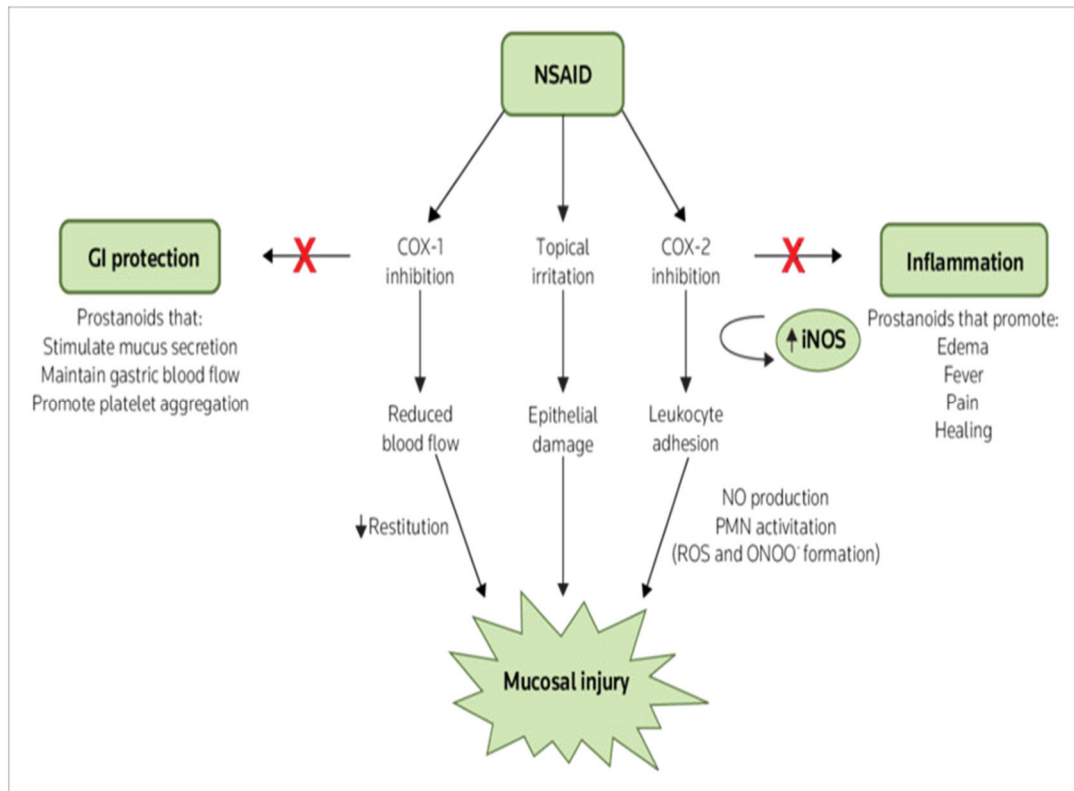
Jojoba is utilized in compostable lube and as a biodiesel fuel made from it. It's a fresh approach to fuel in the near future. However, the majority of Jojoba oil study has



concentrated on the oil's alcoholysis and the NO<sub>x</sub>, CO, and CO<sub>2</sub> emissions associated with using various blends of normal fuel and the oil from jojoba in a diesel engine. Given its medicinal qualities versus viral envelopes, a combination of long mono alcohols (11-eicosenol, 13-docosenol, and 15-tetracosenol) that is formed after crystallization has a high market value; nevertheless, the co-product may be utilized for energy extraction.

It might serve as the foundation for the installation of a biorefinery. Calendula is utilized as an attractive crop and as a supplement (20–30% of protein of oil-free meal) in food for animals, cosmetics, drugs, and waxes. Once the oil is extracted, the plant material is called nut a meal or and it contains 29–30% nitrogen. Simmondsin, on the other hand, is toxic to livestock, but these harmful substances can be broken down and the meal can be utilized as an element in animal nutrition. Simmondsin possesses antifungal properties, insecticides, and antifeedant properties. NSAIDs that or non-steroidal anti-inflammatory

NSAIDs as or non-steroidal anti-inflammatory agents, are among the most often given medications worldwide. Their primary advantages are their anti-inflammatory and analgesic properties; however, the use of these drugs is not safe as opposed to non-NSAID users, since they primarily raise the risk of heart disease and GI (gastrointestinal) issues. NSAIDs cause topical mucosal irritation and deplete prostaglandins generated from COX-1, which damages both the upper and lower gastrointestinal tracts. Patients who are at risk for side effects from NSAID medication should be prescribed COX-2 selective inhibitors or co-therapy of NSAID with gastroprotection (PPI or Cytotec) as preventative measures. The anticipated release of NO-NSAIDs shortly could provide those suffering from high blood pressure with an additional treatment alternative.

**Figure No 1.10: MOA of NSAID**



# NEED FOR STUDY





Medicinal plants were applied for millennia in India and other regions throughout the globe to alleviate an array of illness, years before healthcare were developed. For a lot of this globe, particularly nations who lack availability of professional medical care, alternative therapies continue to be commonly utilized. Furthermore, academic study is needed to figure out the biological activities of medicinal plants throughout a lot of Asian countries whereby the costly price of treatment pharmaceuticals has led this continued reliance in alternative therapies. Results about those investigations could validate historically utilized for health reasons valuable plants along with allow for optimum use of their qualities.

Transdermal distribution of medications has greater advantages favorable for oral plus parenteral transport; such, one may achieve a greater steady state concentration of drug in pus, minimize gastrointestinal (GI) adverse reactions effectively initial therapeutic result, then eliminate it upon removal. However, the corneum structure becomes a roadblock to this tactic. Therefore essential to go past the cornea when creating cutaneous administration methods; many methods are used for enhancing its penetration into the superficial layers of the skin.

The capillary injection of medications might be enhanced through a variety of harmless techniques, like the use of chemical improvements, also referred to as the synthetic approach, or physiological techniques, such as ionizing radiation sonophoresis, through electroporation and magnetophoresis. Numerous recent investigations have revealed improved transdermal administration of medications from applying pressure that penetrate the skin during the desired concentration.

According to old customs, practically every element within a plant—including its roots, foliage, the fruits, the seeds, the gum—has enormous therapeutic worth. The International Union for Conservation of Nature and Natural Assets' (IUCN) Red Data Book lists *Buchanania lanzan* as a warned herbal remedy. Indian tribes employ a type of decaying evergreen to the order Anacardiaceae for variety chronic illnesses. Using a naturally occurring herb extract, only three primary substances with strong therapeutic potential—celidoniol, vomicine, and epinitol—have emerged. They primarily show anti-inflammatory, wound-healing, anti-diarrheal, antioxidants, hypoglycemic, and antihyperlipidemic effects, among additional therapeutic qualities.

Punjabi bushes are now the subject of intense interest because their berries include a particular kind of beeswax known as its oil, which is extremely like paraffin produced by whale egg. For arid and marginal regions, chia is seen to be a viable product; however, it also contains likely useful in halting earth permeability and desertification in arid regions.

Apricot appears to be an unconventional seed for dry and fragile regions, despite its reputation as withstanding extremes of temperatures with salinities. This species is used for its fruit and seeds, that consist of a high melting point liquid wax in them. Lots of items, which involves as oil, makeup, drugs, and biofuel, a use such oil. It covers a number of grain crops topics, such as a scientific overview, grain as well as reducing production techniques, Objective growing the article being to provide gardeners along with experts with a resource with mehndi agricultural while maintenance.

Simmondsia chinensis and B. lanzan have great potential because an immense supply with miracle compounds who can certainly benefit humanity over generations ahead. Thereby might be assumed that B. lanzan and Simmondsia chinensis are herbal medicines who classical Indian vaidyas while ethnic groups generally occupancy, however more examination and validation needed. They will call out any underestimation as well as emphasize the practical possibilities. Additionally, scientists plan to give an overview of the proposed upcoming efforts to shed light on the infections who the drug might have able treat with.

The ultimate goal to better transdermal delivery devices and wound dressing materials is to continuously enhance their economics, longevity, or degradation. And a result, substances from nature receive more attention from researchers in the field to be utilized as components of these networks. Throughout long ago, flowers are used in healthcare is an essential source of termed "typical remedies" has a vast variety and structural diversity that still beyond the powers of modern technologies to adequately describe or at least recognize such. Still, with regard to contemporary dermal and transdermal delivery techniques, their positive effects remain partially realized. The key objective if this study was to study novel therapy options with diseases includes gout, or who are often caused by a number different illnesses, including RA, suffering, even aggravation concerning malignancies. An oral regimen that permits the use of NSAID pills is part of normal course of therapy for these kinds of disorders. But all traditional NSAIDs

feature a long list of drawbacks. Under the nation of India, Ayurveda has been practiced to earn a long time, as well as numerous healing plants are utilized to alleviate a wide range for illnesses under the kind of granules liquid infusions.



# **AIM AND OBJECTIVES**



The ultimate goal to better transdermal delivery devices and wound dressing materials is to continuously enhance their economics, longevity, or degradation. As a result, substances from nature receive more attention from researchers in the field to be utilized as components of these networks. Throughout long ago, flowers are used in healthcare is an essential source of termed "typical remedies" has a vast variety and structural diversity that still beyond the powers of modern technologies to adequately describe or at least recognize such. Still, with regard to contemporary dermal and transdermal delivery techniques, their positive effects remain partially realized. The key objective if this study was to study novel therapy options with diseases includes gout, or who are often caused by a number different illnesses, including RA, suffering, even aggravation concerning malignancies. An oral regimen that permits the use of NSAID pills is part of normal course of therapy for these kinds of disorders. But all traditional NSAIDs feature a long list of drawbacks. Under the nation of India, Ayurveda has been practiced to earn a long time, as well as numerous healing plants are utilized to alleviate a wide range for illnesses under the kind of granules liquid infusions.

Additionally, mms was stated had fewer negative side effects than the allopathic drugs that were sold for healing comparable ailments. The intention of this inquiry is to identify the relationship between the penetration activities displayed with particular botanical species and multiple plant-based compounds that, absorbed in its entirety extract, exert a combined impact. Additionally, the research effort attempts to formulate both helpful and helpful ingredients in a dose regimen the fact that will improve user comfort while maintaining stability and efficacy.

While ingestion is currently recognized as a more patient-friendly and convenient approach, there are two major disadvantages: low pill absorption or inadequate retention. Both a result, this study aims to apply medications superficially to try to generate irritation in particular areas of the outer layer and in spaces that divide the layers. The goal of this investigation aims to build transdermal formulations of a few anti-inflammatory drugs, such as preparations from the pods belonging to the Simmondsia chinensis and B. lanzan families of Anacardiaceae. The main goalmouth of this study was to express a formulation using extracted from therapeutically useful plants that are often employed within Hinduism while having been earlier documented to be effective sources of saturated fats. This is obvious from the literature review.

**Objective of the Study:**

The goal of this investigation aims to build transdermal formulations of a few anti-inflammatory drugs, such as preparations from the pods belonging to the Simmondsia chinensis and B. lanzan families of Anacardiaceae. The key goal of this education was to verbalize a formulation using extracted from therapeutically useful plants that are often employed within Hinduism while having been earlier documented to be effective sources of saturated fats. This is obvious from the literature review that in order to exist penetration enhancer activity it must have higher percentage fatty acids which may be responsible for drug molecules to enter into the systemic circulation through stratum corneum. So the current study was taken to isolate the mucilage and oil from seed and evaluate it as penetration enhancer.

**Objectives of work:**

A vast summary of literature survey gives some views, which hypothesized as follows,

- To Collect and identify, authenticate of plants materials and seeds.
- To study Morphology and microscopy of plant material.
- To study Isolation methodology
- To perform Qualitative analysis for isolated oil
- To study Toxicity of isolated penetration enhancers.
- To perform preformulation study of isolated components (oil)
- To prepare formulation using isolated oil.
- To evaluate formulated product (Medicated gel)
- To perform comparative drug release studies (*in vivo and ex vivo*)
- To establish of Pharmacokinetics in rat
- To establish of release kinetics.
- Accelerated stability studies



# **REVIEW OF LITERATURE**



Seeds of *B.lanzan* family Anacardiaceae and extracts of seeds of *Simmondsia chinensis* are Indian tribes utilize this miraculous medicine extensively for managing an array of illnesses. The physiological characteristics, pharmacognostic research, and botanical study on both of those extractions from seeds are reviewed in publications.

**Mitra et al., (2015)** Priyal, often referred as either "Chironji" or "Charoli," belongs to the *Buchanania lanzan* Spreng genus of flora. Pharmacognostical characteristics of the *Buchanania lanzan* Spreng stem its grain, as well as commercially available forms of "Chironji," was detailed by this study. These details are crucial for an assessment assess the pill's promise.<sup>40</sup>

**Abhijit B et al., (2015)** Lanza, *Buchanania* Indian tribes frequently employ Spreng, a dry deciduous forest tree in the genus Anacardiaceae, to alleviate a variety health ailments. Through a plant herb extract, three key substances with strong therapeutic potential—celidoniol, vomicine, and epinitol—have emerged. They primarily show anti-allergic, wound-healing, anti-diarrheal, an antioxidant hypoglycemic, and antihyperlipidemic effects, among multiple additional therapeutic qualities. Plants produce special plastics like microfilms that could play a significant role throughout medicine. It aims for a comprehensive, up-to-date guide to today's evolving fields that exist around this tree, particularly in the field of phytomedicine with drugs.<sup>41</sup>

**Mehta SK et al., (2010)** *Buchanania Lanza* (Anacardiaceae) stems is believed to provide significant medical benefits. HPTLC methods were used to perform environmental screening, which included both quantitative while quality analytical evaluations. Employing chemistry, care, or HPTLC procedures, the leaves of *Buchanania lanzan*, an evergreen member of the Anacardiaceae family, were subjected the authentication, disparity, for quantity of their volatile contents. A total of only two primary types major metabolites with secondary structure found: cyclic molecules and sugars. These outcomes also helpful to prove a connection amongst the root concentrate's makeup of chemicals that the functions of *B. lanzan* that already have been documented. They could also indicate another prospective purpose for *B. lanzan* extract in the treatment underlying societal issues.<sup>42</sup>

**Bhatnagar S et al., (2022)** This perennial *Buchanania Lanza* plant has delicious kernels and fruit but can also be beneficial for medicine. Bisexual, pentamerous, whitish-, whole, & placed in spikes over the crop's both sides. The recorded crop's annually expanding period



prolonged roughly twelve months. Such spherical, undeveloped, drupe-like nuts took 80–87 days to fully ripen. Only 5–25 fruits were produced each flowering, compared to an average of 580 blooms for each terminal among the main explanations for unsuccessful reproduction is a lower ratio from berry to germination and flowering to harvest. According to morphological investigation, *B. lanzan*'s endocarp is multifaceted, with a frame of cubicles in the innermost five or six cell types intertwined and prismatic outside cells and crystals. Investigations in morphology revealed exalbuminous, heterogeneous nuts that varied by size. Four sizable plano-convex them are present around the pale yellow shell in the baby. There was not any research done on the mechanical structure of *B. lanzan* fruit or stone. Finding additional information on the ecology is the seeds and fruits besides the roots of their disappearance in nature are the primary aim of the study. This highly valued variety including tree form India's Western Ghats becoming disappearing on account of a mix of strong coated seeds supply, insufficient sprouting aptitude, a brief life of the seeds period. The results will aid managers while add significantly to our understanding of this critter.<sup>43</sup>

**Rajput BS et al., (2018)** One superb versatile plant, Charonji, Charoli, or Char (*Buchanania lanzan* Spreng.) belongs part of the genera Anacardiaceae and is native from the Indian subcontinent. According to old customs, practically every aspect of the plant—including its roots, foliage, fruit, seeds, even gum—has enormous therapeutic worth. Currently, this grows inside forests as a previously underutilized apple that provides a monitory benefit with nation's indigenous society. Naturally occurring throughout the tropical beech woods about the province, Occidental, among South India, this tree can be found growing unmanaged within the hilly regions of Kashi as Mirzapur, the the parts place, as well as parts throughout the States of Chhattisgarh, Jharkhand, along with the Indian state of Madhya Pradesh. The vegetation might be spotted in Australia, the Solomon Islands, as well as tropical Asian nations in addition to Indian. The World Combination for Preservation of Wildlife and Natural Fisheries' Red List Bank contains information about *B. lanzan*, another botanical medicine that is considered fragile. Given such, it has become imperative to establish appropriate technologies that would enable the animal to easily reproduce, regenerate, and be conserved while also providing tribes with appropriate data and instruction.<sup>44</sup>

**Sengupta A et al., (1977)** In accordance with ammonium synthesis while gasoline through liquid chromatography (g.l.c.), the crude fatty acid content of *Buchanania lanzan* oil

extracted from seeds is defined as follows: myristic, 0.6; palmitic, 33.4; stearic, 6.3; oleic, 53.7; and linoleic, 6.0%. The proportion is triglycerides in blood. The fat contents within the glycerol and related 2-fatty acids generated by pancreatic lipase hydrolysis have been applied to compute native crop butter with related randomized synthesis.

The ratios of trisaturated, single-saturated disaturated, diunsaturated, monosaturated, et triunsaturated glycerol in the fat are 3.2, 35.8, 45.5, or fifteen percent, accordingly. A ratio from 22.7, 31.0, and 11.3% dipalmitoolein, dioleopalmitin, or triolein in order, correspondingly, constitute a unique feature on *B. lanzan* oil extracted from seeds. Through randomization, the petrol's Genetics3 content rose via 3.3 and 7.5%. The mineral oil produced a product with a slip point of 41.5°C upon aimed exciting, whose may have been employed as an additive for delayed-action capsules. Furthermore, it seems to be of promise for a competitive supply of olive along with palmitic-based acidic solutions.<sup>45</sup>

**Shende S et al., (2005)** The indigenous and delicate *Buchanania lanzan* (Spreng) species is native within the tropical regions of Indian. Considering quick autologous growth of *B. lanzan*, a cell growth method evolved. The wrapped plants were planted in a medium containing magnesium sulfate supplemented via different ratios of auxins that are as well as peptides called either separately or together. It was discovered that a mix of the chemical alcohol (NAA) with benzoyl peptide adenosine (BAP) had been preferable to BAP and indole butyric acid (IBA). The creation pf most sprouts was aided by the addition of 22.2 µM of BAP, which was or 5.37 per cent µM for NAA to a Murashige-Skoog (MS) media. Also, the started buds underwent prolific roots when placed in MS medium containing 23.3 µM the latter. In this section, we suggest another useful method to obtain quick genetic replication is simultaneouslaunchcreation.<sup>46</sup>

**Bothara SB et al., (2012)** The Ebenaceae parent shrub *Diospyros melonoxylon* Roxb., occasionally referred to as Tendu in Hindi, which means constitutes a tiny tree featuring a somewhat thin stalk and silky, gray bark. *Buchanania lanzan* spreng, or Char in Hindi, is a tree in the Anacardiaceae group of trees that grows to a height of 12 to 15 meters and has a cylindrical body. *Manilkara zapota* (Linn.) P. Royen syn., a huge, evergreen oak tree that grows to a peak of over three meters, is a member of the Saporite genus and is also referred to as Chiku in Hindi. Three of these readily accessible herbs are traditionally used to treat a variety of illnesses in the jungles of Odisha. The microscopical investigations,

phytochemical assessment, fluorescence analysis of seed extracts with various reagents and the existence of elements involving CHNS, which is or heavy metal were all evaluated in the pharmacognostic research involving these crops. All three plants were examined under a microscope, and the results showed distinct characteristics that could be recognized carbohydrate, proteins, fats, and oils were detected in the extract of each of the seeds by phytochemical testing.

Seed specimens exhibit varying hues when exposed to distinct chemicals. The aforementioned phytochemical and pharmacognostic investigations will help with the precise recognition and authentication of *D. melonoxylon* Roxb., *B. lanzan* spreng, and *L. zapota* (Linn.) seed.<sup>47</sup>

**Singh S et al., (2020)** The goal of the research undertaken was to make a verbal bio-based mucoadhesives polymer using the pulp of *Buchanania lanzan* spreng seeds, which is a member of the Anacardiaceae group of plants. The waterproof property of detached muck is evaluated against to the polymer that is already in use. The shear values for the cellulose were  $0.099 \pm 0.0001\text{N}$ , and its grip was similar to that of methocel E5 ( $0.098 \pm 0.0008\text{N}$ ). The amount of force needed to separate the methocel E5 capsules and fruit cellulose and the digestive tissue's muco was  $0.0049 \pm 0.0006$  of (N) and  $0.0276 \pm 0.0019$  (N), accordingly. When examined alongside methocel E5 and lactose pills seed cartilage showed significantly ( $P < 0.01$ ) higher detachment time, erosion time, in-vitro wash-off interval, and ex-vivo resident. According to an in vivo test, seed mucus pellets outperformed methodical E5 in sticky ity and prevented breakdown for at least eight hours. The mucilage-based & polymer-like tablets performed similarly when it came to the swell indices and soaking interval. It outperformed methocel E5 in terms of moisture absorption, relative drinking water, and matrix erosion, with values of  $18.57 \pm 0.036$ ,  $50.00 \pm 0.051$ , and  $8.30 \pm 0.155$ , respectively. The sticky qualities of *B. lanzan* seeds' mucus were found to be similar to those of guar gum and methocel E5, suggesting that it may be used as a bioadhesive pharmaceutical excipient.<sup>48</sup>

**Von TI et al., (1988)** The anatropous, unitegmic, while pachychalazal mandarin a single acquires to produce campylotropous, pachychalazal grain; known as amorphous seed exterior possesses a mixed their heritage, emerging along a line adjacent to the pachychalaza; The term "peritesta" is used to refer to the small, band-like integumentary

anatomy that forms the harvest's shell; the saddle-shaped chalazal anatomy is vital and is associated with a tanniniferous hypostase; the pathology or arrangement of the vegetation is reviewed; the pachychalazal grain via inert plant rub likely describes the group Mangifereae. After implementing into account various types amongst granule properties, which becomes apparent that the Anacardiaceae is phylogenetically one of the more evolved wood orders according to widely recognized standards.<sup>49</sup>

**Malik SK et al., (2012)** The underappreciated berries, *Buchanania lanzan* Spreng., sometimes known as "Chironji," is vital to indigenous communities in the north, west, east India's central region. In the Indian states of Rajasthan, Gujarat, as well as and the state of Madhya Pradesh, an analysis and sample harvesting plan was conducted. The results suggested that *B. lanzan* occurs naturally in the wild in forests, fringe regions, as well as even the agricultural crops. Agro-morphological features for these significant tree type varied greatly within the 72 distinct accessions that were gathered across the diversity-rich regions. It having a significant economical significance, supporting the local tribal members and having enormous prospects for agricultural profit. Many gastronomic plus therapeutic benefits can be derived from both nice mature fruits and extracted seed cores. Numerous Indian meals are prepared using seeded ear or harvested germ oil. According to old local wisdom, practically every component of the plant—roots, departs, berries, seeds, et gum—is extremely important as a variety of therapeutic purposes, including treating diseases of the blood, a cold, blisters, pain throughout the body, nausea, vomiting, the condition, venomous snake, and more. The direct removal of commercially valuable tree parts from their native habitat has put *B. lanzan*'s DNA in grave danger of going gone, necessitating rapid action to preserve them.<sup>50</sup>

**Siddiqui MZ et al., (2016)** The gum of *Buchanania lanzan* Spreng (Anacardiaceae) is widely utilized in medicine treat a variety of ailments. This investigation assesses antioxidant activity, physico-chemical characteristics, and flavonoids in *B. lanzan* Spreng oral discharges. Seven chewing gum drip instances of *B. lanzan* Spreng were obtained using traditional methods to examine deviations in the primary phytochemicals as well physico-chemical buildings, as well as antioxidant capacity from Dindori district and Umaria (the Madhya Pradesh), Bilaspur (Chhattisgarh), Simdega and IINRG farm (Jharkhand), and Mirzapur, India (Uttar Pradesh). During health care, *Buchanania lanzan* Spreng (Anacardiaceae) bubblegum is used extensively for treating an assortment of conditions.

This study evaluates the flavonoids, physico-chemical properties, and antioxidant capability of buccal discharging from *B. lanzan* Spreng. In order to investigate variations with main phytochemicals, also physico-chemical structures, and capacity for antioxidants, 7 oral dripping scenarios of *B. lanzan* Spreng were isolated through traditional approaches from the Indian states of Mirzapur (Uttar Pradesh), Dindori district and Umaria (Madhya Pradesh), Simdega and IINRG farm (Jharkhand), and Bilaspur province (the Indian state of Ch). Demonstrate the noteworthy intra-specific differences in terms of quantity and quality that exist between *B. lanzan* gum fluids that are obtained in various locations, with regards to their phytochemicals that are physic-chemical characteristics, including the effectiveness of antioxidants.<sup>51</sup>

**Vijay MK et al., (2022)** The plant *Buchanania lanzan* Spreng, often known as Chironji, belongs within the Anacardiaceae family. This displays a broad range of medicinal benefits, who have helped improve the ethnic local well-being. It is demonstrated that plant components like leaves, seeds, bark, and kernels may hold onto a wide range of highly promising metabolites. *B. lanzan* is currently classified as a minor forest product that is not regulated that is extensively spread throughout forest-covered districts. Its continuation is severely threatened by indiscriminate and improper harvesting, climate change, extensive gentrification, plus industrial activity. Several organizations have indicated that it was officially designated as a redlisted medicinal plant species of Indian provenance, requiring a full safeguarding approach. The primary subject when planting or domesticating this type of plant is the poor fertilization rate, which is caused by stiff egg coatings that are resistant to fertilization as well as mold growth during keeping seeds. Additionally, plant reproduction is yet to prove to be viable among this plant. Therefore, sufficient study funding is a critical need to tackling the issues and promoting expansion in forests in order to enhance its sustainable production and protection. Additionally, it's important to raise consciousness among every party about the necessity to conserve these priceless wildlife.<sup>52</sup>

**Ajith S et al., (2018)** The Western G Hats of India are home to an endangered medicinal tree in the genus Anacardiaceae is *Buchanania lanzan* Spreng. Because its environment is being destroyed, it's is experiencing increased slumber, shrubs are being uprooted, when its nuts are being overused for their outstanding usefulness in treating skin, diabetes, while diarrhea-related conditions. An effective way of standardizing on thawing out of stored seeds that are a full year ago. After 4% magnesium chloride is applied to the embryos'

exterior for ten seconds, the seed coat is removed with light tapping. The sprouts were scarified using varying degrees of hot and cold water, and they were also chemically treated using a variety of H<sub>2</sub>SO<sub>4</sub> and GA<sub>3</sub>. Each person planted fifty seeds in a greenhouse's starter flats, and during 30 days, hatch was monitored every single day. The embryos' sterility was effectively broken by therapy using 200 ppm GA<sub>3</sub> and 4% H<sub>2</sub>SO<sub>4</sub> solution which produced 90% and 61% of growth, however. Merely 56% of the plants underwent chilly water medication, whilst just one-quarter of the untouched seedlings exhibited fertilization. Furthermore, fertilization couldn't transpire in the intact seeds that possessed an impenetrable egg shell. Findings suggestive of beneficial reactions to interventions, On the other hand, undamaged controlling eggs' protracted latency might be caused by impervious egg coverings.<sup>53</sup>

**Kannan P et al., (2022)** The term "our infancy rescued" describes the embryology technique that prevents egg abortion and is utilized for growing vegetation with underdeveloped fetuses. The aim of this research was to use a fertilized egg rescue technique to generate a wild type of tree, *Buchanania lanzan*, via vitro for therapeutic purposes. To assess simulated growth, separate juvenile, badly formed embryos were cut out of identified eggs obtained from 15-year-old trees and cultivated in Woodland Plant Matter (WPM). After the fertilized eggs were introduced on the medium supplemented with 50 mg/L-1 of arsenic sulphate (AS) and 1.5 mg/L-1 of 6-benzylaminopurine (BAP), 100% baby hatching was observed. In addition, the transplants from a week-old planting, specifically the cotyledonary nodal with fetal axis, and had been chosen to investigate laboratory serial proliferation. Whenever 1.5 mg/L-1 6-benzylaminopurine (BAP) was added to the media, that cotyledonary node displayed the highest median spike quantities ( $4.2 \pm 1.80$ ) and spike heights ( $4.0 \pm 0.98$  cm). In terms of gunshot responsiveness and repeated shoot introduction, blood oxygenation was found to have characteristics superior to Kinetin, or (Kn). Following separated out of several sprout clusters to check for intact renewal, the roots were added to a half-strength WP mixture enriched with indole-3-butyric acid (IBA). IBA showed 90% anchoring response at 0.5 mg/L-1, with maximum mean roots ( $4.9 \pm 0.98$ ) per shootlet. After being planted in the laboratory, the seedlings then placed in polyethylene sacks with heated humus, as red earth, and farmyard dung (1:1:1) to acclimate them to a temperature of  $25 \pm 2$  °C. Such leaflets were afterwards gradually moved to agricultural conditions. At 3 months, a survivor ratio of roughly 70% remained noted. Fast doubling might assist towards the in

situ preservation of the critically endangered tree, *B. lanzan*, by restoring viable embryos from poorly developed immature fertilized eggs, as per the methodology provided in current research.<sup>54</sup>

**Michelson AO et al., (2022)** In insect Sudano-Sahelian region of the African nation of Cam trials took place out in both 2017 and 2018 to examine the feeding habits of the blowfly subspecies *Chrysomya putoria* (Diptera: Calliphoridae) on *Ricinus communis* (Euphorbiaceae). In order to accomplish this, insect browsing factors have been documented and castor bean plants were marked. By contrasting unrestricted and limited racemes, the effect of blowfly activity on pollination and fruiting rate of *R. communis* were examined. Of all fifteen anthophilous insects that were collected, *Chrysomya putoria* accounted for 82.33% of the total number of flower trips. Gathering for nectarines and pollen took place all day, in a significant rise occurring between 8 and 9 am. There were roughly 300 explorers per vine at any given number. Male and female flower visits were noticeably longer than average, so this led to a forage flow of three to five blooms per moment, thereby improving *R. communis* crossing. Approximately 11% more of the castor beans fruited as a result of *C. putoria*'s blooming movement, while on the other hand, the same plant was found as a significant food source for the survival of its primary blossom visitor. The blowfly subspecies plus castor beans appear to have a mutualistic interaction.<sup>55</sup>

**Gentry HS et al., (1958)** In numerous aspects, *Simmondsia chinensis* is distinct. Its large, ongoing, hefty petals set it apart from its numerous contemporaries. Native to the Sonoran Desert of Mexico and the United States of America. Half of the oil from these broad, flavorful seeds is extracted straight away for frying as oil for the hair. The substance is ideal for a wide range of applications in industry and medicine. It is a liquid wax biologically, but it can be quickly hydrolyzed to become a diligently, white paraffin. Nevertheless, the unique qualities of agave as a barren shrubs pose numerous challenges to its growth as a planted species.<sup>56</sup>

**Sturtevant D et al., (2020)** *Calendula* (*Simmondsia chinensis*) kernels offer a plentiful for sustainable source of liquid wax esters, which are valued additions in personal care commercial industrial greases and oils. Jojoba is placed under a distinct botanical family, so their chronology cannot be fully understood from the existing genomic data. Here, we present the excellent 887-Mb chamomile genome, which has been assembled into 26



chromosomes containing 23,490 proteins that code for proteins. The sesame genome lacks any modern duplicate work but only shares the whole-genome triplication ( $\gamma$ ) with other a few exceptions. In addition to providing much-needed insight into the genetic genealogy for these scientifically separated dioecious plant variety, these genomic information goods, in conjunction using copious amounts of transcript sequence, proteins, and lipidome data, assisted in defining heterogeneous pathways and machinery for lipid synthesis and the facility. They will also aid in initiatives to enhance the agronomic qualities in jojoba.<sup>57</sup>

**Abbassy MA et al., (2007)** Six glucosides that were separated from the pods of a jojoba plant, *Simmondsia chinensis* (Link) Schneider, were examined for their repellent, antifeedant, overall antifungal capabilities. The plant germ extract prepared with chloroform was fractionated using a bioassay technique on silica gel columns, and the resulting two glucosides, simmondsin and simmondsin 2'-ferulate, were obtained by recrystallization of Spectroscopic investigations and physico-chemical properties verified the structure of these glucosides. With LD50 values of 1.49 and 2.58  $\mu\text{g/larva}$ , correspondingly, simmondsin and simmondsin 2'-ferulate demonstrated a high insecticidal activity against the third instar larvae of *Spodoptera littoralis* Boisduval (Lepidoptera: Noctuidae) in the topical use experiment. At a dosage level of one, each substance demonstrated antifeedant effect towards *S. littoralis* in a reliant way. Furthermore, against four plant pathogenic fungi, the compounds isolated exhibited mild to severe antibiotic efficacy. This research replaces the initial one.<sup>58</sup>

**Tietel Z et al., (2021)** The olive, *Simmondsia chinensis* (Link) C.K. Schneider is a deciduous shrubs who grows mostly in Israel, the Middle East, South America, Africa, the Indian continent, that Australasia. Species is grown over commercial purposes as well as is mainly used as a source of their environmentally friendly, unappealing grease. Because of its special shape and advantageous negative health effects, it is frequently employed in pharmaceuticals and cosmetic formulation. Furthermore, a great deal of research on the plant's health-promoting properties—which range from antioxidant properties toward cancer treatment—has been published. Since jojoba is a rich source of natural liquid wax, much study on the species is concerned with its uses and how to best utilize the leftover vegetative elements that are collected during synthesis. Currently, a number of strong phytochemicals have been linked to its therapeutic.<sup>59</sup>

**Arya D et al., (2016)** The versatile, resilient to drought biennial species *Simmondsia*



chinensis, known as a member of the Simmondsiaceae relatives, has begun to acquire significant attention due to its unusual oil that is essentially an oily wax—that is, an ester of long-chain fatty acids and alcohols. Imported to India in 1966, jojoba has become a major driver of wealth for those engaged within the sebum crude oil industry as well as the people that cultivate the crop in places like Sriganganagar, Sikar, Jhunjhunu, Churu, also, and Udaipur. Jojoba seed oil can be used for a variety of purposes, contingent upon the location and its alteration. It is a particularly special plant-based oil since it contains almost no glycerine and can be altered by hydrogenation, sulfurization, halogenation, sulfurhalogenation. Jojoba oil has an important market share due to its use in the fields of oil, petroleum-based, visual, and medicine sectors. In order to fully maximize the possibilities of a particular vegetation, comprehensive knowledge about its genetic makeup, science, and additional uses is essential prior utilizing it for commercial uses. In summary, this work provides an overview of the shrub's chemical characteristics, growing needs, and location within India. The objective behind the work reviews various multiplication methods, provides information on manufacturing the oil plus kernel food, as well as a thorough physico-chemical description of jojoba oil and cake. Additionally, it provides information on the value of jojoba oil and its uses.<sup>60</sup>

**Reddy MP et al., (2009)** In addition to its growing use as grease, wax esters may have significant uses in the culinary, personal care products, etc medical sectors. Of the primary explanations why those whales had been targeted to almost annihilation had been the worth of their glue, resulting to the subsequent prohibition on harvesting and the search for substitutes. Global demand for jojoba is rising as a result of its discovery as a substitute for virgin whale oil. The species is grown as a crop in a number of semi-arid regions and dry regions of the world due to its durability, enabling it to be grown even on wilderness with little water. Moreover, raw protein-rich oil from the seed de-oiled cake might be utilized to make commercial enzymes and as animal feed. Because of the group variability, the organism is monogamous & shows extreme fluctuation in the men : female ratios within a specific group, without the males typically greater than female plants. This results in lower harvests as predicted. To increase produces, high-yielding varieties are those chosen from research farms, and techniques for vegetative replication are being used to produce anatomically homogenous, well-known male seedlings. Despite having a high demand, jojoba waxes is hard to find for many uses since they are in shortages. With the development

of biological the field, new avenues for modifying the composition of plant lipids have become possible. Additionally, oilseed crops that are suited for a certain environment can be engineered to yield high wax ester levels in their oil. The next section covers the cultivation process, mutations in genes for increased oil concentration and yields, the cleanup of cake to be used as feed for cattle, along with certain features of micropropagation of this plant.<sup>61</sup>

**Prat L et al., (2008)** The impacts of extra gibberellin (GA4 + GA7, 150 mg L<sup>-1</sup>) or cytokinin (benzyl-adenine, 150 mg L<sup>-1</sup>) on the growth or blooming development of five-year-old branches from four chia genotypes were investigated throughout this research. Around the fifth of October 1999, in springtime, the plant growth regulators were administered, then the crops evaluated 120, 240, and 360 days later. There was a significant variance in shoot length, total number of nodes, and number of branches clusters across copies, yet not across growth-regulating administrations. Treating with benzyl-adenine (BA) resulted in a substantial rise in the general number of flowers on both clones, while pretreatment with gibberellin or caused a considerable decrease. Despite a rise in floral abortion, baseline 180-every day post-application seed production lacked any statistically significant distinction between the control sample. Just one copy Compared to the other group, the seeds subjected to gibberellin or exhibited a considerable drop in both size or density.<sup>62</sup>

**Subramanian K et al., (2023)** The main goal of this study aim transforming leftover *Simmondsia chinensis* kernels into power. The chemical methyl acetate (MA), an emerging like sustainable section, is combined with *Simmondsia chinensis* biodiesel (SCB) in a CRDI diesel car engine. Different fuel injection strategies and exhaust gas reuse (EGR) may be used. The gasoline was then contrasted with diesel-powered gasoline in an effort to enhance ignite rates to lower pollution pollutants. Because non-edible biodiesel is more viscous with gas, it emits more pollutants. Thus, MA, a new aerobic cumulative, was tested as a promoter of flame. Diesel at 10% EGR and DBMA20 (50% Diesel, 30% SCB + 20% MA by vol.) at 10% EGR were first used in the procedure. The brake thermal efficiency (BTE) dropped while pollutants rose, according to the outcomes. Additionally, work was done to modify the default settings for the EGR at full load circumstances, pilot fuel injection quantity (PFIQ), and piloted time for injection (PIT). The studies carried out using PFIQ (10, 15, and 20% by vol.) and PIT (35°bTDC, 40°bTDC, and 45°bTDC) with a suitable mixture of PIT

to DBMA20 at 10% EGR.

Compared compared to the DBMA20 outputs with 10 percent EGR at conventional input circumstances, findings revealed that and maximal load, PIT 45° at PFIQ 20%, the BTE increased by 1.71%, BSFC lowered by 21.87%, SO reduced by 26.61%, HC reduced by 47.69%, CO reduced by 56.41%, and NO<sub>x</sub> reduced by 11.34%. The PIT 45° at 20% PFIQ and 10% EGR was therefore superior to the other operating conditions. Therefore, it was possible to increase productivity as lower emissions in CRDI diesel engine applications by utilizing biodiesel in conjunction alongside a test run fueling strategy under running settings.<sup>63</sup>

**Hani AQ et al., (2014)** In addition to cold pressing extraction for seed, plant tissue were treated with heated extracting using solvents with varying polarities (hexane, ethanol, and ethanol). Additionally, phenolic substances such as phytosterols and toccopherols, and fatty acids were identified along with simmondsin and three of its swaps, which is Simmondsin-3'-ferulate, 4, 5-Didemethylsimmondsin, and 4-Demethylsimmondsin-2'-ferulate, after the compounds that are active were obtained using preparative thin-layer chromatography methods. Such resulted by combining different chromatographic and spectroscopic evaluation methods with reagents made from chemicals. By using the 2, 2-Diphenyl-1-picryl hydrazyl (DPPH) free radical scavenging method in comparison to ascorbic acid operation, the antioxidant efficacy of the preparations was assessed namely the use of agar well distribution and diffusion via disc techniques have been applied to carry out antibacterial and antifungal activities against (*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia* and *Candida albicans*).<sup>64</sup>

**Feki F et al., (2021)** Simmondsins and flavonoids of extracted Silicone cake were separated employing a closed-vessel, Box-Benkhen layout method. Four separate factors were examined: the solvent/cake ratio, ethanol concentration, extraction time, and microwave energy. The outcomes of the models were significant at the level of trust equal to 95%, according to the ANOVA findings. The maximum microwave power (500 W), longest extractor duration (15 min), plus mild solution as wafer ratios (41–45 mL/g) were determined to be the ideal extractor parameters. The greatest yield of simmondsin (23.35%) occurred while using just water as the binding agent. However, the highest levels of quercetin synthesis (2.33%) and ORAC antioxidant activity (656 µmol TE/g) were found in

46.79% or 42.04% bourbon when it was diluted with milk. Simmondsin and tannin concentrations were shown that they were positively linked with ORAC antioxidant properties. Our results suggest that ME is a useful method for removing nutrients from argan contaminants that are useful to the culinary or medical sectors.<sup>65</sup>

**Wardlaw IF et al., (1984)** Between pollen until wisdom, the progress of the golden container its germ was monitored at seven various temperatures schedules, including 15/10 to 36/31 C (8/16 h; photoperiod 16 h). After the start of fast (linear) seed growth, however existed a latency during which the capsule grew. At 15/10 C, the time frame varied between 106 working days to seven hours at 36/31 C. The paraffin concentration of the granules increased even though they had reached 70–75% of their final dry mass. It had been low earlier in the growing process a little increased kindness, the maximum rate of dry matter accumulation in the seed increased to 33/28 C. while the seed size under development remained largest at 18/13 C due to an extra growing phase at a low temperature. In line with present studies, extended time at conditions above 36/31°C or below 15/10°C may be detrimental to the growth of flax kernel. Joining many other southern plants, jojoba is tolerant of temperatures as low as 15/10°C's and has a highly desired temperature of 33/28°C for seed growth. But the less favorable (18/13 C) optimal temperature seed weight at maturity was rather similar to what is found for regional maize.<sup>66</sup>

**Feki F et al., (2022)** The purpose with this work was to look into the liver-protective properties of solutions from flax seed cakes in acute paracetamol (PC) intoxication. *Simmondsia chinensis* seeded cakes were used to generate with describe three watery gathers: a simmondsin-rich extract (WE) and a simmondsin-hydrolyzed extract (the NE) utilizing enzyme Viscozyme L. Following processor therapies, the amount of simmondsin dropped from thirty-three percent to 3.0% and the amount of glucose increased from 16.2% to 27.3%, both of which were indicative of simmondsin degradation. Various rat subgroups received each extract by ingestion (0.6 g/kg b.w.) prior to PC treatment (2 g/kg b.w.) for a period of time each time for per week. The poisoning with Computer changed the cats' urine indicators, antioxidant state, as the levels of the proteins Bax, which is Bcl- 2 are and the cytokines Furthermore, histological testing of the organ's materials demonstrated hepatic inflammation and severe damage. The in vitro radical scavenging (ORAC) and averting activities (HORAC) of the Us with Nh extracted were comparatively strong, and polyphenols contents of three percent and 2.9%, resp. The two compounds demonstrated

potent in animal liver protective action towards PC-induced damage by enhancing the anti-oxidative state of the hepatocyte and inhibiting the production of genes (TNF- $\alpha$ , Bax, and Bcl-2), which are implicated in inflammation and liver damage. Nevertheless, despite NE's decreased simmondsin content, the enzyme method increased its liver-protecting efficacy. This improvement can be attributed to reactive ingredients' synergistic effects with the novel hydrolytic in nature merchandise, such as arabinose as the sugar glucose, uronic acids, and simmondsinaglycons. The results imply that sebum waste may have use in the development of a liver-protect medications.<sup>67</sup>

**Tong et al., (2011)** have developed electro-responsive hydrogels containing PVA, which was crosslinked along diethyl acetamidomalonate, hydrogels formulated using polyaniline as responsive element and formulated into cylindrical devices containing the drug indomethacin. The physicochemical as well as physico-mechanical profiles of gels are been evaluated. Conductive property and responsiveness of gels were analysed by cyclic voltammetry. 65-70% was the efficiency range of drug entrapment. The pulsatile release ("ON-OFF") of drug from the developed hydrogels was evaluated at 0.3–5.0 V at interval of every minute for hour and release of drug was 4.7–25.2% after end of 4h. The release of indomethacin was relying on amountof crosslinking agent from various formulations 1.2V was used to perform Box- Behnken experiment for baseline difference. Therefore, it showed proper swelling and drug diffusing property, it was increased on applying high conduction. AMBER- force field experiment was performend on devices to examine the release of NSAID from it. It was also evaluated by various factors for the reaction between polyaniline and applied energies externally. The above technique can release the drug on applying external energies in delicate working condition.<sup>68</sup>

**Saluja et al., (2013)** have created wearing digital delivery (WEDD®) sleeves including donepezil is to treat cognitive impairment at provided present doses of 0.13, 0.26, 0.39, and 0.13 mA. Utilizing both HPLC and non-compartmental examination, the donepezil that was isolated through circulation was tested. It was discovered that areas under the curve (AUC) and the amount of medication administered over the bald skin of rat increased in accordance to the provided levels at that time. At 0.13, 0.26, and 0.39 mA, peak plasma levels of 0.094, 0.237, or 0.333 g/ml are attained. After the present flow stopped, the time to peak plasma concentrations was uniform for every current level setting. Due to the cache creation, the

medicinal product's transdermal elimination half-life was significantly extended from its genuine worth of 3.2 hours, allowing for full ingestion. This drug was effectively administered iontophoretically in sufficient quantities to yield pharmacological effects. Switch dynamics after iontophoretic treatment showed polynomial dynamics at present values.<sup>69</sup>

**Rajesh Kumar., (2016)** have synthesized and characterized carboxymethylcellulose- graft-copolymer in which *N*-vinyl caprolactam was grafted onto carboxymethylcellulose has been carried out in inert atmosphere using free radical initiator. This compound was utilized as a reducer and the potassium bromate was used as an oxidizing agent. When acidic media, they responded generating electrons. The product of ions attacking NVCL or CMC is Cc-graft-copolymer. The surgery has been further verified using thermal gravity analysis involving the transplanted monomers and data from spectroscopy using FTIR.<sup>70</sup>

**Indermun et al., (2014)** outlined the applications of gels in regulated medication delivery as well as its application in drug release upon electric stimulation. Electro-conductive hydraulic jellies (ECHs) originate using semi-interpenetrating networking (semi-IPNs), which included poly(ethyleneimine) (PEI) and 1-vinylimidazole (VI) chemical mix. However, earlier electro-active organisms demonstrated electro-responsive uptake of drugs using these pathways. The semi-IPNs ions were composed of polyethylene glycol alcohol (PVA) and polyacrylic acid (PAA).

By using a probabilistic test approach, the different characteristics of the electro-responsive ECHS, which are taken into consideration and examined. By building a Box–Behnken type method, the enzyme complex component been systematically optimized. The formulation's performance depended on the following factors included in the proposed structure: applied voltage, 1-vinylimidazole size, and poly(ethyleneimine) size. Formulas introduced to different settings were tested of electro-responsive release of medications in order to determine the perfect setting for their intended release. A gravity-based investigation on water content and swelling was also carried out. The matrixResilience profiles were acquired to provide an understanding concerning the ECH's ability to return to its initial configuration after stressed. The results of the investigation unquestionably demonstrate the effectiveness of electroresponsive medications. The results of the research will be applied towards the creation of electroresponsive medication delivery systems that will distribute

medications in a more secure and effective way. The optimal medical electro-responsive administration (0.8 mg) of indomethacin was obtained with volumes of poly (ethyleneimine) (>2.6 mL) and 1-vinylimidazole (>0.7 mL).<sup>71</sup>

**Zuo et al, (2014)** have investigated the relationship with a number of pharmaceutical characteristics and overall dermal the use of i impact. During this research, a variety of Antidepressants were utilized. We investigated the oil-water ratios based on the medicines used. Hydrogel carbohydrates basis was used to create the hydrogels. Adding a voltage boost significantly improved the medicament's experimentally distribution over the rat's skin. A high level of medication permeability could result from strong the material's lip. Nonetheless, the critical factor in determining the transcutaneous improvement impact of electromotive drug administration was the medicine's dissociation extent (measured in pKa). There was a significant separation between the medication and the transcutaneous improved consequence of iontotherapy. The chronic inflammation in rats was better managed using drug-loaded the gels and iontotherapy. The results of the test showed that the 5- carboxylfluoresce in hydrogels with the application of iontophoresis is more penetrating throughout the the epidermis, skin type, and the outermost layer of more profoundly than the treatment of medicines alone. Improved dermal medication administration can be achieved by using an isotophoresis prism rectifying that corrects the unordered arrangement of skin intercellular lipids, significantly increases mobility, and creates an unstructured stratified organization with excellent protection and effectiveness. One method that shows promise is a process called.<sup>72</sup>

**Kalaria et al., (2014)** have investigated the delivery of pramipexole (PRAM) under iontophoretic condtion. PRAM is dopamine loving used in treating Parkinson's disease, in this study it is determined that required amount of PRAM can be delivered through skinor not. Iontophoresis method is used to measure the in vitro drug delivery across the skin using ear of porcine and abdominal skin of human. In vivo permeation rate of drug was confirmed by pharmacokinetic study by using male wistar. The relase rate of PRAM on application of current (0.5 mA/cm<sup>2</sup> for 6 h) was  $60.2 \pm 5.3\%$  and on addition of Na metabisulfite (0.5%) rate increased upto  $97.2 \pm 3.1\%$ . In Vitro delivery of PRAM under iontophoretic condition was enhanced. 2.5 to 4 fold enhancements in permeation of drug is observed with increase in the density ofelectric stimuli from 0.15 to 0.3 and 0.5 mA/cm<sup>2</sup>. Co-iontophoresis of acetaminophen demonstrated that electro-relocation was the prevailing electro- transport



system and here was absence of electro-osmotic stream with any thickness. In addition, combined iontophoretic saturation through human and procaine skin was shown to be factually proportionate. For PRAM high transport and delivery efficiencies have been achieved. Using steady and time-variation models, the plasma fixation profiles acquired concentrates in iontophoresis. The in vivo drug input rate indicated that PRAM electro-transport concentrations would be appropriate for therapeutic delivery and Parkinsonism treatment.<sup>73</sup>

**Malinovskaja et al., (2014)** have studied effect of steady and pulsed electric flow on the vehicle of nonapeptide leuprorelin acetate on epidermis of porcine. Likewise, evaluation of drug delivery system was carried for the delivery of identical peptide. The advantages of pulsed current ( $T_n = 2.59 \times 10^{-4}$ ) over continuous flow ( $T_n = 1.7 \times 10^{-4}$ ) for percutaneous antigen transport were shown by the current investigation. Due to reduced passive transport and electro-osmotic transport on application of pulsed current increased electro-osmotic marker was observed. Furthermore, using transfer of electrons the use of threads researchers showcased a possible useful technique for controlling the release and iontophoretic transdermal delivery of mediators. Leuprorelin methanol was guaranteed to be energized for the ion-exchange teams of cation-exchange fibers once unbiased charges seemed progressively liberated by floats across an external solvent. Because the acrylamide grafting Smopex-102 fibers discharge drugs more effectively than sulfonic acid grafted Smopex-101 fibers ( $J_{ss} = 0.31 \text{ lg/h cm}^2$ ), cutaneous flux from the former fibres stayed larger.<sup>74</sup>

**Kalaria et al., (2014)** have investigated the delivery of pramipexole (PRAM) under iontophoretic condition. PRAM is a dopamine loving used in treating Parkinson's disease, in this study it is determined that required amount of PRAM can be delivered through skin or not. Iontophoresis method is used to measure the in vitro drug delivery across the skin using ear of porcine and abdominal skin of human. In vivo permeation rate of drug was confirmed by pharmacokinetic study by using male wistar. Studies disclosed that on applying current, enhancement in permeation was seen up to  $60.2 \pm 5.3\%$  of its initial value. Where as upon adding Na metabisulfite (0.5%), associate inhibitor, enhances to  $97.2 \pm 3.1\%$ . Procaine skin was used to study the pram transport under iontophoretic condition. Cumulative permeation was increased by 2 to 4 folds by increasing the current density. With raising electricity, a two-fold rise in PRAM concentration was seen. Excellent



uniformity has been identified relating PRAM flux that the current being used frequency as well as the drug concentration in the composition. The level of plasma distributions found in the iontophoretic studies in vivo were modeled using both fixed or time-variant inputs approaches; the former offered a better fit. PRAM electrotransport speeds should be adequate to successful dissemination and therapy of schizophrenia, according to the in vivo input rate of medicine.<sup>75</sup>

**Zuo et al., (2014)** have documented affinities in the cutaneous enhancing impact from iontophoresis and the physicochemical characteristics of medications. As experimental medications, non-steroidal antibacterial medicines (NSAIDs) such as ibuprofen, aspirin, and a drug called in were utilized. NSAID-containing gels based on carbohydrate were made. The process of i markedly improved transdermal distribution over the rat skin in vitro. Good fluidity may contribute to an exceptionally low medication absorption rate. Chronic chronic inflammation in rats was better handled by drug-loaded gels and iontotherapy. The therapeutic use of the procedure led to in a poor crustal organization, dramatically improved mobility, as more unordered arrangement of skin intercellular triglycerides. The process of i is therefore a viable strategy for enhancing topical administration of medications that is both environmentally friendly and highly effective.<sup>76</sup>

**Bhatia et al., (2014)** looked into the possibility of laser the procedure technology to administer lidocaine hydrochloride though animal skin. Both actual current and no direct energy were tested. Straight & pulsating power were utilized with a 1%w/v solution of lidocaine hydrochloride either twenty minutes as well as two hours (0-1 h and 4-5th h). He delivery system was evaluated for amount of drug permeated into the layers of skin and extracted skin was further evaluated for amount of drug present in amount of skin layers. At predefined period samples were collected from receptorcompartment any analyzed. After 2h of DC current  $1069.87 \pm 120.03$  mcg/sq·cm of lidocainewas delivered through porcine skin and  $744.81 \pm 125.41$  mcg/sq·cm of lidocaine was delivered after altering the DC current. Owing of its iontophoretic force, diclofenac was administered twelve times. on average than when it was delivered passively ( $91.27 \pm 18.71$  mcg/sq·cm). When juxtaposed with inactive administration, modified intratophoresis improved the passage of lidocaine hydrochloride through swine epidermis. 1 kHz recurrence was observed to be nearly identical with equal replacing electricity for two hours, and with a steady DC electric current for one hour.<sup>77</sup>

**Zorec et al., (2013)** have published comparisons between various setups of extended low power (LV) as well and square wave short high voltage (HV) electroporation of bursts. The laboratory tests show whilst brief HV pulsing solely produce insignificant calcein passively transmitted, larger LV bursts greatly boost subsequent passive transport of calcein through dermatomed human skin through the skin. Significantly less calcium traveled altogether whenever short period HV pulses preceding lengthy Ventricular pulse. A computational chemistry driven approach to the progression of each individual local transport region (LTR) under the utilized LV shock was utilized to explain what happened. According to the speculative hypothesis, HV pulsed change the basement corneum's composition in an approach way prevents sufficient warmth from being produced by the LV pulses to start LTR contraction. Theoretically forecasts plus observations simultaneously demonstrated that the exact order in which a variety of pulses are delivered is crucial in explaining the overall osmotic transport, while aggregate pulse intensity is not sufficient to explain it.<sup>78</sup>

**Pescina et al., (2013)** have reported delivery of methylprednisolone hemisuccinate with iontophoresis. Further performed the study with concentrated drug solutions and applying electric stimuli for short period to mimic the iontophoretic conditions of in- vivo studies. The concentration of drug to be delivered from donor compartment through porcine skin was 45 mg/ml under passive condition and after applying electric stimuli for 2-15 min. In the other part of study, the drug delivery was carried at 0.9–7.2 mA intensity for 5min. On withdrawal of drug donating compartment, unleash of drug up to 24h was seen. In cathodal iontotherapy, there was increase in accumulation of drug between the charge 0.3 and 1.44 Coulomb. When the charge was enhanced to 2.16 Coulomb along with enhanced time or intensity there was no improvement. This conduct can be credited to significant medication adsorption on the scleral tissue, as exhibited through spilling expected investigations, with the ensuing increment of the electroosmotic stream that restricts tranquilize transport. The study suggested that could help in carrying the in vivo studies using animal models and help in decreasing number of in vivo experiments.<sup>79</sup>

**Blagus et al., (2013)** have developed and evaluated delivery of radioactive particles through transdermal route. Multi-array electrodes are used for Electroporation (EP) of mouse skin, which can deliver the electric current within electrodes of 70 to 570V. The developed films were applied on the skin prior and after to the electroporation which are treated with fluorescein-isothiocyanate dextran (FD), antibiotic drug or painkiller. The delivery of FD

from developed systems through the region of treated skin was determined using fluorescence microscopy. It resulted that the transdermal delivery of FD enhanced upon application of electric stimulus, and thus started to decline with higher amplitudes. Whenever cassette revealing was utilized for a feedback mechanism, oral administration gradually grew through raising the intensity associated with the electricity transmitted, reaching even greater levels. The effects of EP at 360 and 570 V pulse amplitudes on the delivery of cutaneous and systemic medications were measured and confirmed through non-invasive observation of the fluorescent chemical chemotherapeutic DOX insertion. The results of administering FEN at 360 and 570 V pulse amplitudes were verified by assessing the physiological responses of mice using the level elisa FEN milk. These measurements were made using Od and the drug DOX.<sup>80</sup>

**Djabri et al., (2012)** have looked into giving youngsters ranitidine as monohydrate by dermal iontophoretic distribution. Ranitidine was delivered in vitro via continual DC anodizing iontotherapy on dermatomed pig skin. Employing water solutions, the effects of donor vehicle, current intensity, and drug concentration were first investigated. Distribution of drugs was seen to be higher at pH 7 (donor: 5 mm Tris) than at pH 5.6 (donor: water). Ranitidine, also administration rose exponentially with supplied amperage in spite of tiny amounts of competing background electrolyte, but it was unaffected by donor drug concentrations. The study's final section assessed two Pluronic® F-127 gels as possible delivery systems for ranitidine. Studies of electrical conductivity, optical density, and inactive permeability have been utilized to characterize the compounds. Compared to liquid solutions, the iontophoretic transport of alkalizer through the jellies seemed only marginally impacted. Overall, the findings showed that appropriate ranitidine dosages for children (newborns: 0.09–0.17  $\mu\text{mol/kg h}$ ; children aged 1 month to 12 years: 0.36–0.71  $\mu\text{mol/kg h}$ ) could be simply obtained using a gel patch (0.2–1.5  $\text{cm}^2/\text{kg}$ ) had an area of contact that might be placed transdermally for the procedure.<sup>81</sup>

**Gratieri et al., (2013)** Have looked at ketorolac's (the company) iontophoretic transport efficiency. The early research revealed how KT iontotherapy was used to profit from the outermost layers of humans as well as pigs under physiological experimental settings. According to the findings, KT electrotransport was linearly dependent on drug quantity, ranging from 5 to 20  $\text{mg/ml}$ , with present intensity, spanning 0.1875 to 0.5  $\text{mA/cm}^2$ . A 2% hydroxymethyl cellulose gel's iontophoretic KT penetration was comparable to an oral

solution via a substitute dosage mixture. The simulations' reliability was confirmed by the comparative comparability of cumulative permeation and steady state flow between pig & human skin. The drug's dissemination in skin cells was evaluated. A substantial rise in KT concentrations beneath the dermis was observed by iontophoretic administration for 30 minutes, which proved to be more effective than inert cutaneous treatment for one hour. Apart from enhancing the bioavailability, iontophoretic administration of KT demonstrated a distinct characteristic for native distribution to the therapeutic site's femur's striated muscles. These findings showed that the ketorolac a process called permits concentrated, increased applied to subjacent muscle; this could have therapeutic uses in the control of regional discomfort and swelling.<sup>82</sup>



# **MATERIALS AND METHODS**



Seed extracts from the *Simmondsia chinensis* family of Simmondsiaceae and the *B. Lanza* family of Anacardiaceae

### **Sample preparation**

Before being used for assessment, the seeds had been scrubbed, evaporated and kept within an airtight, refrigerated vial.

### **Research of phytochemistry**

Routine steps were followed while analyzing for alkaloid substances, glycosides of the heart, tannins, and the saponins.

### **Metalexamination**

The debris was treated with 3M hydrogen chloride to dissolve the elements, and the atomic absorption spectrophotometer was used to measure the amounts of calcium, magnesium, manganese, or iron; the flame photometer was used to measure sodium and potassium.

### **Analysis of vitamins**

The technique of a scalar was used for estimating the composition of the unable to dissolve in nutrients, niacin and thiamine, and while the technique of AOAC was used to assess their ascorbic acid level.

## **PHOTOCHEMICAL RESEARCH**

Material from plants must be authenticated and extracted, assessments must be conducted both qualitatively and quantitatively, and separation and Pharmacology active evaluation might be done in parallel with this.

### **Biochemical and atomic constants**

Plant parts that have been sun drying and pulverized are utilized to calculate the physiochemical constants in compliance with the WHO criteria.

## **REVERSAL OF ASH PRINCIPLES**

While evaluating the originality and caliber within a powdered basic medicine, ash readings can be useful. The substance left over from embodiment is the substance's amount of ash, which is merely a chemical salt that is either readily occurring in the

medicine or is included as a kind of counterfeiting to make it adhere to or become edible. The elemental residue that remains after burning and is made up of inorganic compounds that are either present by default in the drug or have been purposefully added to it as a means of adulteration is known as the ash value of a crude drug. As a result, it is employed to assess the grade and integrity of unprocessed medication that has been powdery.

**EntireAsh**

The overall ashes approach's goal is to determine the entire quantity of materials that have been left. Whole Charcoal The total ash method is used to determine the overall quantity of material left over following an ignition. They are made up of two types of ash: medical ash, this is derived from the crop's genuine tissue that and non-physiological smoke, this is the residue left over when foreign items cling to the crop's foliage. Following a fire.

They consist of both biological ash, which comes from the actual plant tissue, and non-physiological ash, what is left over when foreign objects stick to the outer layer of the plant's leaves.

**Method:** The quartz beaker was placed in a dryer and fired to a red temperature for thirty minutes. In high tarred quartz dish, torch 2 to 3 g accurately measured of the powdered substance at temperatures not to exceed 4500C. Once the sample is carbon-free, chill it in desiccators and weigh it. The resulting ash was examined. It was established as a proportion of all ash.

**Moisture-soluble ash**

Was the amount of weight that differentiates the whole ash and the residue following the ash's treatment in water.

**Method:**

The entire amount of ash boils for ten minutes with twenty-five milliliters of steam; insoluble materials are gathered in ashless filter cloth, scrubbed with hot water, and ignited for fifteen minutes at a temperature not to exceed 4500. Take this residue's weight in milligrams and deduct it from the overall weight of ash. Determine how many milligrams of insoluble in water ash there are in per gram of air-dried material.

**ASH WITH ACID unable to dissolve:**

Following the entire ash is boiled in a solution of hydrochloric acid to produce leftovers, the residual inert substances are burned and quantified. It indicates how much of silicate present, especially in sand and siliceous earth.

**Process:** 25 millilitres of diluted hydrochloric acid are added to the anvil that holds the sample's total ash. After gathering the insoluble material on ashless filter paper (Whatman 41), boiling water is used for washing the material until the resultant filtrate is impartial. To the beginning paper for filters, add the insoluble material.

$$\text{Water soluble ash} = \frac{\text{Weight of residue obtained}}{\text{Weight of the sample taken}} \times 100$$

**ASH WITH ACID UNABLE TO DISSOLVE:**

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**END OF ASH**

To determine how much of a test's remainder hasn't volatilized, utilize the sulfurous dung test. Such tests are often performed to ascertain the mineral percentage.

**Method:**

The silica crucible was heated to a scarlet temperature for ten minutes, then cooled in a desiccant before being weighed. Two grams of the material were precisely weighed, softly lit, and then completely harrowed. After cooling down, mix the residue with 1 milliliter of sulfuric acid, warm it up gradually until the white vapors stop, and then light it at 800°C unless every the tiny black particles go gone. After allowing the furnace to recede, add some



tablespoons of sulfur dioxide to heated. In the same manner, ignite, let cool, then weight. Unless the subsequent weigh-ins deviate by more than 0.5 mg, this practice is restarted.

$$\text{Acid insoluble ash} = \frac{\text{Weight of the residue obtained}}{\text{Weight of the sample taken}} \times 100$$

### **END OF ASH**

To determine how much of a test's remainder hasn't volatilized, utilize the sulfurous dung test. Such tests are often performed to ascertain the mineral percentage.

#### **Method:**

The silica crucible was heated to a scarlet temperature for ten minutes, then cooled in a desiccant before being weighed. Two grams of the material were precisely weighed, softly lit, and then completely harrowed. After cooling down, mix the residue with 1 milliliter of sulfuric acid, warm it up gradually until the white vapors stop, and then light it at 800°C unless every the tiny black particles go gone. After allowing the furnace to recede, add some tablespoons of sulfur dioxide to heated. In the same manner, ignite, let cool, then weight. Unless the subsequent weigh-ins deviate by more than 0.5 mg, this practice is restarted.

Ten grams of the tested materials were obtained and placed in an evaporated plate covered by bitumen (without first drying). Do not employ a fast processor to prepare specimens. After five uninterrupted hours within the drier compartment (105°C), the samples in the tarred evaporating dish were weighed. Checking then cleaning are done at random until the difference between the next two kilograms is below one twenty-five percentages. Whenever there is a disparity of not greater over 0.001 g between two subsequent weigh-ins following a 30-hour dryer plus 30-hour conditioning period in dehumidifier, the total weight is considered constant. The percentage moisture content is contrasted using the fragment that was dried outdoors.

$$\text{Sulphated ash} = \frac{\text{Weight of the residue obtained}}{\text{Weight of the sample taken}} \times 100$$

**DETERMINATION OF MOISTURE CONTENT:****DECLINEAFTERDRYING**

Twenty grams from the examined substances were gathered and put into an evaporates plate that was sprayed using tar (without being dried first). Don't handle data in a quick microprocessor. Once the samples in the tarred evaporating dish had been in the dry container (105°the C) for five continuous minutes, they were collected. Up until the difference between the following two grams is less than thirty-five percent, cleaning and examination occur at intervals. The overall weight is deemed constant if the difference among two successive a weigh-in after a 30-hour dryer plus 30-hour conditioning period in the dehydrator is not more than 0.0001 g. The portion that the was permitted to dry outside is used to compare the percent of humidity extremely straightforward and highly successful method. It was previously applied on a wide range of resources, such as soils, s, and vegetative and animal material. This substance (DCM) can be used alone or in conjunction with acetic or petroleum as well as solvent–hexane mixtures. Fluids with polarity should not be used solely. A typical Soxhlet procedures eradication requires eight hours or more. Sulfur was also extracted from the soil and sediment tests; this must continue been removed in a later treatment process.

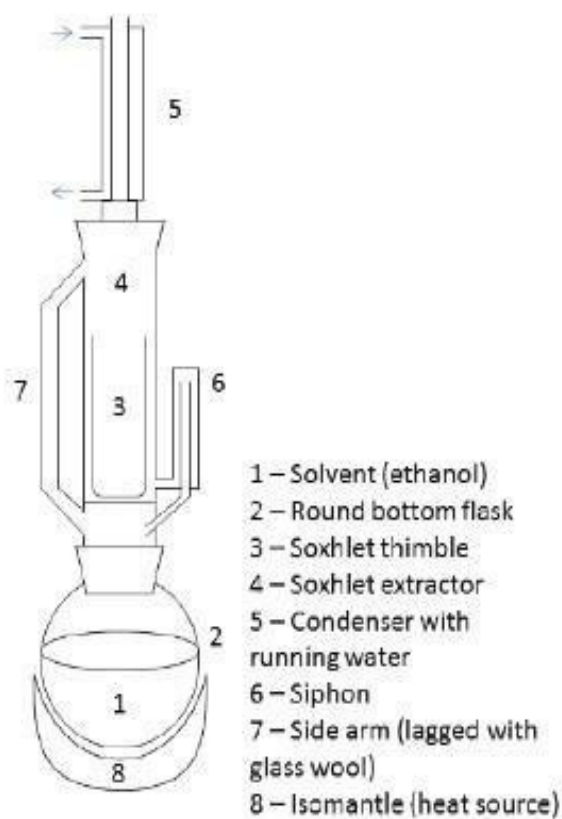
The process of Soxhlet extraction combines soaking and infiltration processes. In 1879, Franz von Soxhlet invented the Soxhlet apparatus, a special tool for executing the extraction procedure.

$$\% \text{ Moisture content} = \frac{\text{Final weight of the sample} \times 100}{\text{Initial weight of the sample}}$$

**EXTRACT PREPARATION****Technique of Soxhlet Separation**

Extremely straightforward and highly successful method. It was previously applied on a wide range of resources, such as soils, s, and vegetative and animal material. This substance (DCM) can be used alone or in conjunction with acetic or petroleum as well as solvent–hexane mixtures. Fluids with polarity should not be used solely. A typical Soxhlet procedures eradication requires eight hours or more. Sulfur was also extracted from the soil and sediment tests; this must continue been removed in a later treatment process. The process of Soxhlet extraction combines soaking and infiltration processes. In 1879,

Franz von Soxhlet invented the Soxhlet apparatus, a special tool for executing the extraction procedure.



**Figure No. 5.1: Soxhlet apparatus**

**Extracts of seeds of *B.lanzan* family Anacardiaceae and extracts of seeds of *Simmondsia chinensis* family Simmondsiaceae**

#### **Method**

2.5 kg of *B.lanzan* or *Simmondsia chinensis* nuts were separated using methanol three times in a 24-hour period at a room temperature of 20–25°C. After that, the solvent was evaporated at 50°C concentrated extract while the working temperature was lowered. 86g of n-hexane extract and the water layer were obtained by fractionating 280g of methanol extract with n-hexane and water. The water layer then extracted with ethyl acetate to gain a 120g ethyl acetate fraction and 90g water fraction. The highest-activity percentage, ethyl acetate, was the main component was separated through chromatography using a combination of n-hexane, ethyl acetate, and methanol with elevated voltage using a Wakogel C200 (Wako Pure Chemical, Japan). Sulfuric acid-ethanol (1:9) was used to extract and purify the main

components, which were subsequently identified using spectroscopic techniques such as mass spectroscopy (MS), ultraviolet (UV), infrared spectrometry (IR), and nuclear magnetic resonance (NMR).

#### Preparation of Gel:

Carbopol 940 gel base, after optimization was formulated by first hydrating required quantity of carbopol in propylene glycol and distilled water q.s. for 24hr. The mixture was stirred by keeping it on mechanical stirrer at 50rpm for 30mins at 25°C, until all carbopol was dispersed and then other excipients like methyl paraben (0.2%w/w) and propyl paraben (0.02%w/w) and triethanolamine were added in order to increase stability of the gel.

Screening of Influential Variables In order to pick out important compositional as well as factors involved in the gel production, a regular 3<sup>2</sup> development was used. The description of high to low levels of different factors, including ultimately and the Shanghai Conference of Nations that were examined for their influence on the evolution of the colchicine gel is shown in Table 6.1.

**Table 5.1: List of variables employed in Regular 3<sup>2</sup> Design**

Factors	Levels		
	(-1)	0	(+1)
Viscosity	0.7	1.7	2.7
Amount of PE(ml)	0.1	0.5	0.9

Table 5.1 contains List of Variables which was employed in Study with their low, medium and high levels. 2 variables Amount of carbopol 934, Amount of PE were select as independent variables under 3 levels (low, medium and high).

**Factorial Batches of gel formulations 7a. Coded levels translated in actual quantities.**

Factors	Levels		
	-1	0	+1
X1 Concentration of gelling agent	0.7%	1.7 %	2.7%
2 Concentration of PE	0.1 %	0.5%	0.9%

**Independent Variables:**

X1 = Concentration of gelling agent (Carbopol 940).

X2 = Concentration of Permeation enhancers.

**Dependent Variables:**

Y1 = Viscosity

Y2 = % Cumulative drug release at 8hrs

**7b. Factorial design layout.**

Batch code	Coded values		Actual values	
			Concentration of Gelling agent in %	Concentration of Propylene glycol
F1	0	0	0.7	0.1
F2	0	-1	0.7	0.5
F3	0	+1	0.7	0.9
F4	-1	0	1.7	0.1
F5	-1	-1	1.7	0.5
F6	-1	+1	1.7	0.9
F7	+1	0	2.7	0.1
F8	+1	-1	2.7	0.5
F9	+1	+1	2.7	0.9

Table 5.2: Composition of gel on the Basis of Regular  $3^2$  Design

Name of Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (%)	1	1	1	1	1	1	1	1	1
Carbopol 940	0.5	0.5	0.5	1.7	1.7	1.7	2.9	2.9	2.9
JJBO/SCO (ml)	0.1	0.5	0.9	0.1	0.5	0.9	0.1	0.5	0.9
Polyethylene glycol (ml)	5	5	5	5	5	5	5	5	5
IPA (ml)	5	5	5	5	5	5	5	5	5
Methyl Paraben (gm)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Propyl Paraben (gm)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
TEA (ml)	qs	qs	qs	qs	qs	qs	qs	qs	qs
Distilled water (ml)	Upto 100	Upto 100	Upto 100	Upto 100	Upto 100	Upto 100	Upto 100	Upto 100	Upto 100

Table 5.2 displays the BL9 and SC9 array for the two-level, three-factor layout used in the present-day investigations. The Department of Environment will produce mixtures of the nine formulae shown in table 5.2 when the info from the corresponding table is entered. In order to choose the important creation and respond characteristics, viscosity and penetration efficiency were the primary responses elements that were carefully evaluated.

### Evaluation of gel

**Viscosity determination:** Viscosity size was determined using the Brookfield viscometer

**Penetration efficiency:** prepared gel was estimated for its penetration efficiency. Formulated gel was taken for its ex-vivo drug release studies. Accordingly optimized formulations were separate out. The formulations in a required dose were spread on goat skin and snake skin. Sampling was done as 5ml sample withdrawn at specific

interval. It was then diluted and prepared solution was taken to make further study of drug release. The samples were analyzed on UV spectrophotometer (Spectrascan2600).

**Transmission Electron Microscopy:** TEM was used to identify the texture of the surface. To do this, a tiny portion of the material was set on an aluminum grid coated via carbon dioxide and, shortly after 15 minutes, The outermost layer were severely degraded by a 1% phosphotungstic acid fluid solution. The gathered objects were inspected with a transmission electron microscope (TEM Hitachi, H-7500 Tokyo, Japan) before their top layer was allowed to dry properly by light. Was chosen was the most suitable approach based on the study's findings.

**Table 5.3: Composition of optimized gel formulation**

<b>Formulation</b>	<b>Carbopol 940(g)</b>	<b>BLO(ml)</b>
BL5	1.7	0.5

<b>Formulation</b>	<b>Carbopol 940(g)</b>	<b>SCO(ml)</b>
SC4	1.7	0.1

### **Preparation of Gels**

**Preparation of Carbopol gel base:** To create a 0.5% connect, 0.5 g of 940 carbopol was measured and mixed gently in 100 ml of distilled water, and left to swell for 24 hours. Afterwards, the gel received two milliliters of glycerin to keep its texture. The gel also contains conditioners (methyl and propyl paraben). Likewise, 2% and 1% Carbopol gels were made.

**Table 5.4: Composition of different gel base**

Formulation	Carbopol (%)
BL4	0.5
BL5	1.7
BL6	2.9

Formulation	Carbopol (%)
SC4	0.5
SC5	1.7
SC6	2.9

**Preparation of gels:** Carbopol 940 gel base, after optimization was formulated by first hydrating required quantity of carbopol in propylene glycol and distilled water q.s. for 24hr. The mixture was stirred by keeping it on mechanical stirrer at 50rpm for 30mins at 25°C, until all carbopol was dispersed and then other excipients like methyl paraben (0.2%w/w) and propyl paraben (0.02%w/w) and triethanolamine were added in order to increase stability of the gel.

#### **Valuation of Gel**

**Determination of pH:** A digital pH measuring device was used to weigh 50 grams of each gel formulation and move them into a beaker with a capacity of 10 milliliters. To treat skin diseases, the oral gel formulation's pH should be between 3 and 9.

**Spreadability:** Each gels' propensity for slipping or drag was used to gauge the colchicine gel formulation's spreading ability. Two acrylic slides were used in the system that was devised and built; the lower glass slide was fastened to a hardwood sheet, and the upper glass slide were connected to an upright via a hook. The calculation used to evaluate spreadability was  $S = ml/t$ , where m is the volume of the pan attached to the main optical tumble, t is the amount of time the slide is the time it takes to move a specific distance, and l is that amount. The mass, length, and "t" were all kept consistent for practical purposes.



**Skin Irritation study:**

Test was performed on three volunteers by applying 1gm formation on the wrist area. The observation was done for 1hr and data was prepared based on the observation.

Draize's skin irritation study: for primary skin irritation test, three volunteers were selected and then colchicine's gel of different batches were applied on the area of 2 square inches of the wrist for 2 hrs and observed the skin for irritation/lesion REF.

**Table No. 5.5: Skin irritation score**

Score	Description
0	No
0.5	Faint, barely perceptible erythema or slight dryness
1	Faint but definite erythema, no eruption or broken skin or no erythema but, definite dryness and may have epidermal fissuring.
1.5	Well defined erythema or faint erythema with definite dryness, may have epidermal fissuring.
2	Moderate erythema: may have few papules or erythema in the cracks
2.5	Moderate erythema with barely perceptible edema
3	Severe erythema (beet redness) may have generalized papules or moderate to severe erythema with slight edema (edges well defines by raising).
3.5	Moderate to severe erythema with moderate edema (confined to patch area).
4	Generalized vesicles or Escher formation or moderate to severe erythema and/or edema extending beyond the patched area.

**Viscosity measurement:** A Brookfield viscometer (DV-II model) was used to assess the thickness of solutions. For precise measurements, the level of viscosity has been measured three times using a T-Bar wheel and a helipath stand.

**Spindle selection:** Error and trial took place in this process, which started at the T95 cycle. The objective was to obtain a viscometer dial or display (% torque) reading between 10 and 100; as the reading gets closer to 100, the amount of error in measuring gets better. The viscosity of each gel was measured using Spindle T 95.

**Immersion of the Spindle:** Liquid T-bar spindle (T95) was lowered perpendicularly in the center, being careful never to strike the gel-filled beaker's bottom.

- (a) **Measurement of Viscosity:** Using gels' stickiness was measured using the T-bar spindle (T95). The method maintains the variables that affect viscosity, such as pressure, temperatures, quantity of sample, etc. There was never a torque reading below 10%. The amount of viscosity was calculated by averaging five values collected at 10 rpm over the course of 60 seconds.

#### **Creation of the Colchicine Standard Curve**

Colchicine, which apiece weighing 100 mg, was precisely weighed and dissolved in 100 ml of PBS (pH 7.5) in a large flask. After dilution to make 5 $\mu$ g/ml of Colchicine, the end product contains approximately 1000  $\mu$ g/ml of each medication. Colchicine's  $\lambda_{\text{max}}$  was measured at 350.0 nm employing an additional focus ultraviolet spectrophotometer to determine sensitivity. The standard calibration curve was obtained by plotting the wavelength readings with the level ( $\mu$ g/ml).

- (b) **Preparation of Analysis of Gel Formulation**

#### **Creation of the Colchicine Standard Curve**

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**Determination of drug content:**

After preparing batches, all the formulations were subjected to determine drug content. 10gm of gel was diluted with 100ml buffer and obtained solution was estimated by Spectra scan UV 2600 (double beam).

- Intermediate Precision
- Day today
- Analyst to Analyst

Differences between testing amenities, including different days, economists, machinery, and so on, indicate an average variation in reliability. After creating the usual the process of d three different batches of each composition underwent to various examinations to evaluate the effectiveness with the developed techniques.

**Selection of formulations for Drug release study:**

Based on the studies like viscosity, Spread ability, Skin irritation study formulation those had shown acceptable results were selected for ex-vivo diffusion study.

**Following formulations were selected for diffusion study:****Table No 5.6: Formulations for diffusion study**

Formulation	Carbopol 940(g)	BLO(ml)
BL4	0.5	0.1
BL5	1.7	0.5
BL6	2.9	0.9

Formulation	Carbopol 940(g)	BLO(ml)
SC4	0.5	0.1
SC5	1.7	0.5
SC6	2.9	0.9

These formulation have shown good result when they were evaluated for pH, Drug content, Viscosity, skin irritation study and Spreadability.

**Method Validation Linearity**

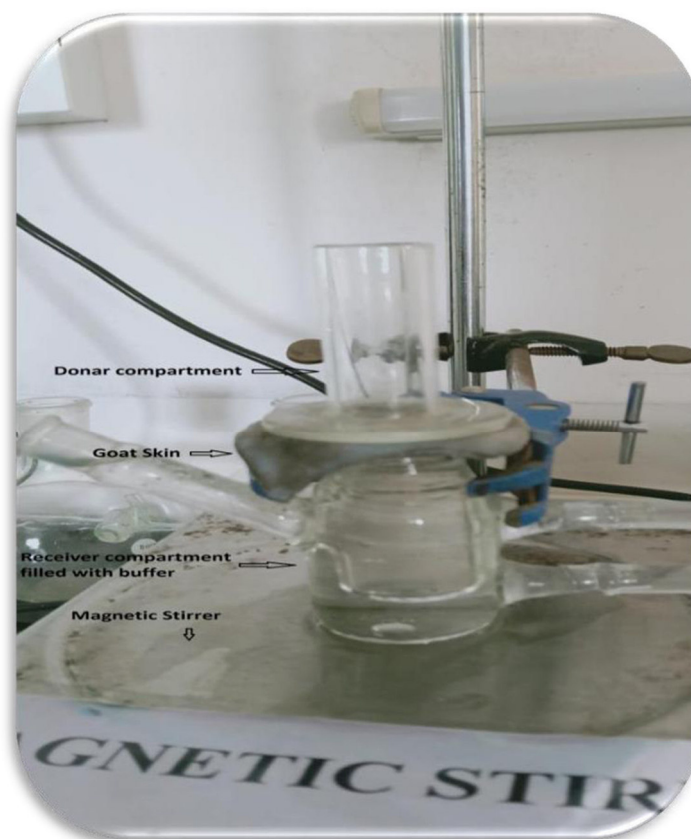
Linearity is the capacity of an analytical method to yield a test between a particular range that is directly associated as the concentration of chemical in the specimen being examined. The calibration plot was made after five distinct levels (between 1 and 5 µg/ml and 10 and 50 µg/ml) were examined. Three measurements of every single concentration's surface took place and the median square was calculated. The regression calculation, relationship directory, and typical izing graph for the drugs are shown. By scaling the recorded AUC by the corresponding concentration value, which was obtained from the combined amount of these two figures, the result ratio—also referred upon as a response factor—was computed.

**Reliability**

In order to verify the accuracy in the developed method, recoveries testing were conducted. After adding a predefined concentration of the standard drug (80%, 100%, or 120%) to the collected mix that had already been reanalyzed, how it recovered was investigated.

**Precision**

Three replicates of each dilution were evaluated on a single day, and the results were scientifically analyzed when benchmark values had been generated. For each average a solution, multiple copies had been created and on different days, an independent investigator looked at them all. An examination of statistics was conducted.



**Figure 5.2: Franz diffusion cell with goat skin**

#### **Handling of in vitro discharge statistics mathematically:**

The statistical review of the results obtained in breakdown/release studies is facilitated by the use of mathematical formulas that express the dissolution outcomes as an outcome of certain of the formulation's aspects.

**Zero-order kinetics:** This pattern is followed by medicinal product dosage forms, which release the same amount of substance throughout time. This method is the best way to release a drug and generate a lasting physiologic effect.

The following relation can, in a simple way, express this model:

$$Q_t = Q_0 + K_0 t$$

where  $Q_0$  is the starting drug concentration in the solution (usually  $Q_0=0$ ),  $Q_t$  is the amount of drug dissolved in time  $t$ , and  $K_0$  is the zero order release constant.

1. **First-order kinetics:** The following relation expresses this model:

$$\log Q_t = \log Q_0 + \frac{K_1 t}{2.303}$$

Where  $Q_t$  is the amount of drug dissolved in time  $t$ ,  $Q_0$  is the initial amount of drug in the solution and  $K_1$  is the zero order release constant.

This produces a line graph showing the decimal logarithm of the drug's delivery volume versus period. Dose forms for medicines that adhere to this disposal outline, including forms that incorporate water-soluble medications in porous matrices, release medication in a way that is proportionate to the amount still inside the container and decreases in quantity released over time.

2. **Higuchi model:** In order to investigate the dispersion of water-soluble and hardly soluble medications in semi-solid and/or solid matrixes, the Higuchi, for model was created by a number of imagined approaches. Formulas for pharmaceutical particles distributed in a homogeneous matrix acting as the diffusion media were calculated mathematically.

The simplified Higuchi model is expressed as:

$$Q = K_H \cdot t^{1/2}$$

Where  $Q$  is the where  $K_H$  is the Higuchi dissolving factor while  $Q$  is the quantity of medication liberated in time  $t$ . The Higuchi has model uses Flick's law, which is squared away time influenced, to characterize the release of medications as a diffusion process. This relationship can be used to explain how pharmaceuticals dissolve in a variety of modified release pharmaceutical dosage forms, including tablet form containing dissolved in water medications and percutaneous systems.

**Korsmeyer-Peppas model:** Korsmeyer *et al.* used a simple empirical equation to describe release behaviour of general solute from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a \cdot t^n$$

Where  $M_t/M_\infty$  is fraction of drug released,  $a$  is kinetic constant,  $t$  is release time and  $n$  is the diffusional exponent for drug release. 'n' is the slope value of  $\log M_t/M_\infty$  versus  $\log$

time curve (**Korsmeyer et al. 1983**). Whatever the excretion process, Peppas claimed suggested the aforementioned solution would sufficiently describe the release of solutes from slabs, spheres, pistons, etc disks (Peppaset al., 1985). Peppas employed that  $n$  figure to describe various discharge structures, coming to the conclusion that a slab should have  $n=0.5$  for Fickian diffusion and higher values of  $n$ , ranging from 0.5 to 1.0, or  $n=1.0$ , for mass transmission that adheres to a non-Fickian model (Table 6.9). The above formula can only be applied in environments where the substance's coefficient of diffusion is relatively dose distinct, such as in the circumstance of a cone when  $n=0.45$  instead of 0.5 and 0.89 as opposed of (Pappas, 1985). Only  $M_t/M_\infty \Rightarrow 0.6$  is to be utilized for determining an exponent in the releasing curved component. Additionally, discharge must occur in a one-dimensional manner and the system's width-thickness or length-thickness relation must have greater than 10 in order to employ the above equation. To account for the interval of time ( $l$ ) at the start of the drug release from the pharmaceutical dosageform, a slightly altered version of the formula below was created:

$$\frac{M_{t,l}}{M_\infty} = a (t - l)^n$$

When there is the possibility of a burst effect,  $b$ , this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

Merely  $at^n$  is employed when there is no lag time or burst effect, along with the values of  $l$  or  $b$  are set to 0. Power Law, a model of mathematics, is being widely applied to characterize form from various pharmacologic controlled releases dose methods.

**Oven Stability studies:** It was determined whether the revised mixtures were chemically and physically stable. Consequently, a spin analysis was done on the mixture. The samples were centrifuged for 30 minutes at 3000 rpm in order to achieve this goal. In the subsequent experiment, whose continued for ninety days, the collected specimens were heated to  $50 \pm 2^\circ\text{C}$  in the oven, cooled to  $5 \pm 2^\circ\text{C}$  in the chiller, and ultimately brought to room temperature ( $25 \pm 2^\circ\text{C}$ ). During this period, the kept formations were observed for their organoleptic characters like color, pH, and homogeneity.

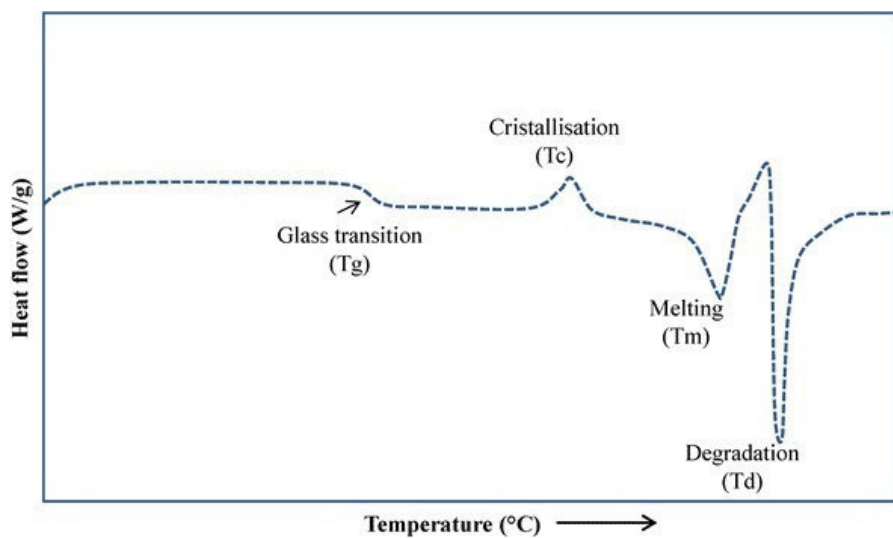
**Effect of storage temperature on drug content:** After storage for a specified period of time of 7, 15, 21, 28 and 60 days, the drug content of the formulations was determined. Drug content in gel was determined spectrophotometrically as discussed previously (6.4.5.).

### **DSC and TGA**

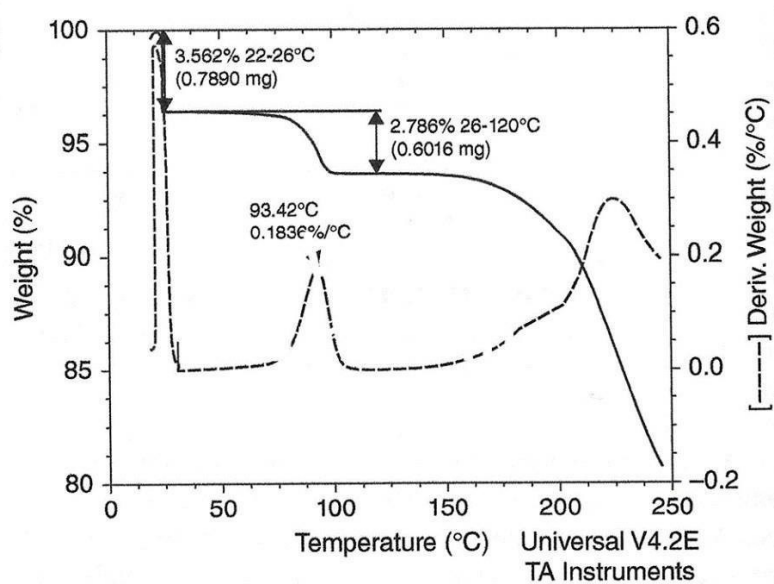
A thermal analysis method called DSC, which stands for differential scanning calorimetry, calculates the difference in heat flow between a standard with a sample as they are both put through a set heating schedule. The heat flow is measured in watts (W) and corresponds to the transmitted power. The change in enthalpy of the sample is determined from the heat flow curve. Endothermic reactions absorb heat, which is indicated by a negative heat flow. Exothermic reactions release heat, which is indicated by a positive heat flow.

TGA heat profiles are often plotted on an axis of representing warmth or time, along with an X-axis representing weight or bulk percentage. An example TGA heat curve showing how a sample of SAR474832 hydrate dehydrates in the image, the initial form is represented. comprises two phases of shedding pounds: 3.6% dryness from 22 to 26 ° C and 2.8% weight loss from 60 to 120 ° C. Typically, DSC as well as TGA are used in tandem to gain a deeper understanding of a pharmaceuticals material's thermodynamic action.





DSC



TGA

**AFM (Atomic Force Microscopy (AFM) analysis)**

Surface topography can be measured using pictures with near-atomic resolution obtained through the use of Atomic Force Microscopy (AFM) analysis. Another name for AFM is scanning probe microscopy. Sample surface roughness can be measured by Atomic Force imaging at one angstrom resolution. Compared to reflecting pictures the use of AFM can provide numerical estimations of object shapes, such as step heights and other metrics. Likewise, advanced nuclear force microscopy detection modalities can be implemented to map many different physical characteristics qualitatively, including as adhesion, modulus, dopant distribution, conductivity, surface potential, electric field, and magnetic domains.

**Measurements of contact angles**

Using the sessile drop method, contact angles between water and diiodomethane were measured against tablets of formulations 1, 4, and 7. SCA20 software (Data physics, Germany) was used to analyze the results under ambient settings after the contact angle system OCA15 plus (Dataphysics, Germany) was used to get the results. A 2 ml drop of diiodomethane and 2 ml of water were poured onto tablet surfaces at a 1 ml/s dosing rate using a micro-syringe. The internal camera was used to record the contact angle of the drop at 0 and 1.2 s. The software built into the device calculated the contact angles that were seen during this time. With both solvents, three determinations of each formulation were made. The angle was used to calculate the polar surface energy and dispersive energy.

**Acute toxicity studies**

According to OECD regulation 425, immediate oral toxicology assessments of the gel ingredients were performed in Swiss mice using the limit test or main test (Up and down approach). Animals that had starved before were given just one oral dosage of 2000 mg/kg of the mix dissolve in DMSO for the purpose of the limit test. For the primary six hours following dosage and for the next fourteen days, creatures were monitored closely for symptoms of poisoning, illnesses, and fatalities. The primary testing dose was chosen using the typical development factor, taking into account the toxic sign's start, stay, and intensity, as well as the morbidity and time of death in the upper bound test. If the primary test was

conducted, the low number at which the dog lived and the high dose at which the individual displayed death were used to calculate LD50 by using AOT software.

For a period of eight days, rats administered varying dosages of extracted up to 5000 mg/kg showed no evidence of mortality or morbidity. As a result, for compositions the median lethal dose (LD50) of extract was greater than 5000 mg/kg.

**The Experiment in Detail:**

Nine trial runs total were carefully organized, with designated levels made using the Design Expert® software. These runs were documented in the provided table. Because required by the methodology, the dosage forms being carefully made then examined for their percentage of drug release (Y1), which was taken into consideration as a response or variable of dependency. To uncover deeper factors, the observed responses were fitted into a variety of mathematical structures, including quadratic, a dual-factor communication (2FI), as well as linear equations. The ensuing analysis of variance (ANOVA) helped determine the created model's statistical significance as well as the statistical importance of the terms that made up the model.

**Visualizing Relationships:**

The Designs Specialist® application was utilized to create 3D response surface plots, 2D contour plots, and perturbation graphs in order to improve understanding of the complex interactions amongst the independent that are both independent and dependent. These graphical representations provided an insightful depiction of how changes in variables influence the responses. To characterize the thin film surface morphology, Molecular Imaging (FastScan Dimension, Bruker) was used in tapping mode to perform AFM, contact angle, and TGA characterization. Typical tip radius of 5 nm silicon cantilevers (Fastscan-A) were used. The resonance frequency of the cantilevers was around 1.25 kHz. The 400 nm scale was used to get the 2D AFM photos. The software WSxM 5.0 Develop 9.1 was used to transform the 2D photos into 3D images.

**Optimization Strategy:**

The pinnacle of the process involved optimizing the colchicine formulation. This was pursued by striving for desirable attributes, the optimized formulation's coordinates were distinctly marked on the overlay plot, highlighting its location.

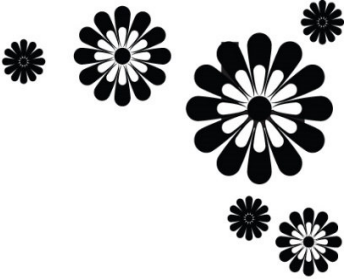
**Validation and Assessment:**

The validation phase encompassed preparing the optimized formulation as determined by the optimization process. This formulation was then subjected to assessment, measuring vesicle size and percentage entrapment efficiency. To gauge the efficacy of the model, a comparison between predicted and observed responses was carried out, yielding the percentage error.

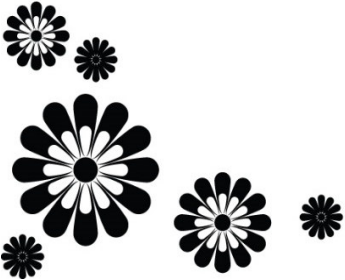
In essence, this comprehensive experimental approach utilizing advanced software and analytical techniques allowed for a systematic exploration of the relationship between variables and their impact on the formulation attributes. It facilitated the optimization process, ensuring the final formulation met the desired criteria while offering a validated model for future applications.

**Estimation of Pharmacokinetics parameters of stand colchicine, topical formulation BL6 and SL06 after topical skin application in wistar rats****Procedure:**

Wistar Rats of either sex weighing 200-300g were acclimatized to laboratory conditions for 7 days. Animals were divided into 3 groups (n=2). The furs of the rats were closely shaved avoiding any abrading to skin. Group I was administered orally with colchicine standard 0.5 mg tablet dissolved in distilled water. Group II and Group III was applied with test formulation BL6 and SL06 respectively. The blood samples were withdrawn under light anesthesia from retro orbital plexus from each animal. The blood was withdrawn after the test compound administration at various time intervals mainly at 0.5, 1, 4, 6, 12, 24, and 48 hours. The blood samples were collected in the heparinized tubes and plasma was separated and used for estimation of concentration of test and stand compound. The HPLC analytical method was adopted for the estimation of plasma concentration.



# **RESULTS AND DISCUSSION**



Different type of studies from the physicochemical to in vitro assay were performed as to optimize and also to assess the potential of the delivery system developed. The same has been represented in the previous chapters. Results and detailed discussion are being given here to convince the rationale for development of delivery system.

#### Studies of Preformulation Organoleptic evaluation:

The medications' hue whereas odor had been examined where it emerged which the fluid of *B. lanzan* was light yellow and that of *S. Chinesis* was pale yellow.

**Table 6.1: Organoleptic property of *Buchananialanzan* and *Simmondiachinesis***

Parameter	<i>Buchananialanzan</i>	<i>Simmondiachinesis</i>
Colour	Light yellow	Pale yellow
Odor	Odorless	Odorless
Taste	Tasteless	Tasteless

#### Preparation of standard curve of Colchicine

After precisely weighing 100 mg of colchicine, the medication was added to a 100 ml volumetric flask along with 100 ml of 7.5 pH phosphate buffer, and the mixture was agitated to dissolve. The end solution was approximately 1000 µg/ml. near acquire a stock solution of 100µg/ml, 1 ml of this resolution is then reassigned to another 10 ml volumetric flask. One milliliter of the stock solution was pipetted into a ten milliliter calibrated volumetric flask. A buffer was used to dilute the sample, and serial dilutions were then prepared. Colchicine's  $\lambda_{\text{max}}$  was measured at 350.0 nm expending a double beam ultraviolet spectrophotometer to determine absorbance. The standard calibration curve was obtained by plotting the absorbance readings over the dose (µg/ml).

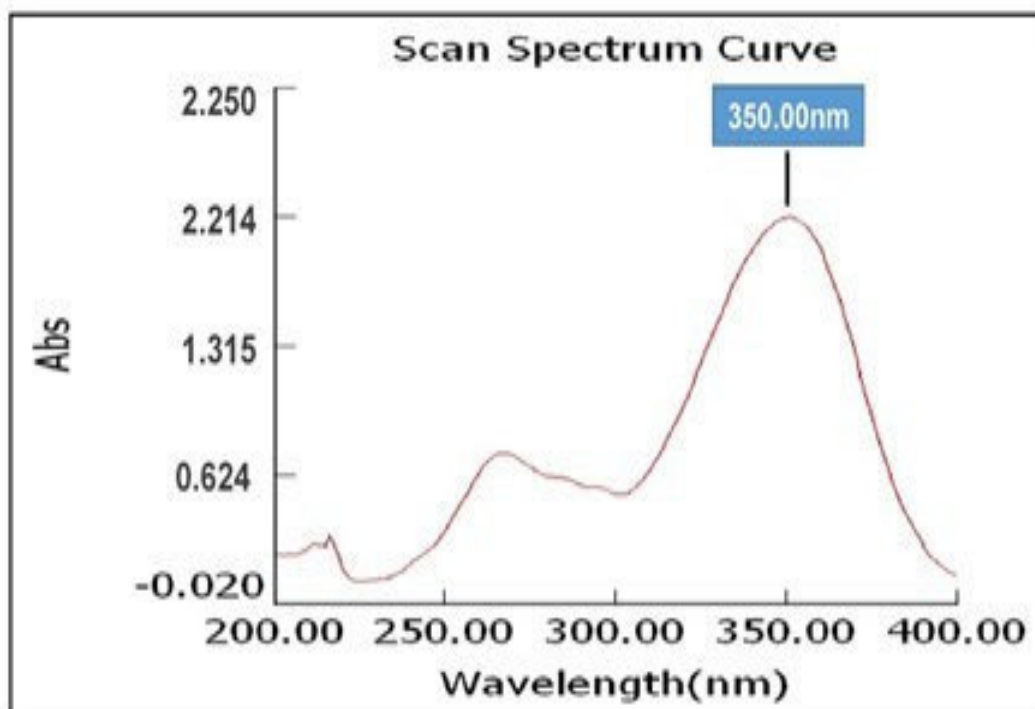


Figure No. 6.1: Wavelength scan of Colchicine in PBS pH 7.5.

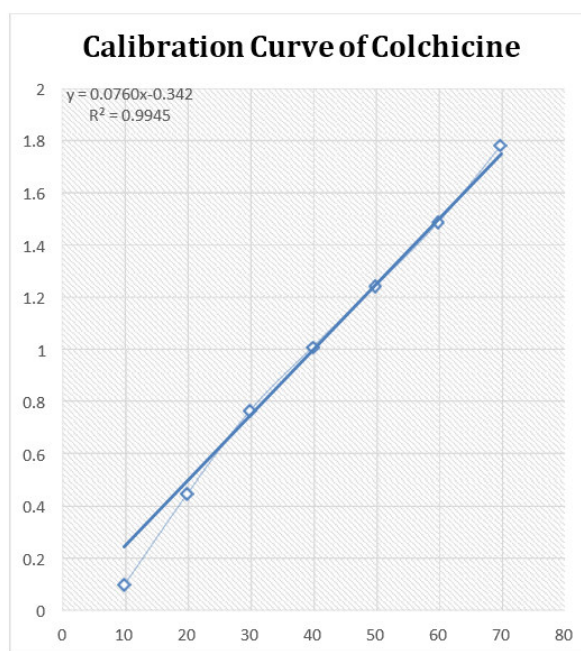
#### Calibration curve of Colchicine in PBS (pH 7.4)

Plotting a measurement graph between concentration and absorbance was done. For colchicine, which the relationship coefficient (or "r<sup>2</sup>") values were computed as 0.999 and 0.998; those values are given in Table 6.3.

Table 6.2: Calibration curve of the proposed method for the estimation of colchicine

Conc. ( $\mu\text{g/ml}$ )	Colchicine (350nm)
	Absorbance*
10	0.103 $\pm$ 0.573
20	0.451 $\pm$ 0.0301
30	0.768 $\pm$ 0.102
40	1.112 $\pm$ 0.071
50	1.445 $\pm$ 0.272
60	1.79 $\pm$ 0.118
70	1.985 $\pm$ 0.019

\*Average of three impressions



**Figure 6.2: Calibration curve of Colchicine in PBS (pH 7.4) at 350 nm**

**Table 6.3: Statistical parameters correlated to standard curve of colchicine**

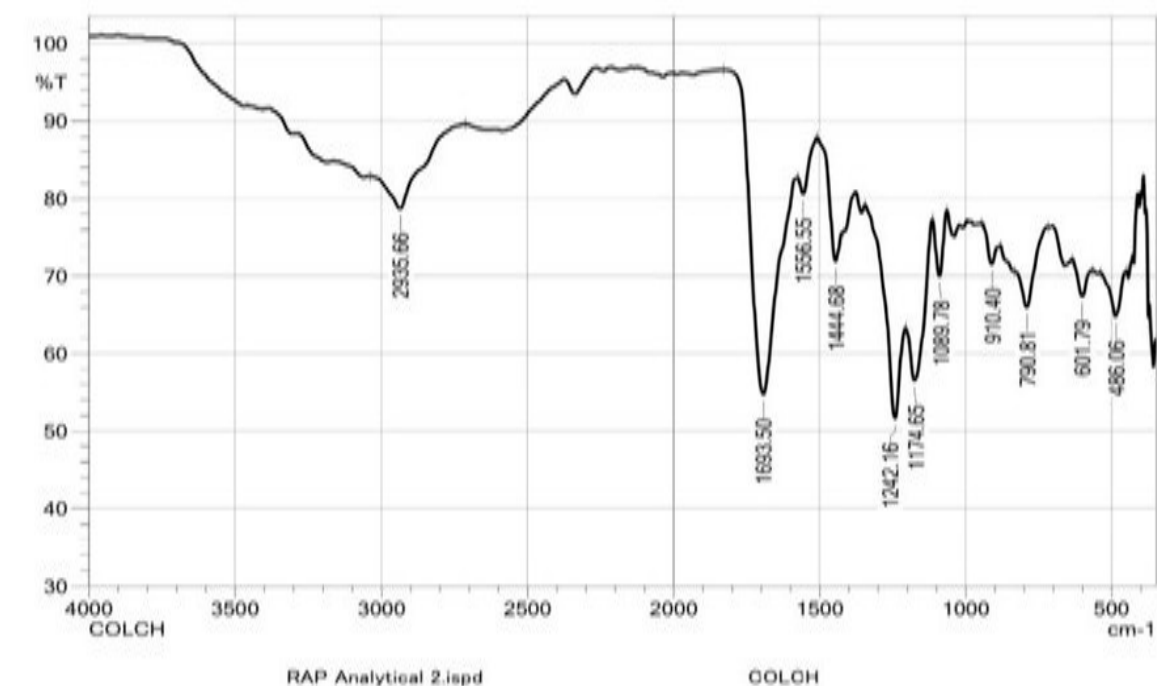
Drug	Parameters	Values
Colchicine	Concentration Range	1-5 $\mu$ g/ml
	Regression Coefficient	$R^2 = 0.9945$
	Equation of line ( $y = mx + c$ )	$y = 0.760x - 0.342$

When a best fit line to the data has y as the response, x as the level, m as the slope, and c as the intercept.

#### **FTIR, or Fourier-Transform Infrared Spectroscopy,**

The FTIR method was used to validate the drug's spectrums and those of the other components. The distinct peaks seen were derived from particular geometrical characteristics of the molecules that were observed. The drug's along with its constituents' FTIR scans are displayed in Figures 6.3 and 6.4, and Tables 6.4 and 6.5 provide the wave indices.





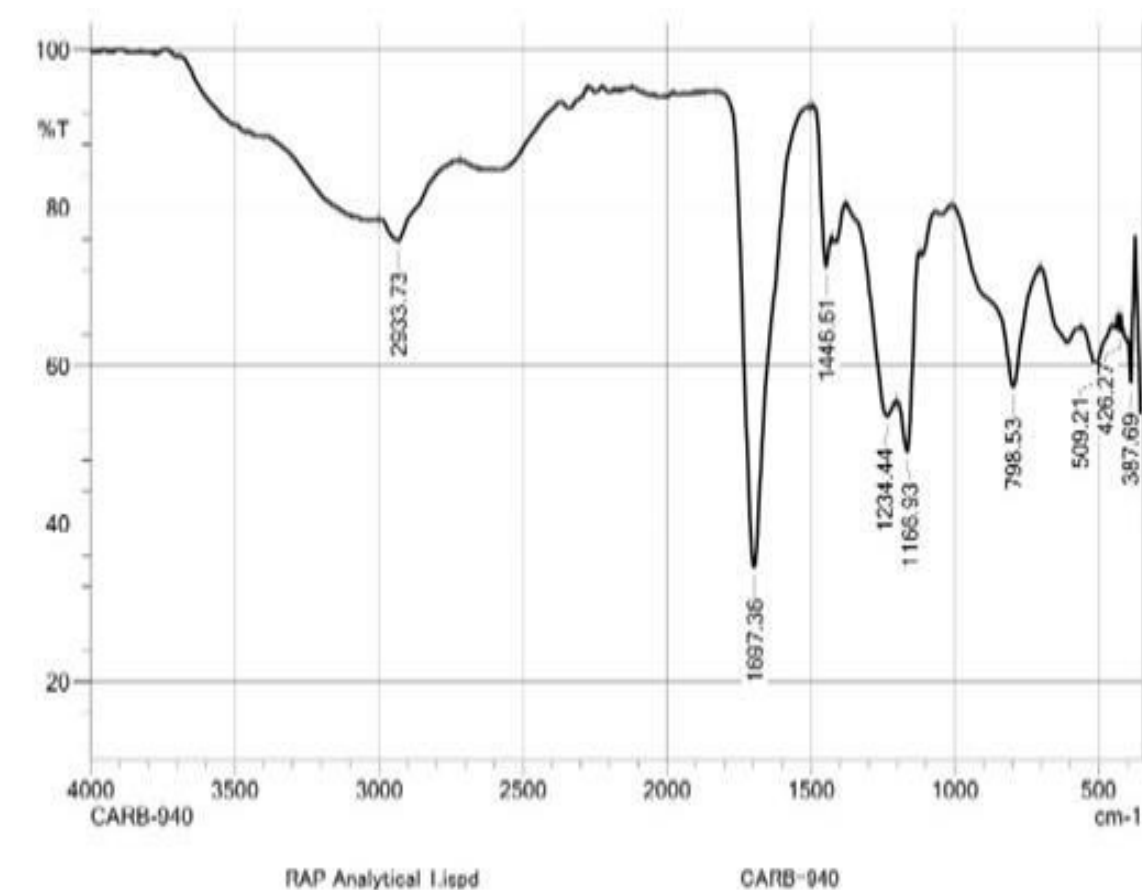
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Comment
1	486.06	64.79	5.78	540.07	451.34	2635.448	223.206	
2	601.79	67.37	4.11	636.51	567.07	2107.197	127.061	
3	790.81	65.97	6.85	835.18	719.45	3367.659	299.054	
4	910.40	71.52	3.69	947.05	881.47	1714.115	99.510	
5	1089.78	69.95	7.90	1114.86	1064.71	1314.510	203.636	
6	1174.65	56.54	11.49	1205.51	1114.86	3324.452	628.263	
7	1242.16	51.63	15.83	1344.30	1205.51	4676.404	678.397	
8	1444.68	71.87	7.24	1508.33	1419.61	1797.764	178.957	
9	1556.55	80.59	3.52	1575.84	1508.33	1088.395	91.516	
10	1693.50	54.72	34.42	1826.52	1575.84	5761.919	3139.073	
11	2935.66	78.70	6.29	3037.89	2711.92	5118.741	633.371	

Figure No. 6.3: FT-IR of Colchicine

Major peaks observed in the FTIR spectrum of Colchicine

Table No 6.4: Major peaks observed in the FTIR spectrum of Colchicine

s. no.	Wave number( $\text{cm}^{-1}$ )	Inference
1.	2935.66	-NH
2.	1693.50	-C=O
3.	1242.16	-CH <sub>3</sub>
4.	1174.65	-CH <sub>2</sub>



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Comment
1	387.69	57.85	7.66	397.34	383.63	534.071	58.598	
2	426.27	64.23	2.69	433.98	422.41	369.989	10.678	
3	509.21	59.80	5.09	563.21	453.27	4099.620	249.775	
4	798.53	57.30	17.56	1010.70	704.02	9510.108	2262.330	
5	1166.93	49.09	14.93	1203.58	1122.57	3404.696	562.973	
6	1234.44	53.51	6.39	1379.10	1203.58	5796.160	172.675	
7	1446.61	72.54	8.59	1492.90	1427.32	1209.236	198.153	
8	1697.36	34.48	59.40	1830.45	1506.41	8094.263	8053.373	
9	2933.73	75.75	4.54	3001.24	2717.70	5400.550	388.559	

Figure No. 6.4: FT-IR of Carbopol

Table No. 6.5: Major peaks observed in the FTIR spectrum of Carbopol

Sr. No.	Wave number( $\text{cm}^{-1}$ )	Inference
1.	3829.67	-OH
2.	3122	-Aromatic
3.	1511.88	-C=O

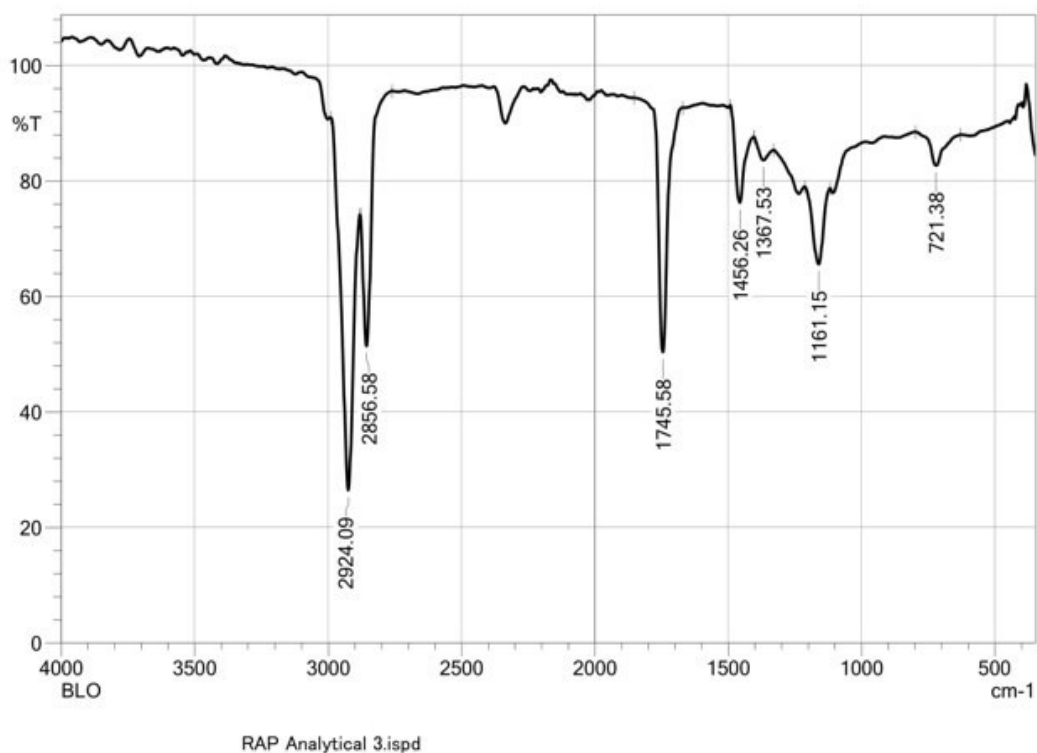


Figure No. 6.5: FT-IR of BLO

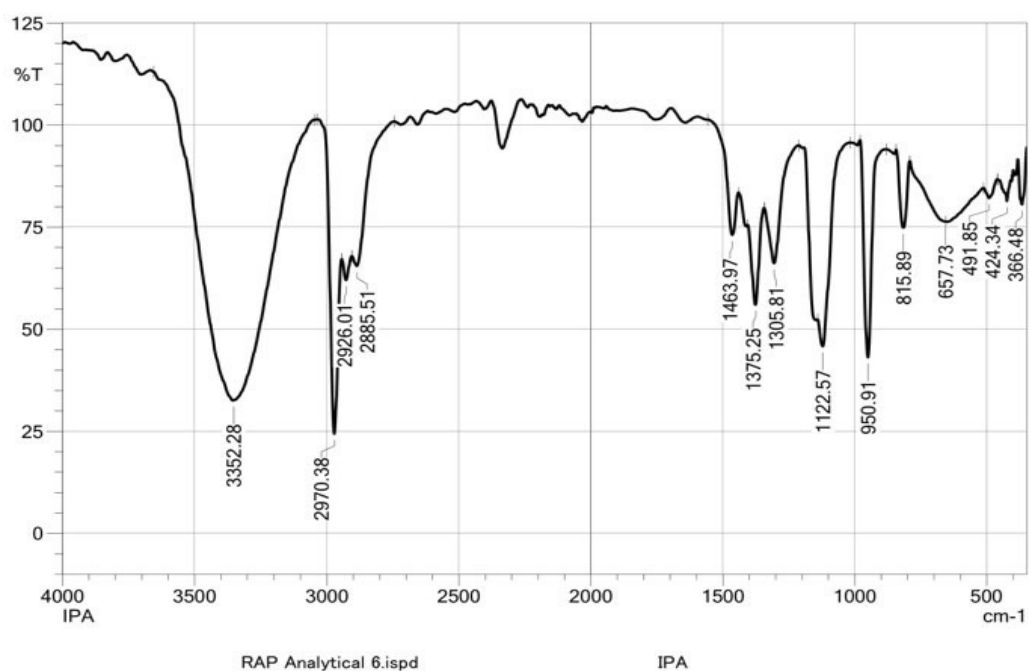


Figure No. 6.6: FT-IR of IPA

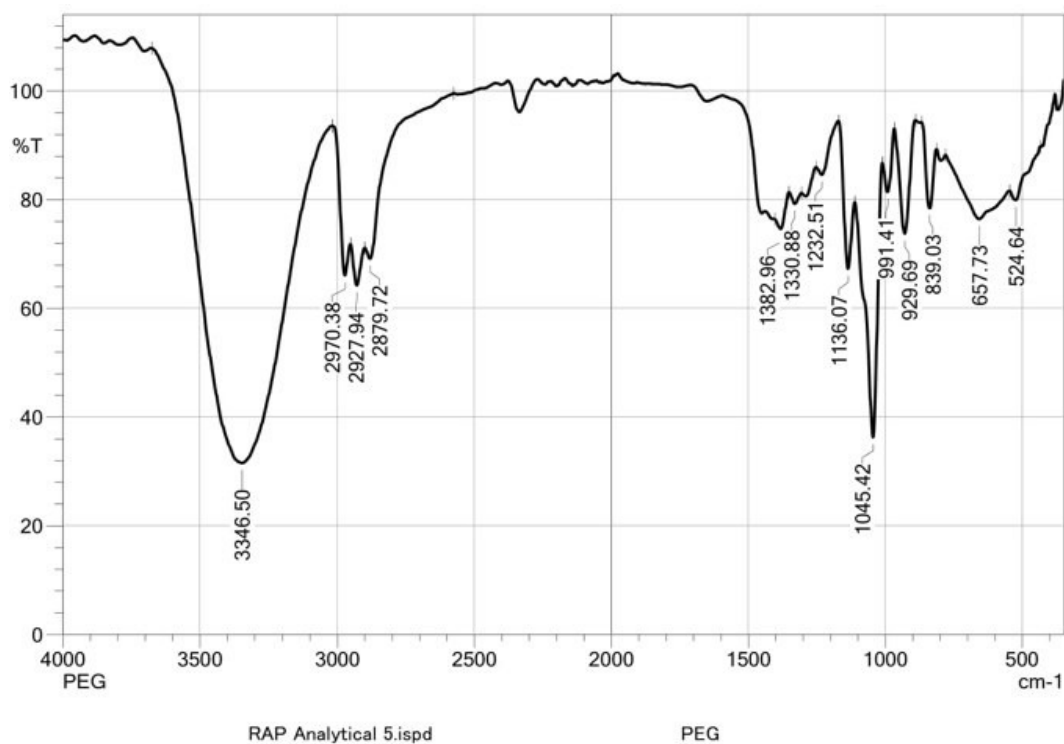


Figure No. 6.7: FT-IR of PEG

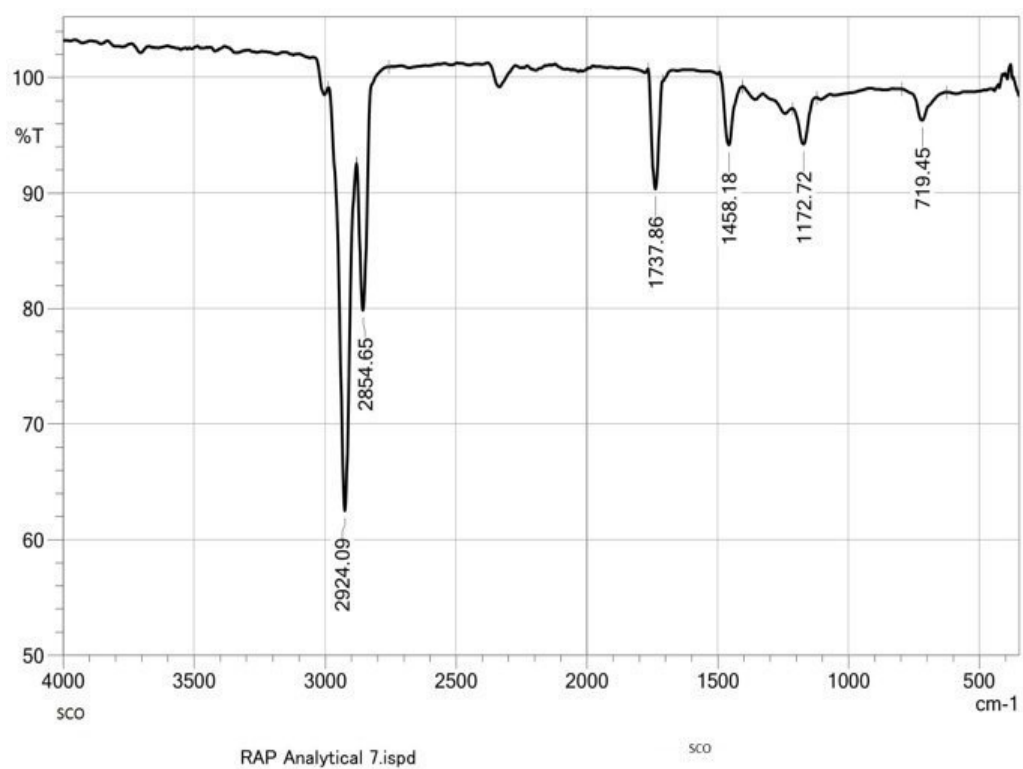
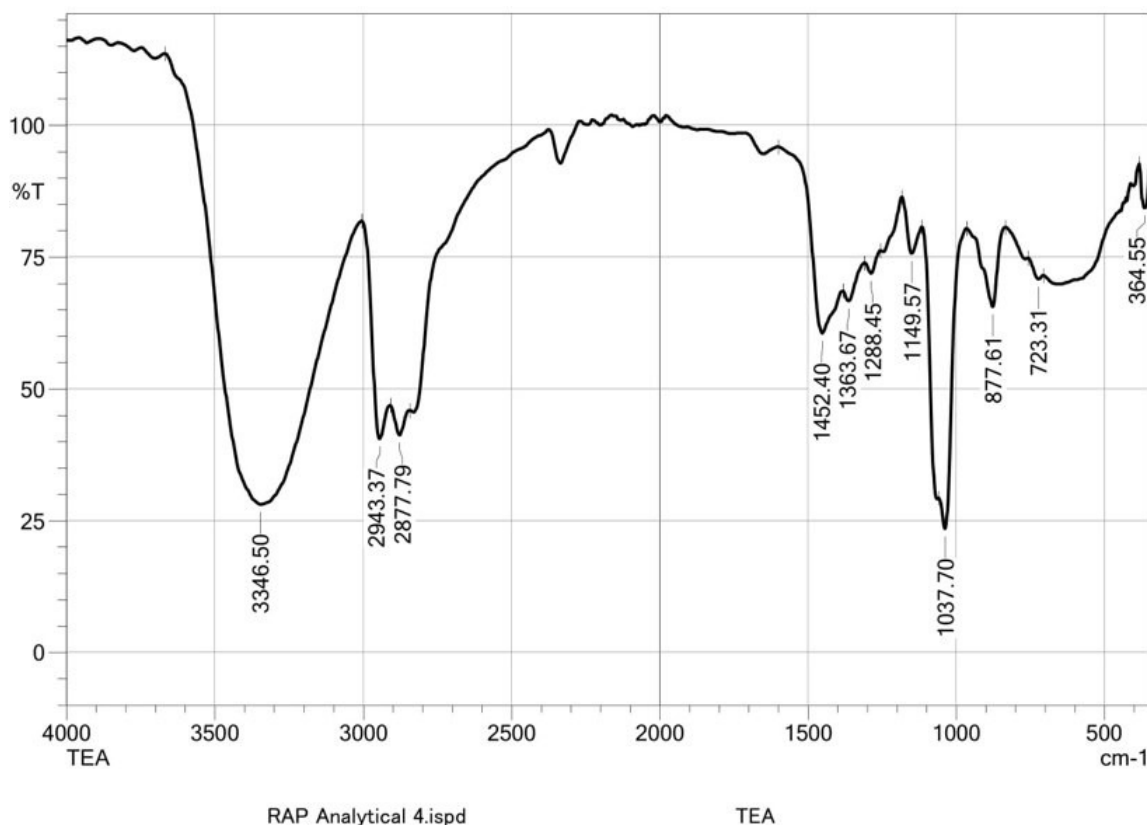


Figure No. 6.8: FT-IR of SCO



**Figure No. 6.9: FT-IR of TEA**

**Discussion:** The peak obtained indicates characteristic groups and the bonds present in the compound. Hydroquinone shows the characteristic peak at  $3829.67\text{cm}^{-1}$  due to OH broadening,  $3122\text{ cm}^{-1}$  was due to CH broadening shuddering and peak at  $1511.88\text{ cm}^{-1}$  C=C stretching vibration. Similarly for Colchicine shows the characteristic peak at  $817.49\text{ cm}^{-1}$  for C=S stretching,  $2956.55\text{ cm}^{-1}$  for C-H aromatic stretch and  $1711.04\text{ cm}^{-1}$  for C=O stretch were obtained.

FTIR spectrum for both the drugs was matched with the ordinary spectrum. It stayed observed that there are similar peaks for functional groups in the standard spectrum which was reported in pharmacopeia and the spectrum was found to be compatible for each other. This shows that the drugs are pure.

#### **LOD:**

To determine LOD firstly weight of empty dish was recorded. Then 1.5 gm of sample placed in dish and again weighed. The total weight was recorded. The dishes with sample of seeds were kept on an oven for 2hrs and weight of dish was recorded intermittently. The final

weight was taken after 2 hrs. The last value was considered as the final value of LOD. The procedure was done in triplicate to obtained precise reading.

#### Ash value:

The ash value determination done by given procedure and performed in triplicate to get standard deviation

The obtained result represented as follows.

The presented data shown that the oil shows acceptable range of values which ultimately shows that the seeds are enrich in their contents and free from any inorganic matter (Although it may present but in negligible quantity)

**Table No. 6.6: Estimation of total ash in *BLO* and *SCO***

Sr. No	Drug	Total ash	acid insoluble ash	water soluble ash value	Alcohol soluble extractable matter	Water soluble extractable matter	Unsaponifiable matter
1.	<i>BLO</i>	3.3±0.17	1.00±0.01	2.36±0.11	0.31±0.017	1.11±0.012	0.32±0.017
2.	<i>SCO</i>	4.96±0.15	1.63±0.115	7.36±0.23	0.42±0.005	1.47±0.017	2.97±0.023

#### Physicochemical Evaluation of BLO and SCO:

**Table No 6.7: Physicochemical Evaluation of BLO and SCO**

Parameter	SCO	BLO
Saponification value (mg/g)	167 ± 1.52	262 ±0.58
Iodine value	167.88 ± 1.45	249.9 ±1.12
Acid value (mg)	5.50 ± 0.04	2.04 ±0.05
Ester value (mg)	161.50 ± 0.25	259.96 ± 0.78
% FFA	2.76 ± 0.11	8.83 ±0.06
% of Glycerol	1.02 ± 0.05	14.2 ± 0.10

From above analysis it was found that the saponification values obtained for both the oils were within the range of their standard values. It can be said that the saponification value of *Buchananialanzan* possesses high saponification value. The lower acid value shows low rancidity of oil. But higher value which was found in the case of *simmond siachinesis* shows more rancid than other one. The percent free fatty acid and glycerol varied from 2.26% to 8.83% and 1.02% to 14.2% respectively.

#### Acute Pharmacological study:

The OECD (TG 423) test standard and toxicological testing was applied to measure the acute poisoning of oil. Albino mice of both sexes were given unlimited access to water but fasted during the daytime. Three distinct pairs of mice were freely assigned to each other. Water was given to the control group. OBL and OSC, the test materials, were administered orally to Groups I through III at a dose of 5g/kg.

#### Clinical observation

During the time of dose until the conclusion of the trial, general observations of each animal were used to assess the behavior of each one. Any alterations or irregularities noted could be a sign of toxicity. The test dogs' demeanor did not significantly change before or following the oral dose of oil was administered, regardless of the dosage level. The two oils under investigation's clinical observations are listed in Table No. 6.8.

Table No 6.8. Evaluation of LD<sub>50</sub> of oil obtained from seeds of *Buchananialanzan* and *Simmondsiachinesis* (linn.) Dose 2000mg/kg BW, Species: Albino mice: Male and Female Date 23/03/2018, duration:15 days, TRE- Tremor, CON- Convulsion, SALI-Salivation, Diah- Diarrhea, LET-Lethargy) (×= Negative, √= Positive), BLO= Oil of *Buchananialanzan* and SCO=oil of *Simmondsiachinesis*

**Table No 6.8: Clinical observation of oils**

Sr. No.	Oil	Toxicit Study		Time of death	Skin	Re sp.	Eyes	CNS	Observation					
		Onset	Stop						Tre	Sali	Diarh	Let	Com	Sleep
1	BLO	×	×	×	×	×	×	×	×	×	×	×	×	×
2	SCO	×	×	×	×	×	×	×	×	×	×	×	×	×

**Body Weight Changes**

Body weight is a crucial metric for tracking an animal's health. Loss of body is often the first sign that a negative consequence is beginning. A dosage is deemed hazardous if it results in a 10% or greater drop in body weight. It is thought to be the dose that, whether or not it is accompanied by other changes, has the least harmful effect. As contrasted to the previous 0 day, none of the animals in both groups that were treated showed a discernible loss in physique over the course of the 14 days, suggesting no adverse effects.

**Loss on drying:****Drug-Excipients compatibility study:****Table No. 6.9: Comparative data of Preformulation studies**

Sr. No.	Ingredients	Ratio	Days	Observation
1.	Carbopol 934 + BLO	1:1	30days	No change observe in mixture
2.	Carbopol 934+ SCO	1:1	30days	No change in mixture
3.	Carbopol 934+ IPA	1:1	30days	No change in mixture
4.	Carbopol 934+ TEA	1:1	30days	No change in mixture
5.	Carbopol 934+ PEG	1:1	30days	No change in mixture
6.	IPA+ TEA	1:1	30days	No change in mixture
7.	IPA + BLO	1:1	30days	No change in mixture
8.	IPA + SCO	1:1	30days	No change in mixture
9.	IPA + PEG	1:1	30days	No change in mixture
10.	TEA+ BLO	1:1	30days	No change in mixture
11.	TEA + SCO	1:1	30days	No change in mixture
12.	TEA + PEG	1:1	30days	No change in mixture
13.	PEG + BLO	1:1	30days	No change in mixture
14.	PEG + SCO	1:1	30days	No change in mixture
15.	Methyl paraben + Carbopol 934	1:1	30days	No change in mixture
16.	Methyl paraben + IPA	1:1	30days	No change in mixture
17.	Methyl paraben + TEA	1:1	30days	No change in mixture
18.	Methyl paraben + PEG	1:1	30days	No change in mixture



19.	Methyl paraben + BLO	1:1	30days	No change in mixture
20.	Methyl paraben + SCO	1:1	30days	No change in mixture
21.	Propyl paraben + IPA	1:1	30days	No change in mixture
22.	Propyl paraben + TEA	1:1	30days	No change in mixture
23.	Propyl paraben + PEG	1:1	30days	No change in mixture
24.	Propyl paraben + BLO	1:1	30days	No change in mixture
25.	Propyl paraben +SCO	1:1	30days	No change in mixture
26.	Colchicine + Carbopol 934	1:1	30days	No change in mixture
27.	Colchicine + IPA	1:1	30days	No change in mixture
28.	Colchicine + TEA	1:1	30days	No change in mixture
29.	Colchicine + PEG	1:1	30days	No change in mixture
30.	Colchicine +BLO	1:1	30days	No change in mixture
31.	Colchicine + SCO	1:1	30days	No change in mixture
32.	Colchicine + Methyl araben	1:1	30days	No change in mixture
33.	Colchicine + Propyl paraben	1:1	30days	No change in mixture

### Discussion:

Drug excipient compatibility study was performed at laboratory level by keeping above combinations in desiccator in the presence of saturated solution of KCL for 30 days. After said periods the sample were observed and data have been shown in above table as there was no significant changes observed in the studies.

### Evaluation of formulations

Various different gel formulation was developed and in order to optimize factorial design was utilized wherein  $3^2$  design was employed for screening of significant formulation and process variables which were involved in the development of gel which is 3 level 2 factor design. Independent variable selected amount of Carbopol 940, amount of permeation enhancer.

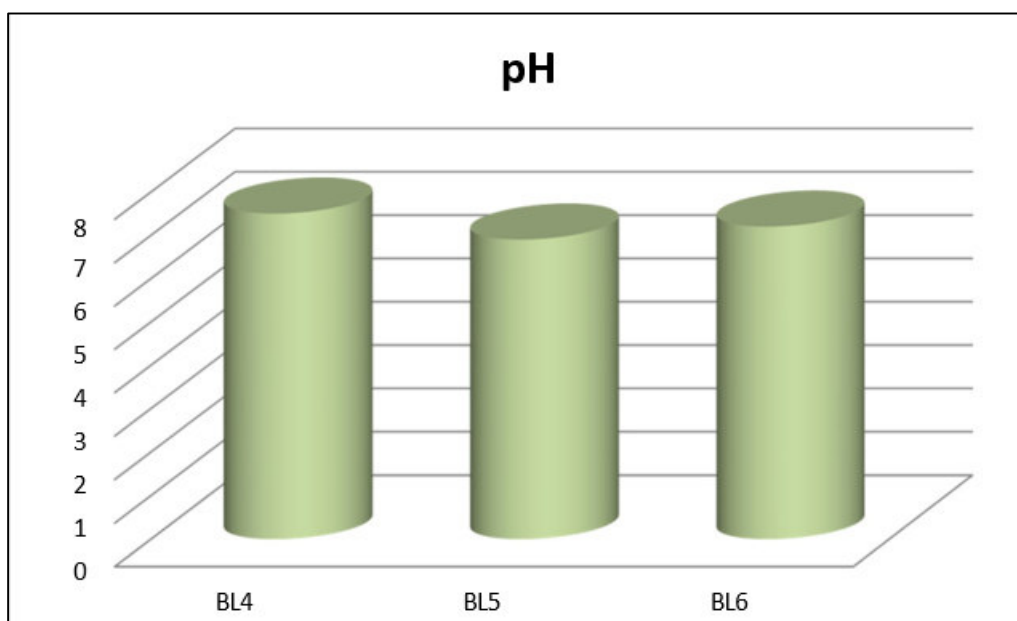
Design of experiment yielded out 09 formulations with different values of the independent variables to be selected at both low and high level.

The evaluation of formulation was done by evaluating their pH, Spreadability, viscosity, Drug content, skin irritation study and organoleptic characters such as appearance.

#### Determination of pH:

**Table No. 6.10: pH values of gel formulations containing *Buchananialanzan* oil**

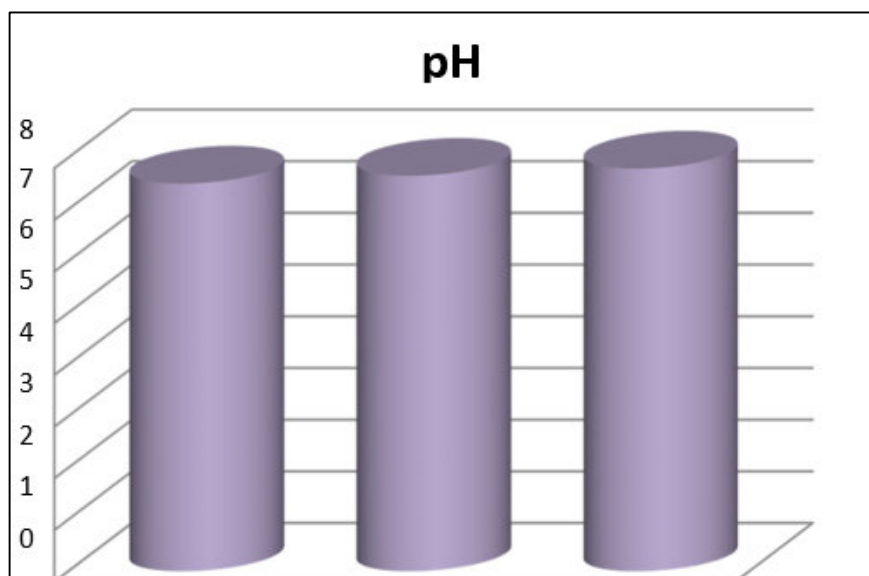
Formulation	pH
BL1	6.70±0.04
BL2	7.25±0.06
BL3	6.85±0.03
BL4	7.5±0.015
BL5	6.90±0.045
BL6	7.25±0.053
BL7	7.30±0.05
BL8	7.2±0.04
BL9	7.10±0.02



**Figure No. 6.10: pH values of gel formulations containing *Buchananialanzan* oil**

Table No. 6.11: pH values of gel formulations containing *Simmondsiachinesis* oil

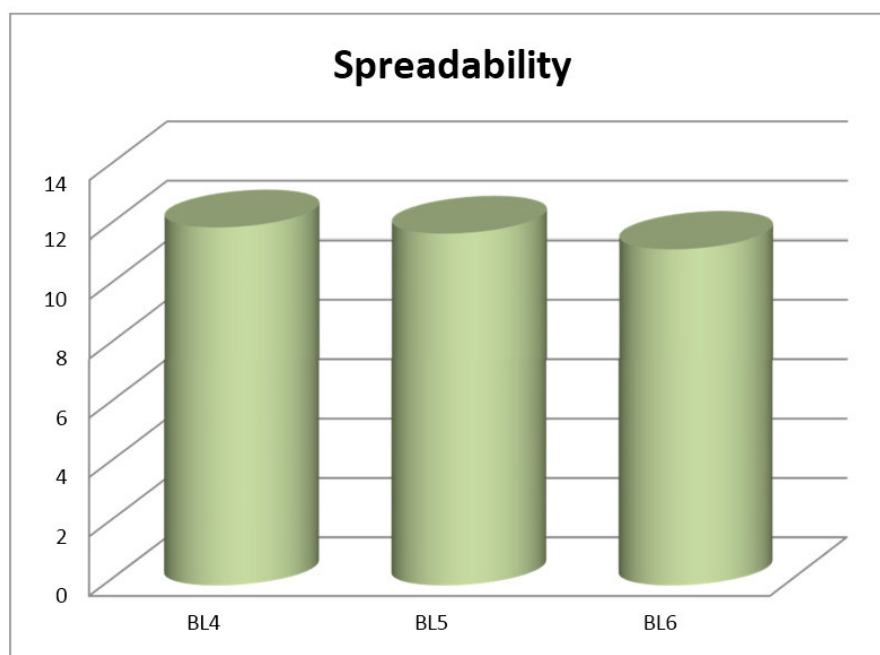
Formulation	pH
SC1	7.79±0.012
SC2	7.95±0.02
SC3	7.79±0.017
SC4	7.50±0.011
SC5	7.65±0.012
SC6	7.79±0.017
SC7	7.65±0.02
SC8	7.65±0.02
SC9	7.50±0.05

Figure No. 6.11: pH values of gel formulations containing *Simmondsiachinesis* oil

The above table shows values obtained for the different gel formulations. It was found that the pH of formulations fall under range of 6.70 to 7.95 which shows its acceptability towards application to skin as all the values are close or near neutral pH.

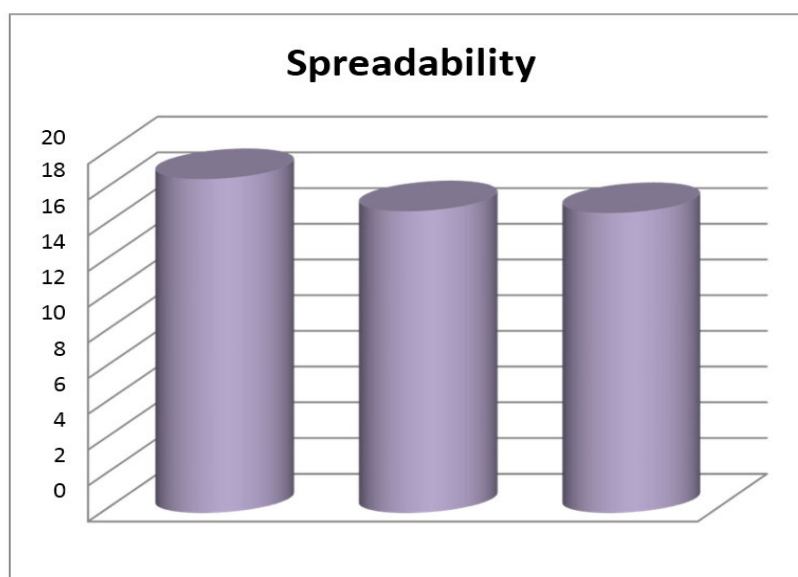
**Determination of Spreadability:****Table No. 6.12: Spread ability values of gel formulations containing *Buchananialanzan* oil**

Formulation	Spreadability
BL1	0
BL2	0
BL3	12.94±0.06
BL4	12.05±0.05
BL5	11.84±0.04
BL6	11.33±0.04
BL7	11.46±0.05
BL8	10.52±0.02
BL9	10.43±0.04

**Figure No. 6.12: Spreadability values of gel formulations containing *Buchananialanzan* oil**

**Table No. 6.13: Spreadability values of gel formulations containing *Simmondsiachinesis* oil**

Formulation	Spreadability
SC1	0
SC2	0
SC3	21.39±0.04
SC4	18.69±0.07
SC5	16.89±0.02
SC6	16.79±0.05
SC7	16.35±0.03
SC8	11.01±0.06
SC9	9.65±0.03



**Figure No. 6.13: Spreadability values of gel formulations containing *Simmondsiachinesis* oil**

The value of Spreadability shows that the prepared formulations are easily spreadable except formulation 1 and 2 of respective oil. Higher the value of carbopol shows the resistance in application to the skin hence higher concentration of carbopol gel formulations may not be suitable to apply on skin. In short Spread ability decrease with the increase in

the meditation of the polymer The Spread ability is considered as one of the central as shows the behavior of gel which approaches out from the tube.

**Determination of Medicine content:**

**Table No. 6.14. Drug content values of gel formulations containing *Buchananialanzan* oil**

Formulation	Drug content (%)
BL1	98± 0.58
BL2	98± 0.76
BL3	97± 0.5
BL4	97.5± 0.29
BL5	98± 0.58
BL6	98.5±0.30
BL7	97±0.76
BL8	97.5± 0.28
BL9	96±0.57

**Table No. 6.15: Drug content values of gel formulations containing *Simmondisiachinesis* oil**

Formulation	Drug content (%)
SC1	98±0.76
SC2	97± 0.5
SC3	97.5± 0.29
SC4	98± 0.58
SC5	98± 0.59
SC6	97.5± 0.77
SC7	97± 0.29
SC8	98.5± 0.28
SC9	98± 0.57

Drug content of formulated gels shows acceptable range as it may be consider that the formulations contents equal amount of drug in it. Which shows that the drug s present near about 100% in each formulation

**Skin irritation test:**

**Table No. 6.16: Skin irritation study of gel formulations containing Buchanania lanzan oil**

Formulation Code	Skin irritation score
BL1	1
BL2	1
BL3	0.5
BL4	0.5
BL5	0
BL6	0
BL7	2
BL8	1.5
BL9	1.5

**Table No 6.17: Skin irritation study of gel formulations containing Simmondsia chinensis oil**

Formulation Code	Skin irritation score
SC1	0
SC2	1.5
SC3	1
SC4	0.5
SC5	0
SC6	0.5
SC7	1.5
SC8	2
SC9	2

Prepared gel formulations were subjected to skin irritation test and allotted score depending on the reaction shown on the skin of volunteers the score below 2 shows acceptability of gel formulations to be applied on skin.

#### AFM-Carbopol control gel-without drug (F1) Area Roughness --

Area	2.52nm <sup>2</sup>
Sa	330.26nm
Sq	410.79nm
Sy	2136.9nm
Sp	1013.5nm
Sv	-1123.4nm
Sm	-18.626fm

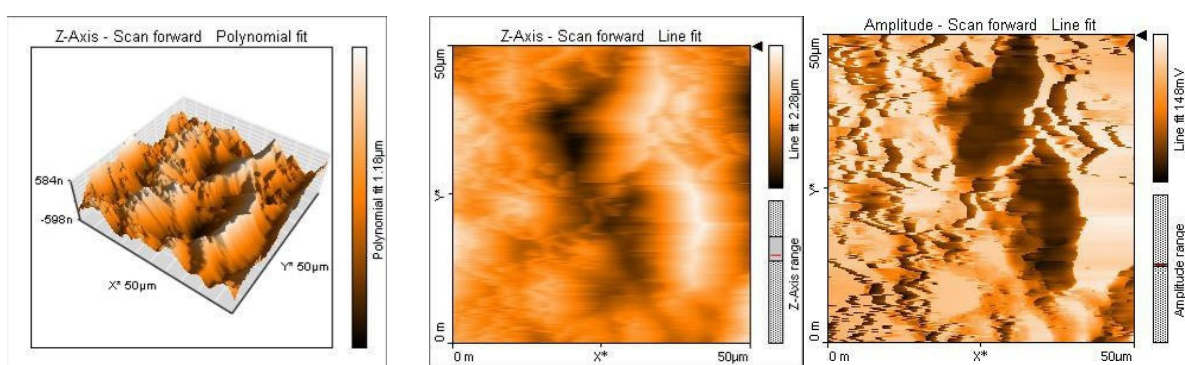


Figure No. 6.14: AFM-Carbopol control gel-without drug (F1)

#### AFM-Carbopol control gel-without drug (F2)

Area	2.52nm <sup>2</sup>
Sa	205.25nm
Sq	254.79nm
Sy	1611.8nm
Sp	866.97nm
Sv	-744.86nm
Sm	-18.626fm



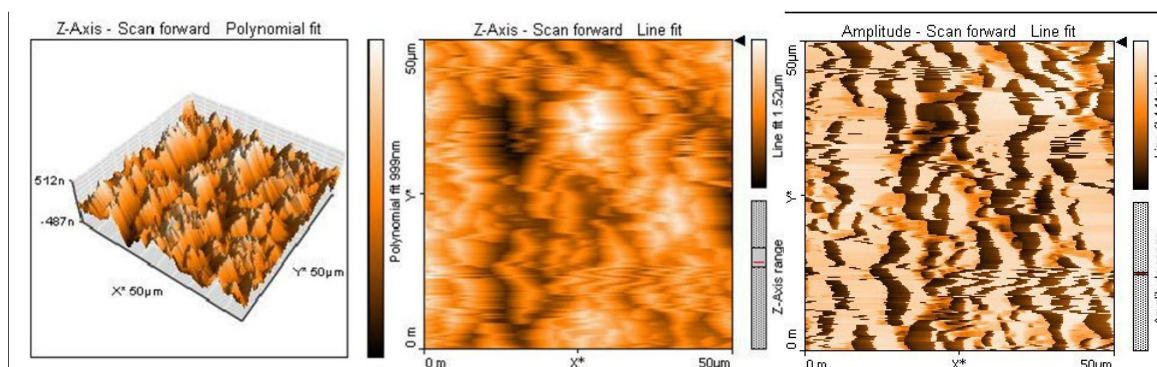


Figure No. 6.15: AFM-Carbopol control gel-without drug (F2)

AFM-Carbopol control gel-without drug (F3)

Area	2.52nm <sup>2</sup>
Sa	247.07nm
Sq	312.08nm
Sy	1754.3nm
Sp	875.95nm
Sv	-878.3nm
Sm	-18.626fm

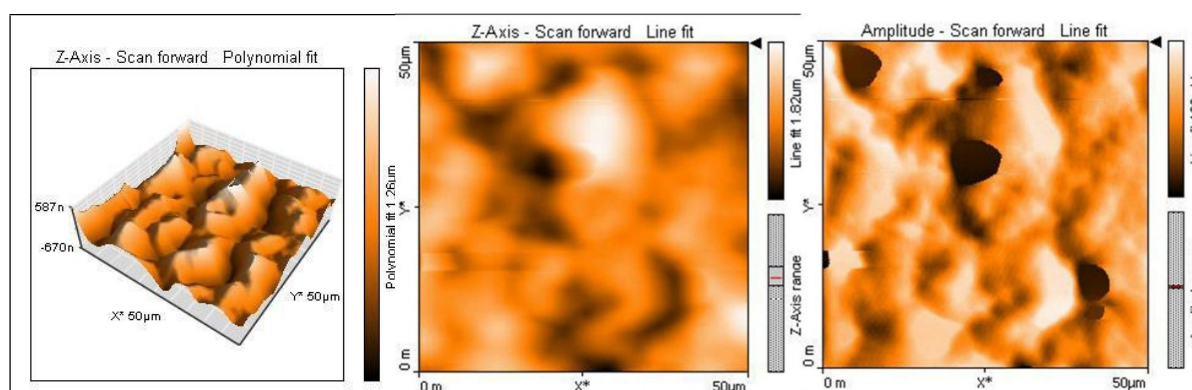


Figure No. 6.16: AFM-Carbopol control gel-without drug (F3)

## AFM-Carbopol gel (F1)

Area	2.52nm <sup>2</sup>
Sa	397.01nm
Sq	502.88nm
Sy	4.7877μm
Sp	1962.6nm
Sv	-2825.1nm
Sm	-18.629fm

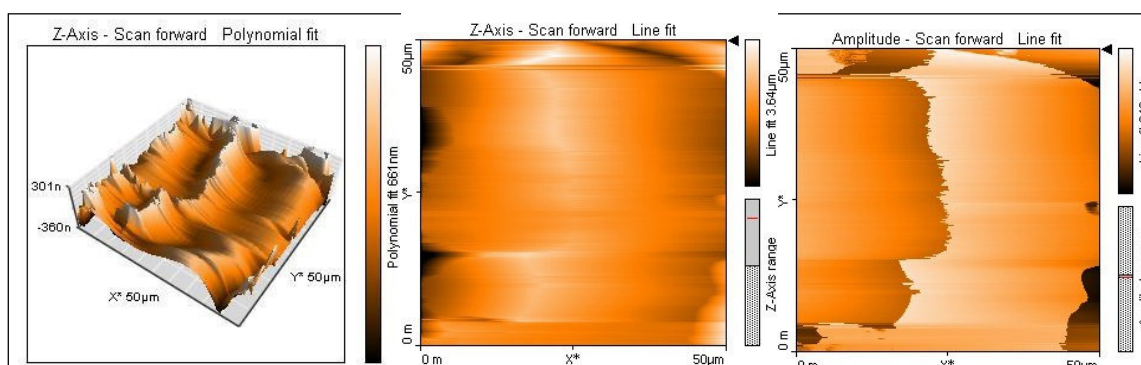


Figure No. 6.17: AFM-Carbopol gel (F1)

## AFM-Carbopol gel (F2)

Area	2.52nm <sup>2</sup>
Sa	609.05nm
Sq	766.5nm
Sy	5.4884μm
Sp	2646.9nm
Sv	-2841.5nm
Sm	-20.339fm

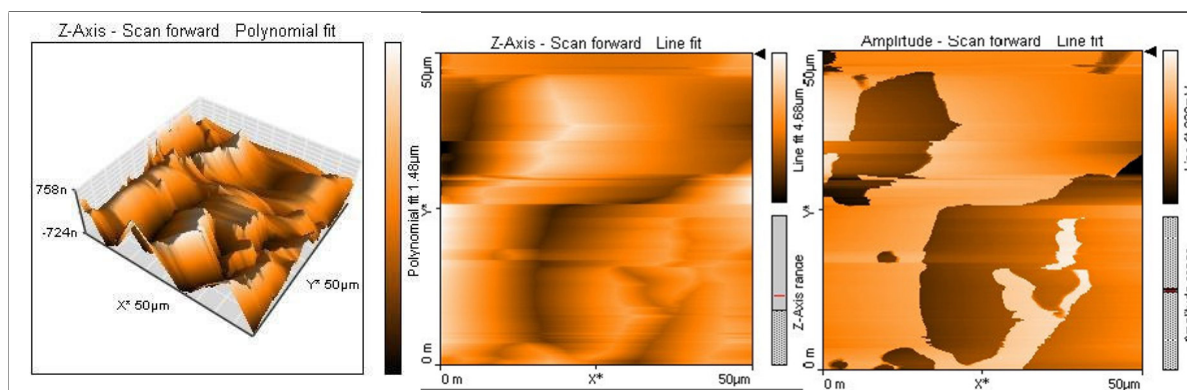


Figure No. 6.18: AFM-Carbopol gel (F2)

## AFM-Carbopol gel (F3)

Area	2.52nm <sup>2</sup>
Sa	892.29nm
Sq	1298.7nm
Sy	7.5323μm
Sp	3.4495μm
Sv	-4.0828μm
Sm	-18.626fm

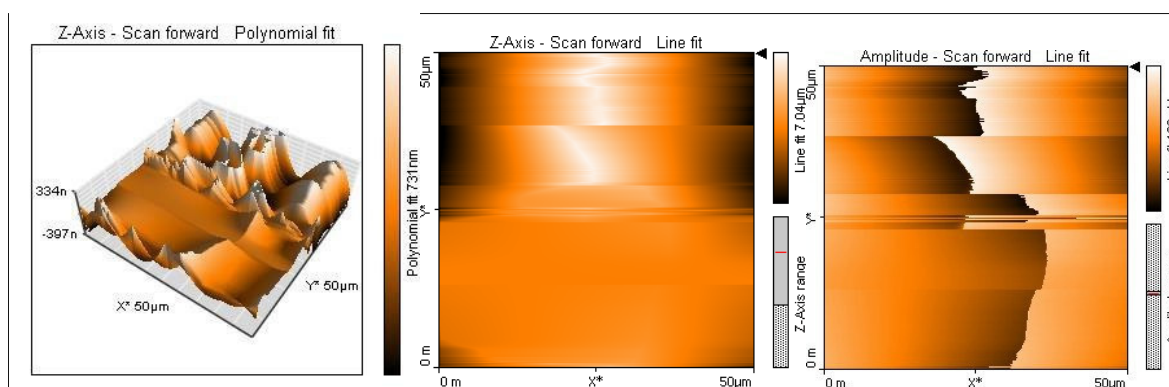
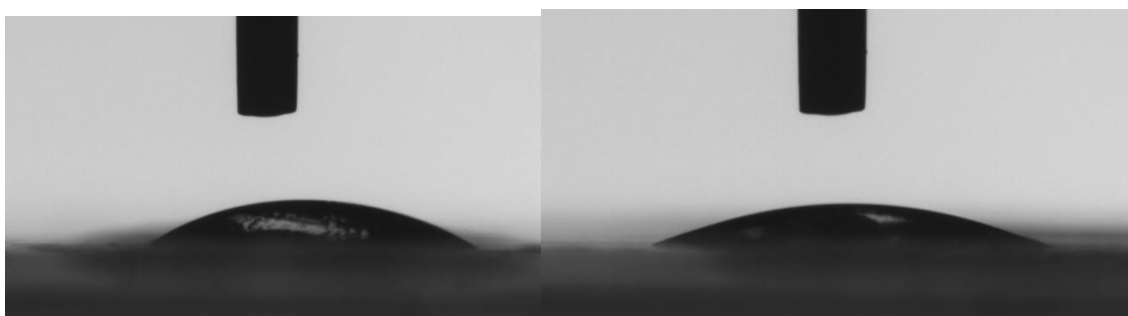


Figure No. 6.19: AFM-Carbopol gel (F3)

**CONTACT ANGLE**

Using calculated molecular descriptions and statistical computation, three approaches were devised for modeling and predicting water contact angle for a heterogeneous series of medications. Theoretically molecules pertaining to structure and physiological attributes were calculated for a set of 34 chemicals, each having an observed actual connection to water inclination. Following that, partial least squares projections were used to the classifiers in order to analyze latent hierarchies. In order to theoretically forecast the water contact angle for structurally heterogeneous supplies, several multidimensional models were developed. The models' individual R<sup>2</sup> and Q<sup>2</sup> values ranged from 0.57 to 0.80 and 0.42 to 0.66. The simulations offered helpful information about the molecular and physicochemical features that influence material angle of interaction with water and had a slight predicted capacity.

**Contact Angle of DI**

**Figure No. 6.20: Contact angle of Drop 1 and 5**

Run-No	CA(M)[°]	IFT[mN/m]	Err[μm]	Vol[μL]
1	34.5929298	0	-999	-999
2	29.2261944	0	-999	-999

## The Contact Angle of E

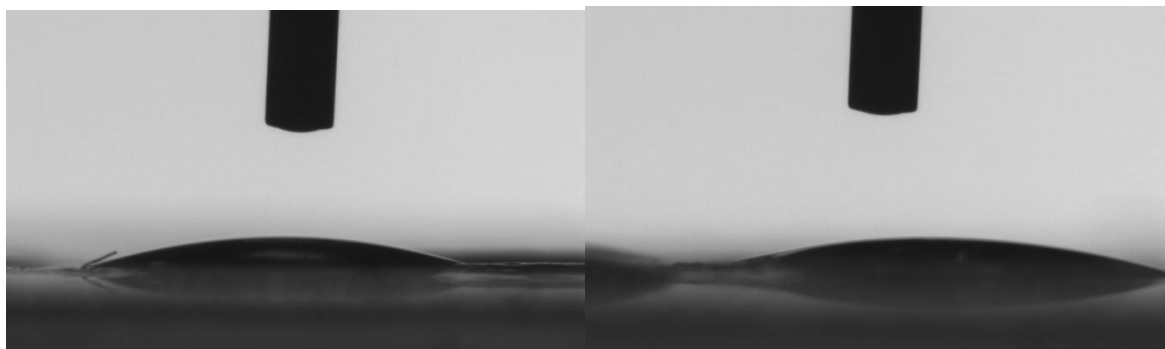


Figure No. 6.21: Contact angle of Drop 10 and 11

Run-No	CA(M)[°]	IFT[mN/m]	Err[μm]	Vol[μL]
1	18.4725018	0	-999	-999
2	17.5838318	0	-999	-999

## Contact angle of F

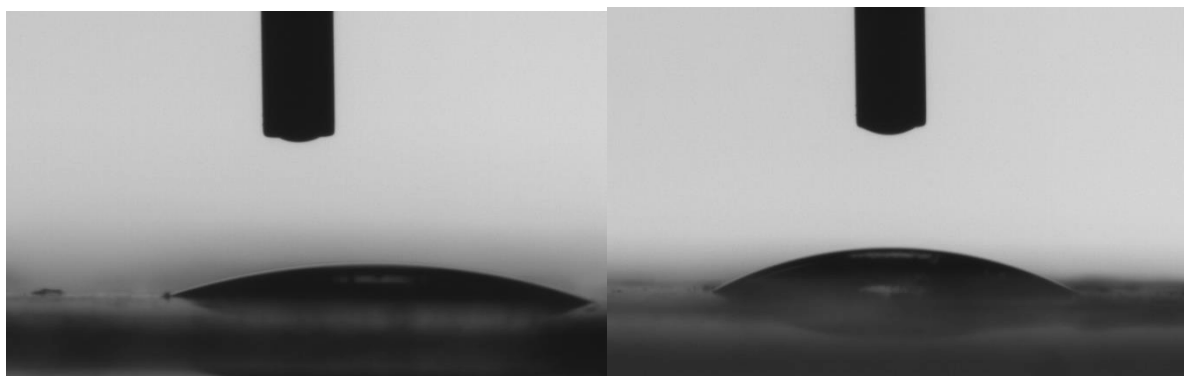
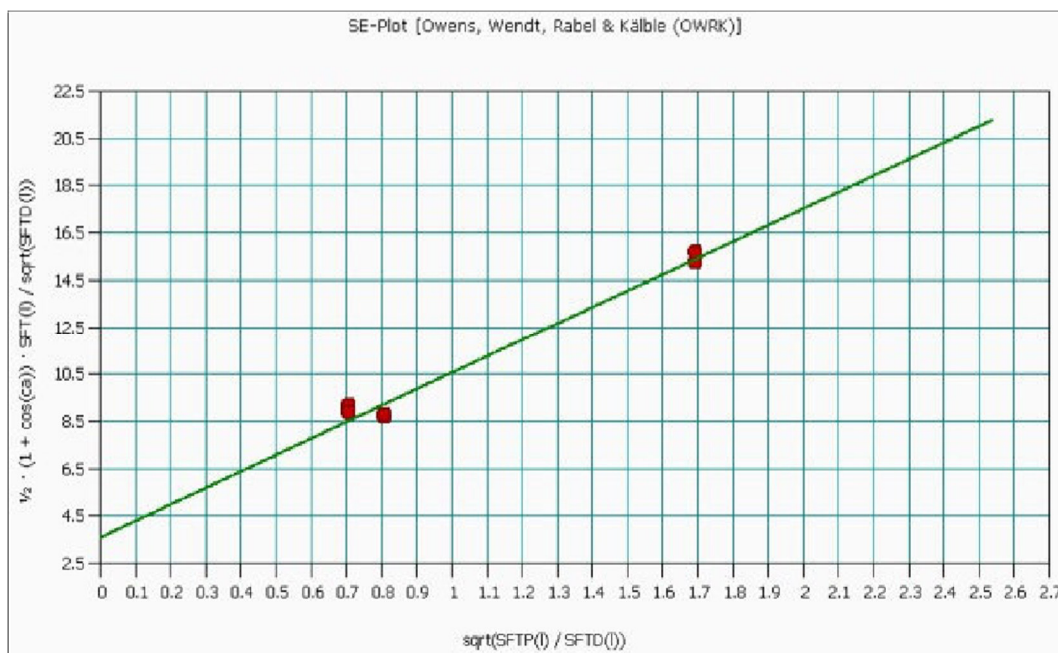


Figure No. 6.22: Contact angle of Drop 8 and 9

Run-No	CA(M)[°]	IFT[mN/m]	Err[μm]	Vol[μL]
1	19.1353989	0	-999	-999
2	27.5673218	0	-999	-999



### DESIGN EXPERIMENT

To enhance comprehension of the intricate relationships between the independent and dependent variables, Design Expert® software was used to create fluctuation diagrams, 2D contouring diagrams, and a three-dimensional reply interface maps. These graphical representations provided an insightful depiction of how changes in variables influence the responses.

### Plots of the BLO's 3D response surface, 2D contour, and perturbations

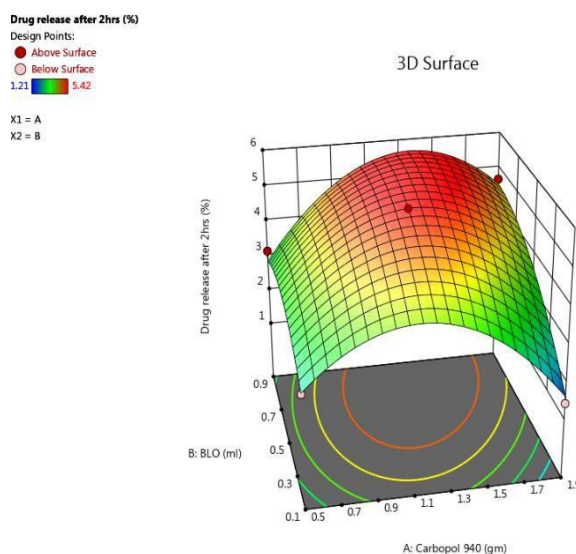


Figure No. 6.23: 3D Image of BLO after 2 hrs.



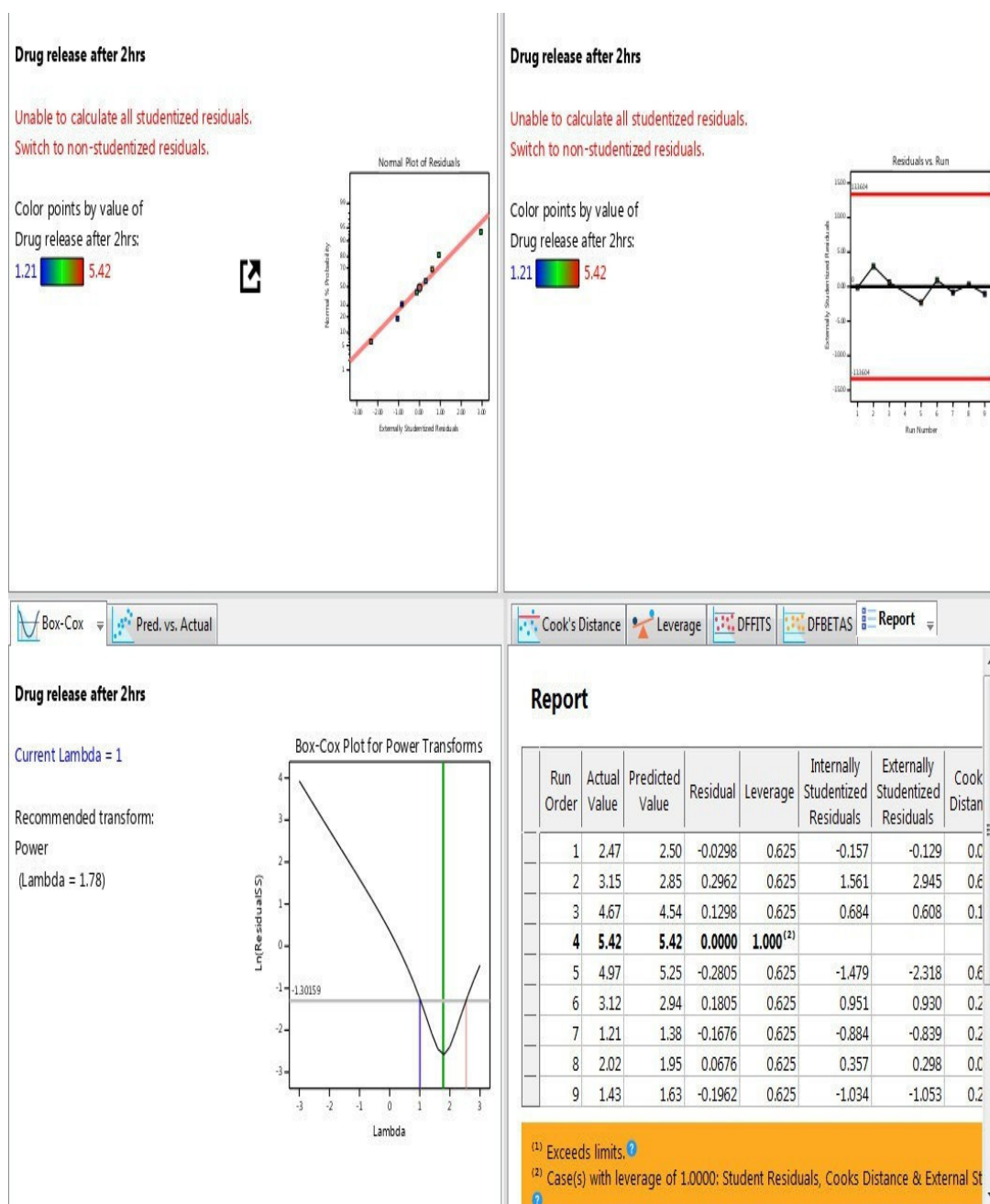


Figure No. 6.24: Diagnostic analysis of BLO after 2 hrs.

## ANOVA for Quadratic model

Response 2: Drug release after 2hrs

Source	Sum of Squares	df	Mean Square	F-value	p-value	
<b>Model</b>	18.95	5	3.79	39.50	0.0061	significant
A-Carbopol 940	0.3303	1	0.3303	3.44	0.1606	
B-BLO	5.34	1	5.34	55.66	0.0050	
AB	1.64	1	1.64	17.08	0.0257	
A <sup>2</sup>	10.25	1	10.25	106.89	0.0019	
B <sup>2</sup>	1.28	1	1.28	13.31	0.0355	
<b>Residual</b>	0.2878	3	0.0959			
<b>Cor Total</b>	19.24	8				

Factor coding is **Coded**.Sum of squares is **Type III - Partial**

The **Model F-value** of 39.50 implies the model is significant. There is only a 0.61% chance that an F-value this large could occur due to noise.

**P-values** less than 0.0500 indicate model terms are significant. In this case B, AB, A<sup>2</sup>, B<sup>2</sup> are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

## Fit Statistics

<b>Std. Dev.</b>	0.3097	<b>R<sup>2</sup></b>	0.9850
<b>Mean</b>	3.16	<b>Adjusted R<sup>2</sup></b>	0.9601
<b>C.V. %</b>	9.80	<b>Predicted R<sup>2</sup></b>	NA <sup>(1)</sup>
		<b>Adeq Precision</b>	15.9838

<sup>(1)</sup> Case(s) with leverage of 1.0000: Pred R<sup>2</sup> and PRESS statistic not defined.

**Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 15.984 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients Coded Equation Actual Equation

## Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	5.42	1	0.3097	4.43	6.41	
A-Carbopol 940	0.2032	1	0.1095	-0.1453	0.5517	1.0000
B-BLO	0.8170	1	0.1095	0.4685	1.17	1.0000
AB	0.6400	1	0.1549	0.1471	1.13	1.0000
A <sup>2</sup>	-1.88	1	0.1816	-2.46	-1.30	1.68
B <sup>2</sup>	-0.6625	1	0.1816	-1.24	-0.0846	1.68

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-collinearity, the higher the VIF the more severe the correlation of factors. For example, VIFs less than 10 are tolerable.

Figure No. 6.25: ANOVA of BLO after 2 hrs.

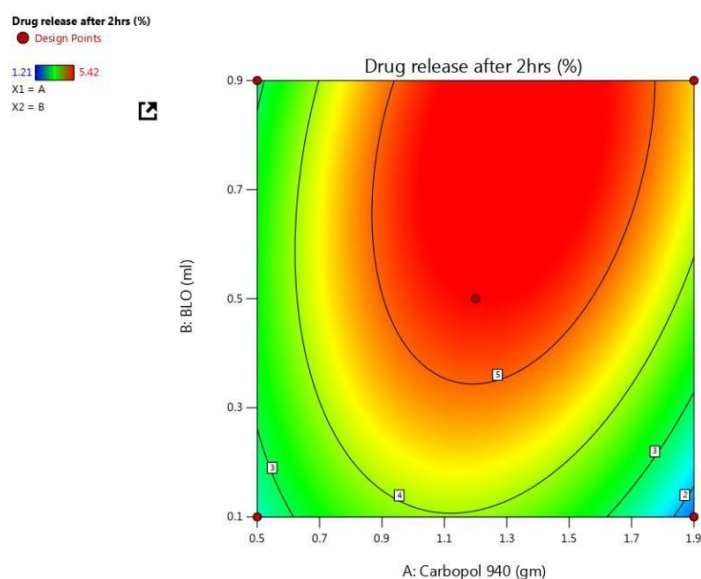


Figure No. 6.26: Conour of BLO after 2 hrs.



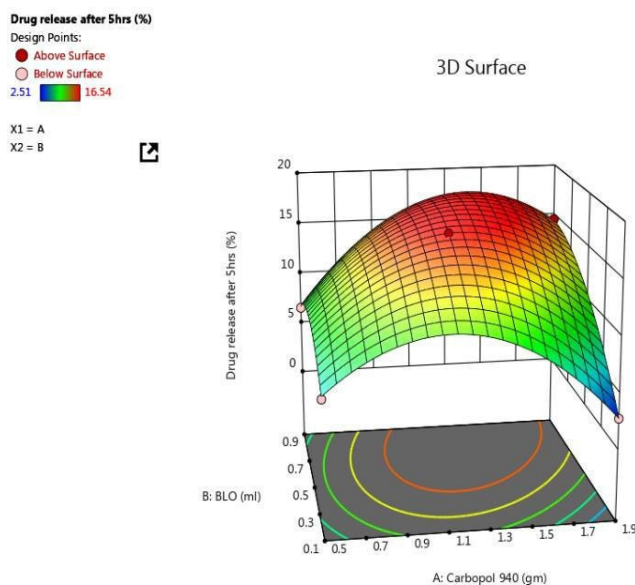


Figure No. 6.27: 3D Image of BLO after 5 hrs.

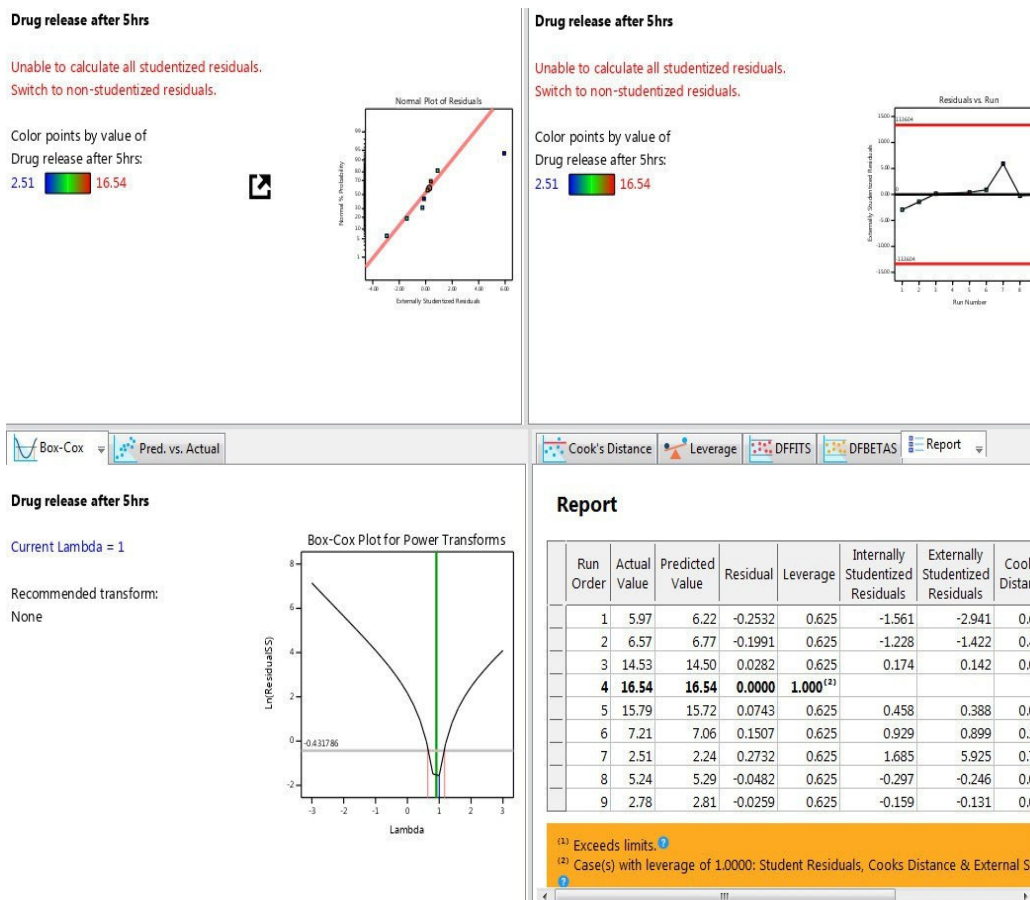


Figure No. 6.28: Diagnostic analysis of BLO after 5 hrs.

## ANOVA for Quadratic model

Response 3: Drug release after 5hrs

Source	Sum of Squares	df	Mean Square	F-value	p-value	
<b>Model</b>	244.91	5	48.98	698.36	< 0.0001	significant
A-Carbopol 940	9.31	1	9.31	132.76	0.0014	
B-BLO	74.93	1	74.93	1068.36	< 0.0001	
AB	31.08	1	31.08	443.13	0.0002	
A <sup>2</sup>	118.74	1	118.74	1692.91	< 0.0001	
B <sup>2</sup>	19.31	1	19.31	275.28	0.0005	
<b>Residual</b>	0.2104	3	0.0701			
<b>Cor Total</b>	245.12	8				

Factor coding is Coded.

Sum of squares is Type III - Partial

The **Model F-value** of 698.36 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

**P-values** less than 0.0500 indicate model terms are significant. In this case A, B, AB, A<sup>2</sup>, B<sup>2</sup> are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

## Fit Statistics

<b>Std. Dev.</b>	0.2648	<b>R<sup>2</sup></b>	0.9991
<b>Mean</b>	8.57	<b>Adjusted R<sup>2</sup></b>	0.9977
<b>C.V. %</b>	3.09	<b>Predicted R<sup>2</sup></b>	NA <sup>(1)</sup>
		<b>Adeq Precision</b>	66.1458

<sup>(1)</sup> Case(s) with leverage of 1.0000: Pred R<sup>2</sup> and PRESS statistic not defined.

**Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 66.146 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients Coded Equation Actual Equation

## Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	16.54	1	0.2648	15.70	17.38	
A-Carbopol 940	1.08	1	0.0936	0.7809	1.38	1.0000
B-BLO	3.06	1	0.0936	2.76	3.36	1.0000
AB	2.79	1	0.1324	2.37	3.21	1.0000
A <sup>2</sup>	-6.39	1	0.1553	-6.88	-5.89	1.68
B <sup>2</sup>	-2.58	1	0.1553	-3.07	-2.08	1.68

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-collinearity, the higher the VIF the more severe the correlation of factors. As a rule of thumb, VIFs less than 10 are acceptable.

Figure No. 6.29: ANOVA of BLO after 5 hrs.

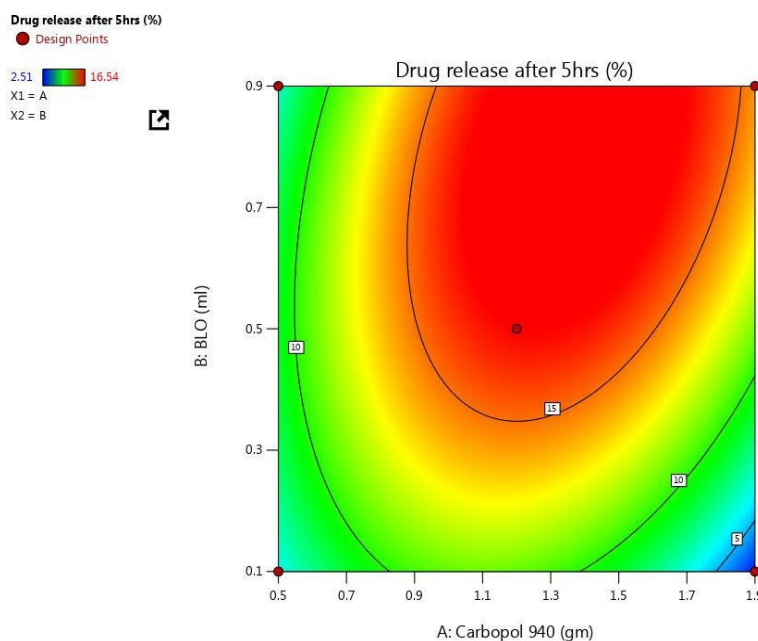


Figure No. 6.30: Conour of BLO after 5 hrs.

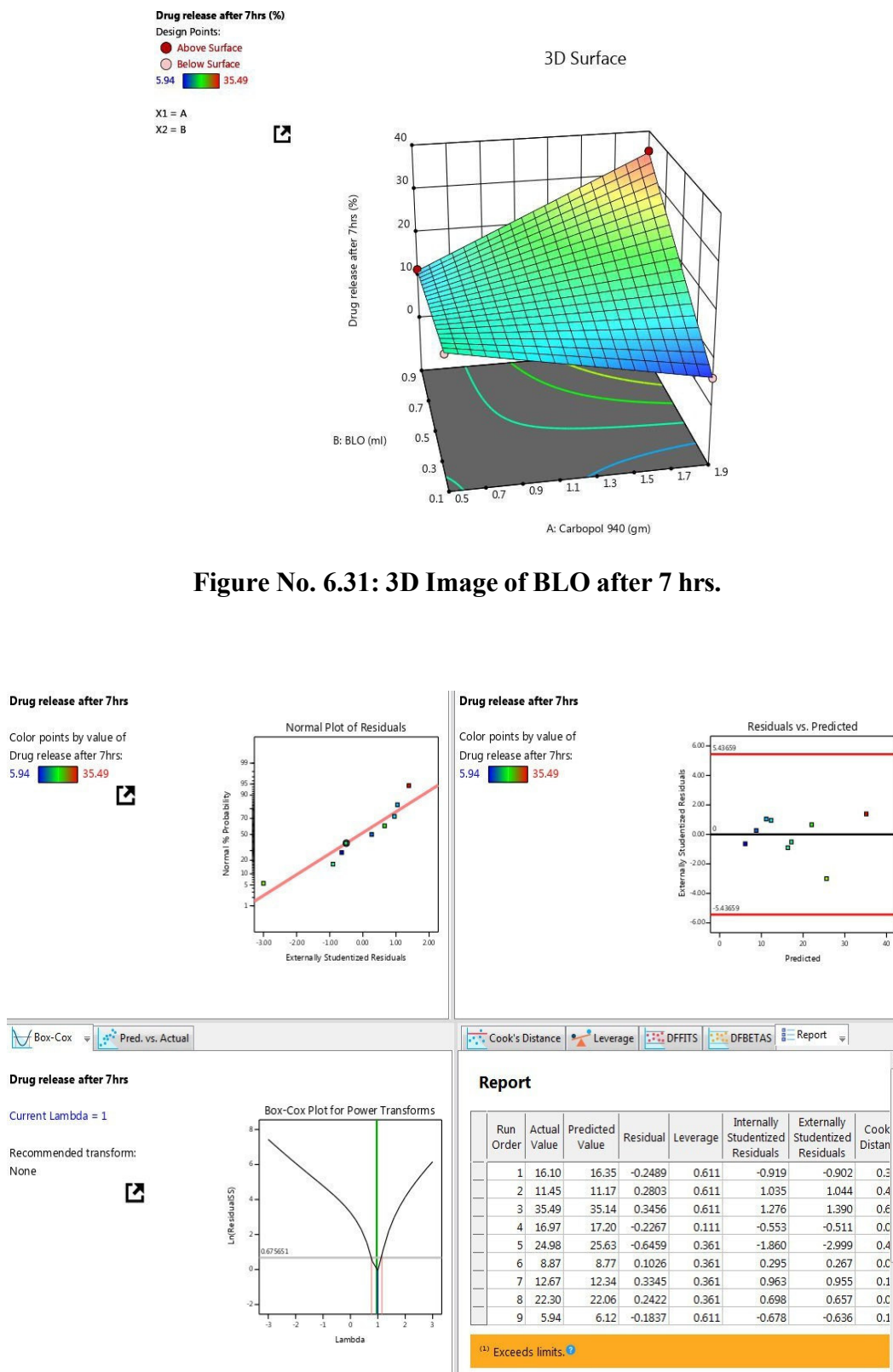


Figure No. 6.32: Diagnostic analysis of BLO after 7 hrs.

## ANOVA for 2FI model

Response 4: Drug release after 7hrs

Source	Sum of Squares	df	Mean Square	F-value	p-value	
<b>Model</b>	671.14	3	223.71	1185.75	< 0.0001	significant
A-Carbopol 940	94.52	1	94.52	501.00	< 0.0001	
B-BLO	284.21	1	284.21	1506.39	< 0.0001	
AB	292.41	1	292.41	1549.86	< 0.0001	
<b>Residual</b>	0.9433	5	0.1887			
<b>Cor Total</b>	672.09	8				

Factor coding is **Coded**.Sum of squares is **Type III - Partial**

The **Model F-value** of 1185.75 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

**P-values** less than 0.0500 indicate model terms are significant. In this case A, B, AB are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

## Fit Statistics

<b>Std. Dev.</b>	0.4344	<b>R<sup>2</sup></b>	0.9986
<b>Mean</b>	17.20	<b>Adjusted R<sup>2</sup></b>	0.9978
<b>C.V. %</b>	2.53	<b>Predicted R<sup>2</sup></b>	0.9948
		<b>Adeq Precision</b>	100.2189

The **Predicted R<sup>2</sup>** of 0.9948 is in reasonable agreement with the **Adjusted R<sup>2</sup>** of 0.9978; i.e. the difference is less than 0.2.

**Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 100.219 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients ☒ Coded Equation ☐ Actual Equation

## Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	17.20	1	0.1448	16.82	17.57	
A-Carbopol 940	3.44	1	0.1536	3.04	3.83	1.0000
B-BLO	5.96	1	0.1536	5.57	6.36	1.0000
AB	8.55	1	0.2172	7.99	9.11	1.0000

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

Figure No. 6.33: ANOVA of BLO after 7 hrs.

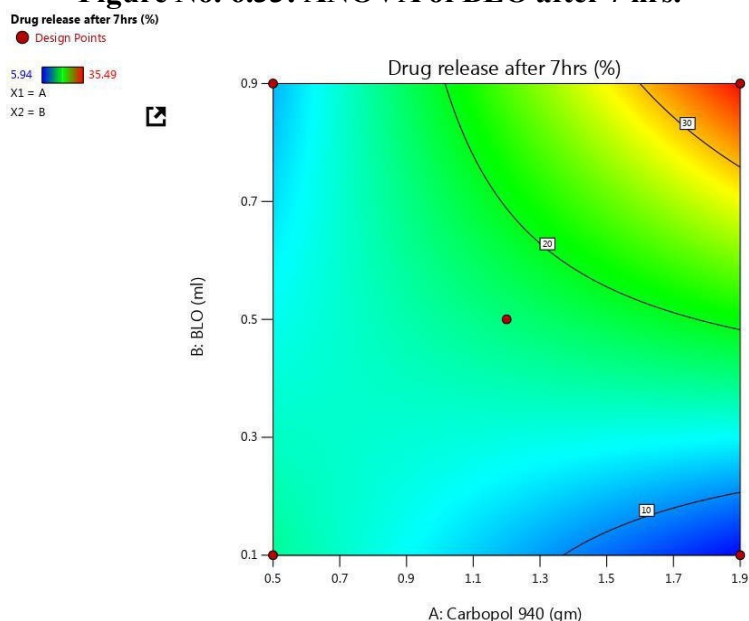


Figure No. 6.34: Conour of BLO after 7 hrs.



## 3D response surface plots, 2D contour plots, and perturbation graphs of SCO

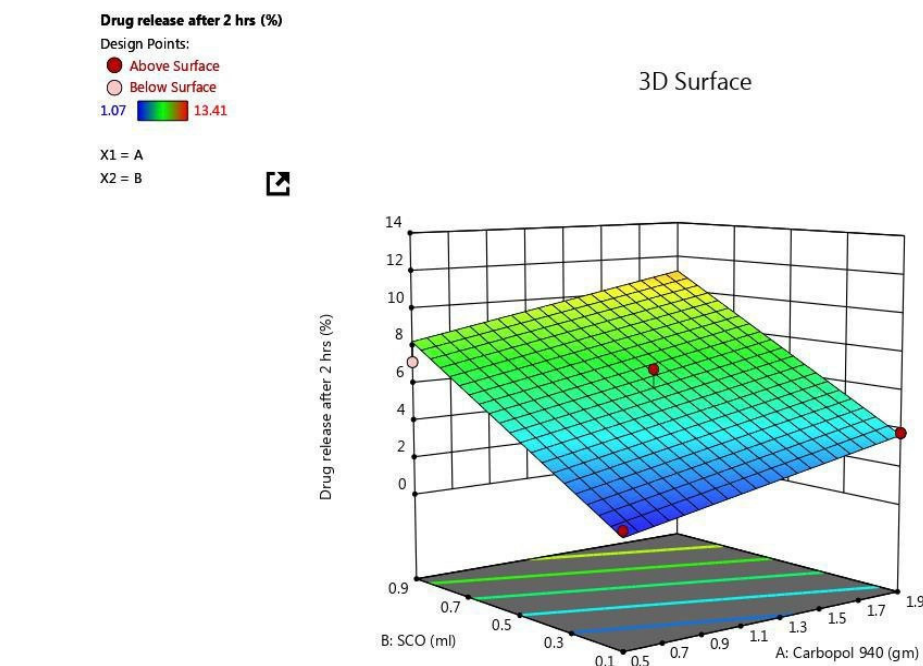


Figure No. 6.35: 3D Image of SCO after 2 hrs.

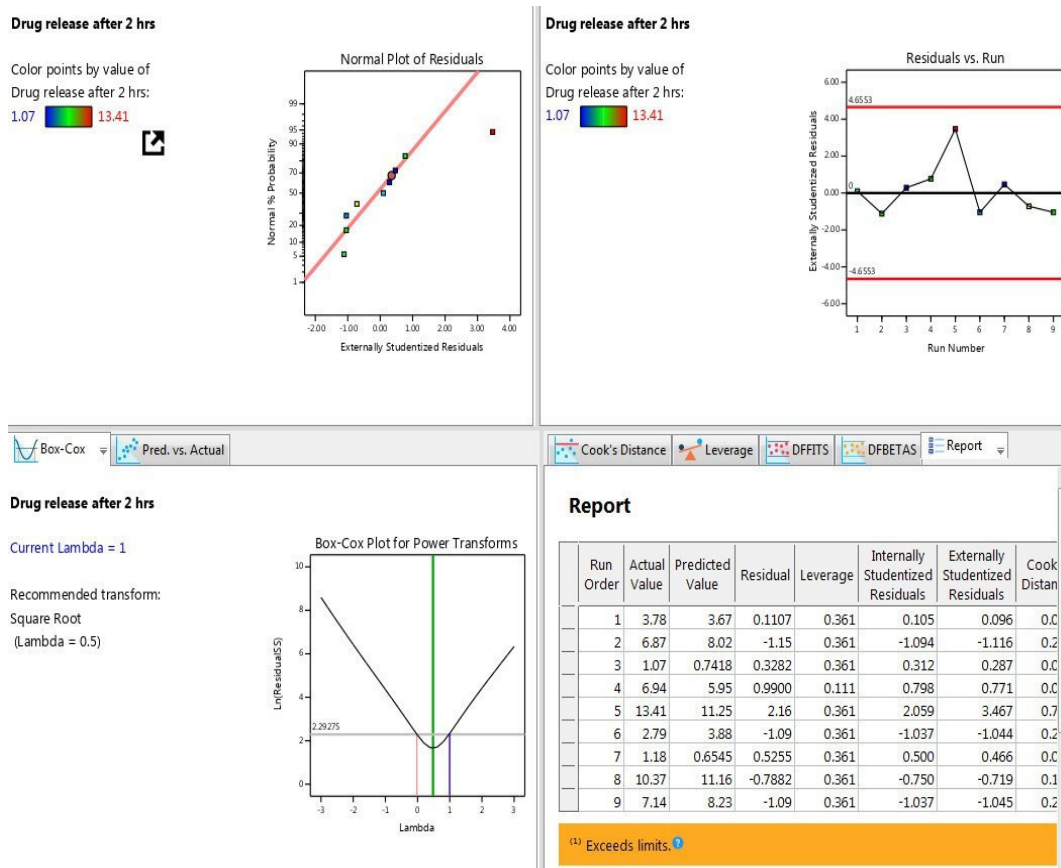


Figure No. 6.36: Diagnostic analysis of SCO after 2 hrs.

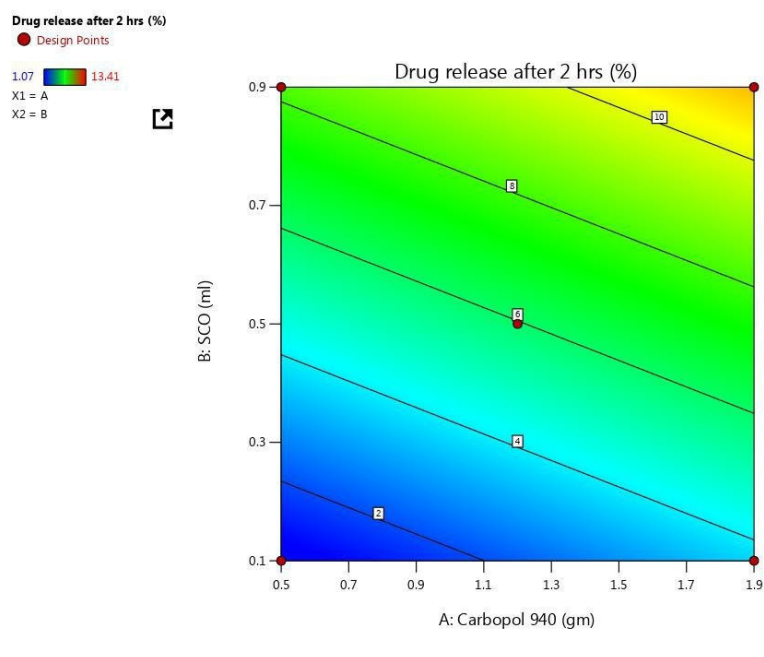


Figure No. 6.37: Conour of SCO after 2 hrs.

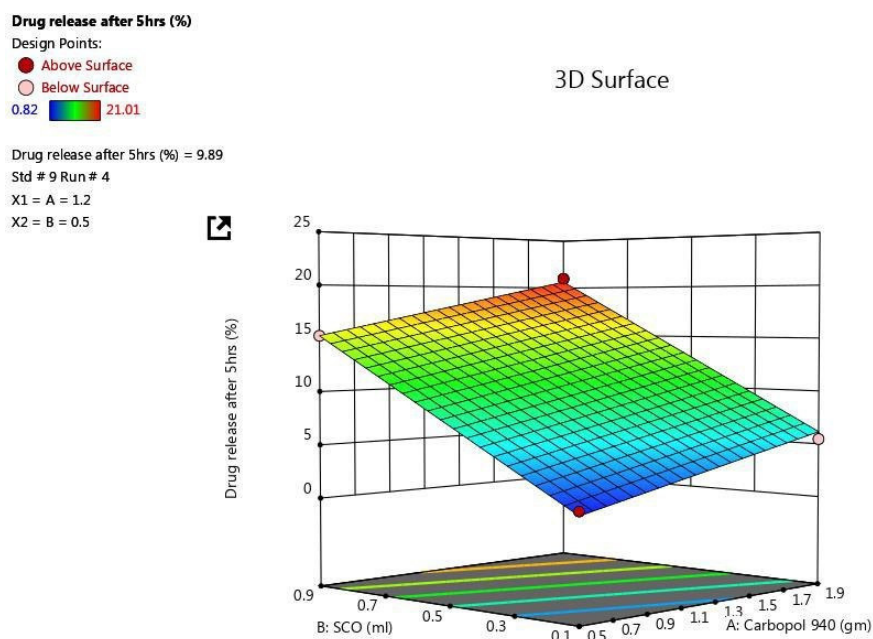


Figure No. 6.38: 3D Image of SCO after 5 hrs.

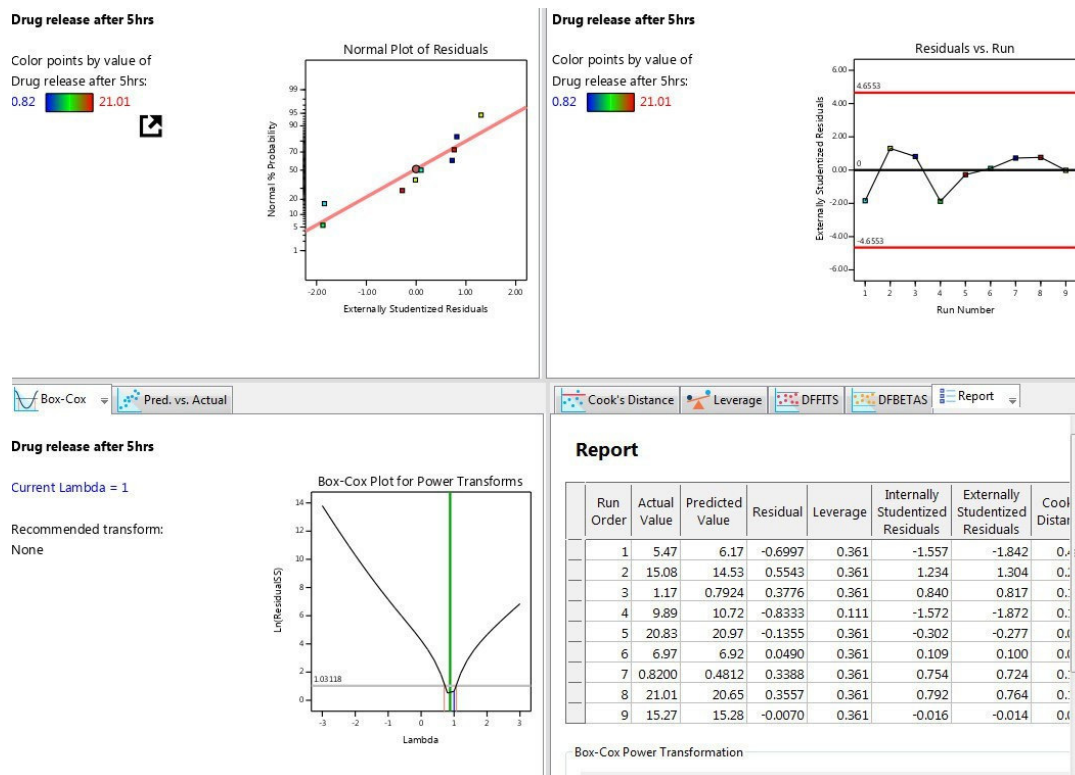


Figure No. 6.39: Diagnostic analysis of SCO after 5 hrs.

## ANOVA for Linear model

Response 3: Drug release after 5hrs

Source	Sum of Squares	df	Mean Square	F-value	p-value	
<b>Model</b>	477.44	2	238.72	755.43	< 0.0001	significant
A-Carbopol 940	57.83	1	57.83	183.01	< 0.0001	
B-SCO	419.61	1	419.61	1327.85	< 0.0001	
<b>Residual</b>	1.90	6	0.3160			
<b>Cor Total</b>	479.33	8				

Factor coding is Coded.

Sum of squares is Type III - Partial

The **Model F-value** of 755.43 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

**P-values** less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

## Fit Statistics

<b>Std. Dev.</b>	0.5621	<b>R<sup>2</sup></b>	0.9960
<b>Mean</b>	10.72	<b>Adjusted R<sup>2</sup></b>	0.9947
<b>C.V. %</b>	5.24	<b>Predicted R<sup>2</sup></b>	0.9920
		<b>Adeq Precision</b>	63.1153

The **Predicted R<sup>2</sup>** of 0.9920 is in reasonable agreement with the **Adjusted R<sup>2</sup>** of 0.9947; i.e. the difference is less than 0.2.

**Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 63.115 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients Coded Equation Actual Equation

## Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	10.72	1	0.1874	10.26	11.18	
A-Carbopol 940	2.69	1	0.1987	2.20	3.17	1.0000
B-SCO	7.24	1	0.1987	6.76	7.73	1.0000

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-collinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable.

Figure No. 6.40: ANOVA of SCO after 5 hrs

Drug release after 5hrs (%)

● Design Points

0.82 21.01

X1 = A

X2 = B

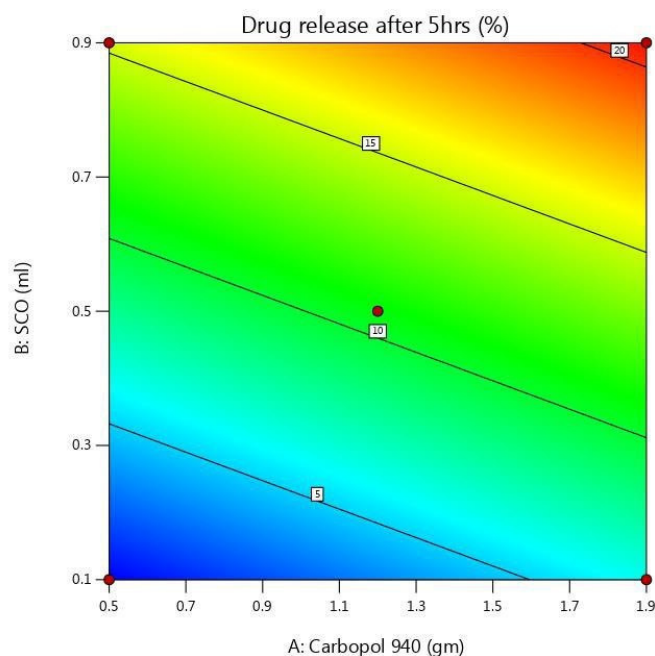


Figure No. 6.41: Conour of SCO after 5 hrs.



Drug release after 7hrs (%)

Design Points:

● Above Surface

○ Below Surface

2.16 63.27

X1 = A

X2 = B

3D Surface

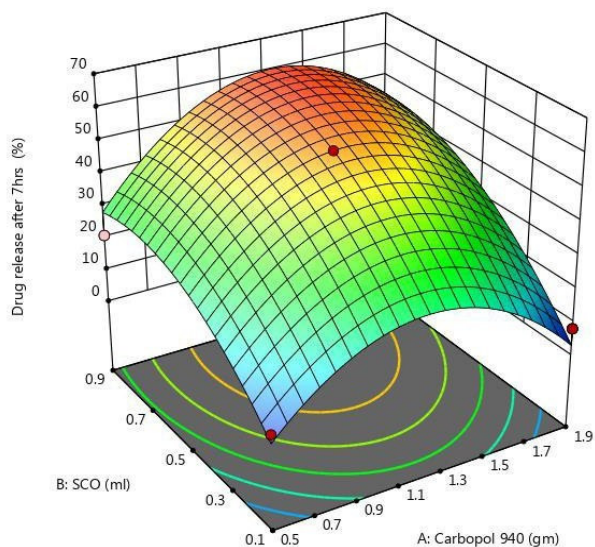
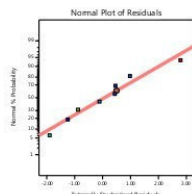


Figure No. 6.42: 3D Image of SCO after 7 hrs.

Drug release after 7hrs

Color points by value of  
Drug release after 7hrs :

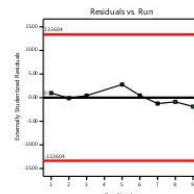
2.16 63.27



Drug release after 7hrs

Color points by value of  
Drug release after 7hrs :

2.16 63.27

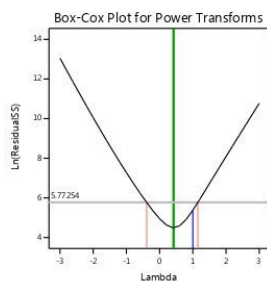


Box-Cox

Pred. vs. Actual

Drug release after 7hrs

Current Lambda = 1

Recommended transform:  
None

Cook's Distance

Leverage

DFFITS

DFBETAS

Report

Report

Run Order	Actual Value	Predicted Value	Residual	Leverage	Internally Studentized Residuals	Externally Studentized Residuals	Cook's Distance
1	8.05	2.91	5.14	0.625	0.987	0.981	0.2
2	12.44	13.14	-0.7008	0.625	-0.135	-0.110	0.0
3	5.64	2.97	2.67	0.625	0.513	0.439	0.0
4	54.02	54.02	0.0000	1.000 <sup>(1)</sup>			
5	63.27	55.22	8.05	0.625	1.545	2.790	0.6
6	4.68	1.89	2.79	0.625	0.536	0.460	0.0
7	2.16	8.12	-5.96	0.625	-1.144	-1.243	0.3
8	39.47	44.23	-4.76	0.625	-0.914	-0.879	0.2
9	21.03	28.26	-7.23	0.625	-1.388	-1.895	0.5

<sup>(1)</sup> Case(s) with leverage of 1.0000: Student Residuals, Cooks Distance & External Studentized Residuals

<sup>(2)</sup> Exceeds limits.

Figure No. 6.43: Diagnostic analysis of SCO after 7 hrs.

## ANOVA for Quadratic model

Response 4: Drug release after 7hrs

Source	Sum of Squares	df	Mean Square	F-value	p-value	
<b>Model</b>	4046.73	5	809.35	11.19	0.0372	significant
A-Carbopol 940	126.60	1	126.60	1.75	0.2777	
B-SCO	2218.87	1	2218.87	30.67	0.0116	
AB	64.24	1	64.24	0.8878	0.4156	
A <sup>2</sup>	1572.88	1	1572.88	21.74	0.0186	
B <sup>2</sup>	363.29	1	363.29	5.02	0.1109	
<b>Residual</b>	217.07	3	72.36			
<b>Cor Total</b>	4263.80	8				

Factor coding is Coded.

Sum of squares is Type III - Partial

The **Model F-value** of 11.19 implies the model is significant. There is only a 3.72% chance that an F-value this large could occur due to noise.

**P-values** less than 0.0500 indicate model terms are significant. In this case B, A<sup>2</sup> are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

## Fit Statistics

Std. Dev.	8.51	R <sup>2</sup>	0.9491
Mean	23.42	Adjusted R <sup>2</sup>	0.8642
C.V. %	36.32	Predicted R <sup>2</sup>	NA <sup>(1)</sup>
		Adeq Precision	7.6790

<sup>(1)</sup> Case(s) with leverage of 1.0000: Pred R<sup>2</sup> and PRESS statistic not defined.

**Adeq Precision** measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 7.679 indicates an adequate signal. This model can be used to navigate the design space.

Coefficients Coded Equation Actual Equation

## Coefficients in Terms of Coded Factors

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	54.02	1	8.51	26.95	81.09	
A-Carbopol 940	3.98	1	3.01	-5.59	13.55	1.0000
B-SCO	16.65	1	3.01	7.08	26.23	1.0000
AB	4.01	1	4.25	-9.53	17.54	1.0000
A <sup>2</sup>	-23.25	1	4.99	-39.12	-7.38	1.68
B <sup>2</sup>	-11.17	1	4.99	-27.05	4.70	1.68

The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-collinearity, the higher the VIF the more severe the correlation

Figure No. 6.44: ANOVA of SCO after 7 hrs.

Drug release after 7hrs (%)

Design Points

2.16 63.27

X1 = A

X2 = B

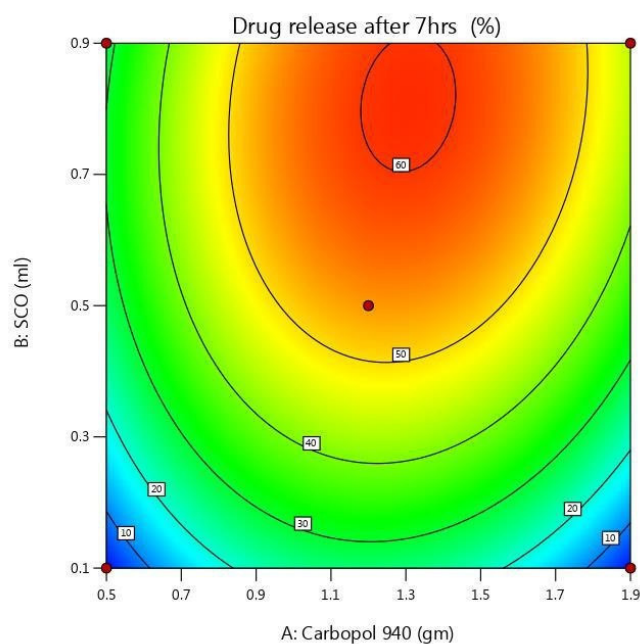


Figure No. 6.45: Contour of SCO after 7 hrs.

**Optimization of Colchicine gel by 3<sup>2</sup> factorial design:**

To investigate the impact of the separate variable, a 3<sup>2</sup> factorial design was built. Nine experiments in all were carried out. The optimum formulation including carbopol 940 and extracted oil of *B. lanzan* and *S. chinesis* was discovered by the application of the factorial design. In order to keep the pH stable, TEA was added together with IPA as a co-solvent. Viscosity (Y1) and permeation augmentation (% cumulative drug release) were regarded as dependencies in the current investigation, whereas the concentration of carbopol 940 (X1) and extracted oil (*B. lanzan* and *S. chinesis*) (X2) were considered separate variables. A pair of variables, each at three levels of evaluation, were examined in this design, and studies took place in all nine conceivable combinations. The reaction was assessed using an empirical framework that included polynomial and interaction components. The following linear answer is produced by this design.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

The regression coefficients are denoted by b1 and b2, Y being the dependent variable, and b0 representing the arithmetic mean response of the nine runs. Multiple linear regression analysis (MLRA) is performed on the response values to determine the correlation between the components that were employed and the response values that were obtained. The amount of formulation variable was optimized following the use of the full factorial design and with the aid of the generated polynomial terms.

## GOAT SKIN DRUG RELEASE OF FORMULATION BL4

Table 6.18: *In-vitro* drug release data for optimization of BL4

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	W <sub>0</sub> -W <sub>t</sub>
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	3.5374	96.4626	1.000	1.984	0.000	0.549	3.5374	4.586	0.056
2	5.681425	94.31858	1.414	1.975	0.301	0.754	2.144025	4.552	0.090
3	8.48515	91.51485	1.732	1.961	0.477	0.929	2.803725	4.506	0.136
4	11.76533	88.23468	2.000	1.946	0.602	1.071	3.280175	4.452	0.190
6	16.18165	83.81835	2.449	1.923	0.778	1.209	4.416325	4.376	0.266
6	21.40428	78.59573	2.449	1.895	0.778	1.331	5.222625	4.284	0.358
7	27.10335	72.89665	2.646	1.863	0.845	1.433	5.699075	4.177	0.465

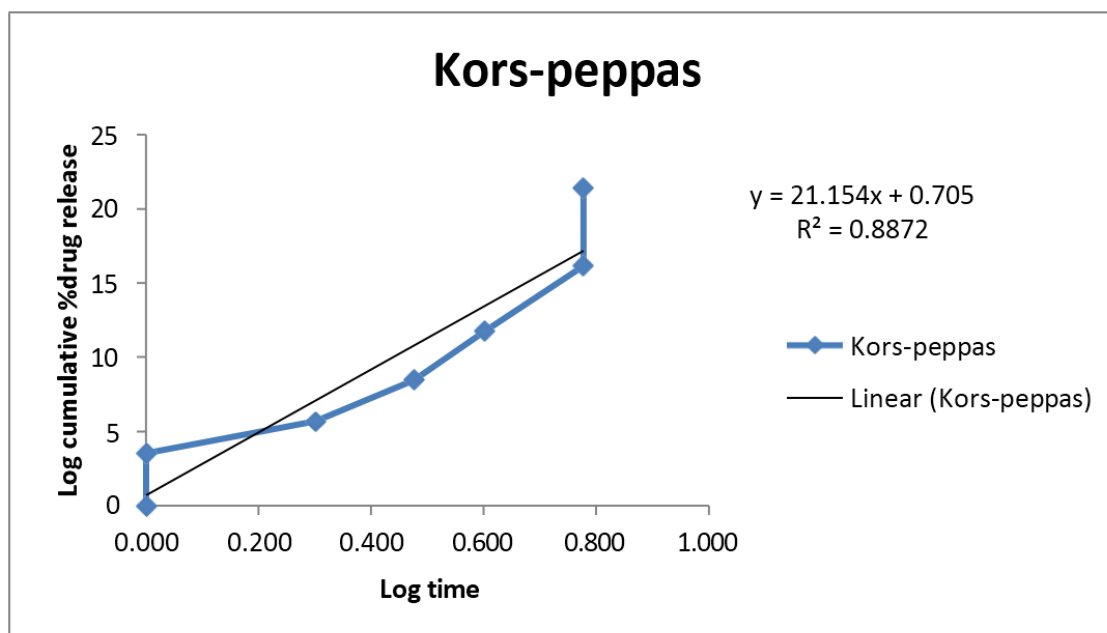


Figure No. 6.46: Log time vs log cumulative % drug release

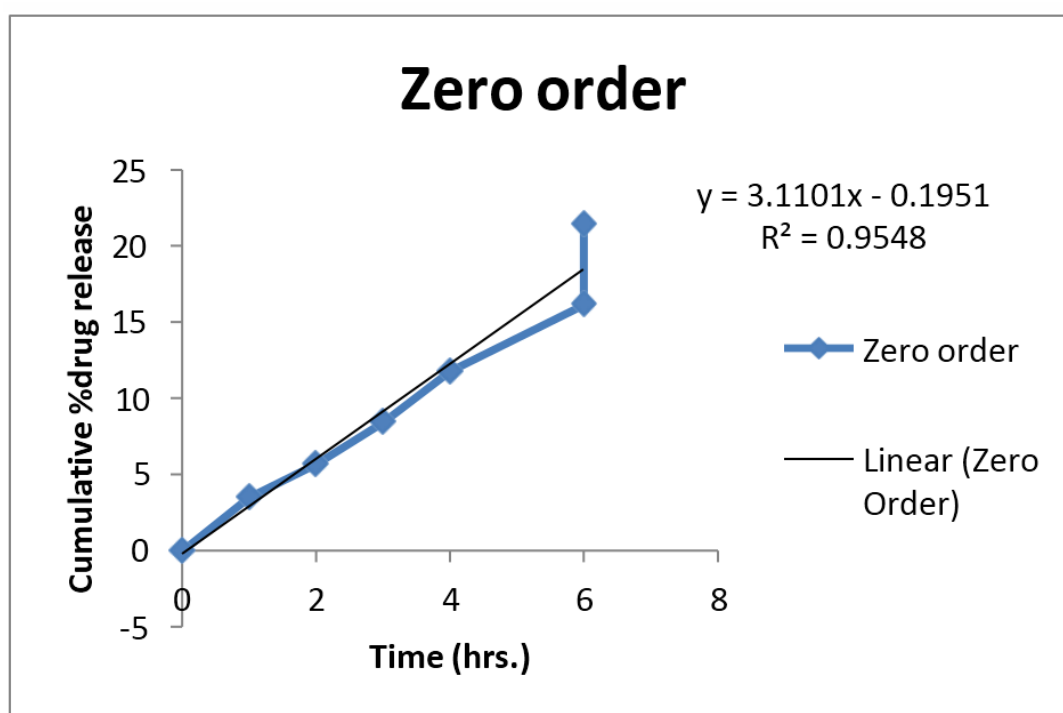


Figure No. 6.47: Time vs Cumulative % drug release

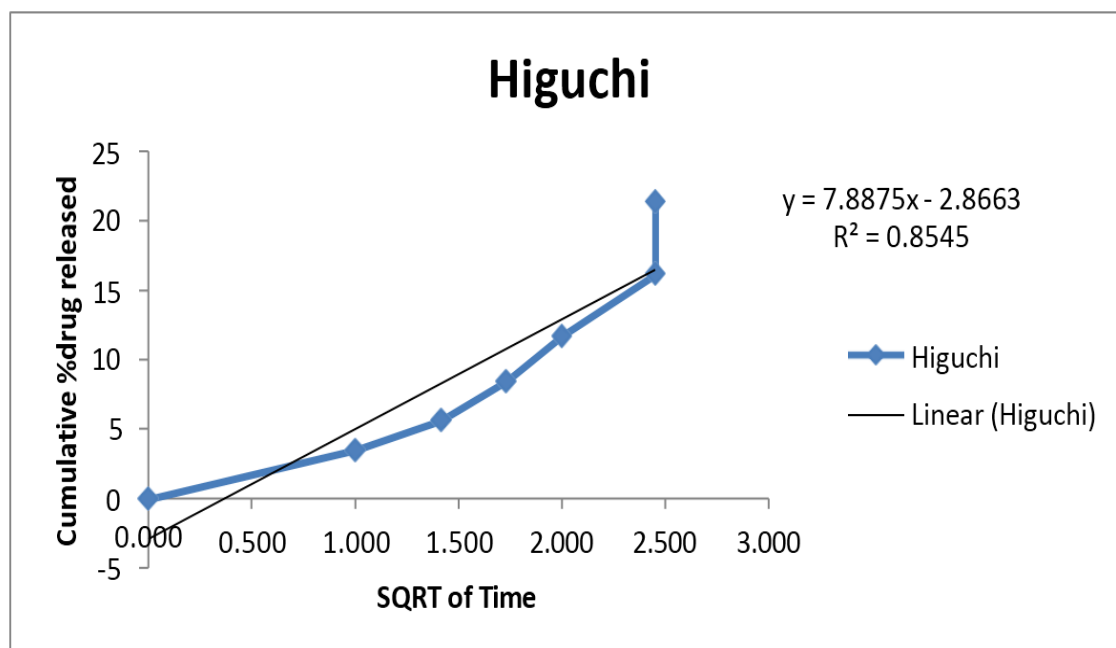


Figure No. 6.48: Time vs Cumulative % drug release graph

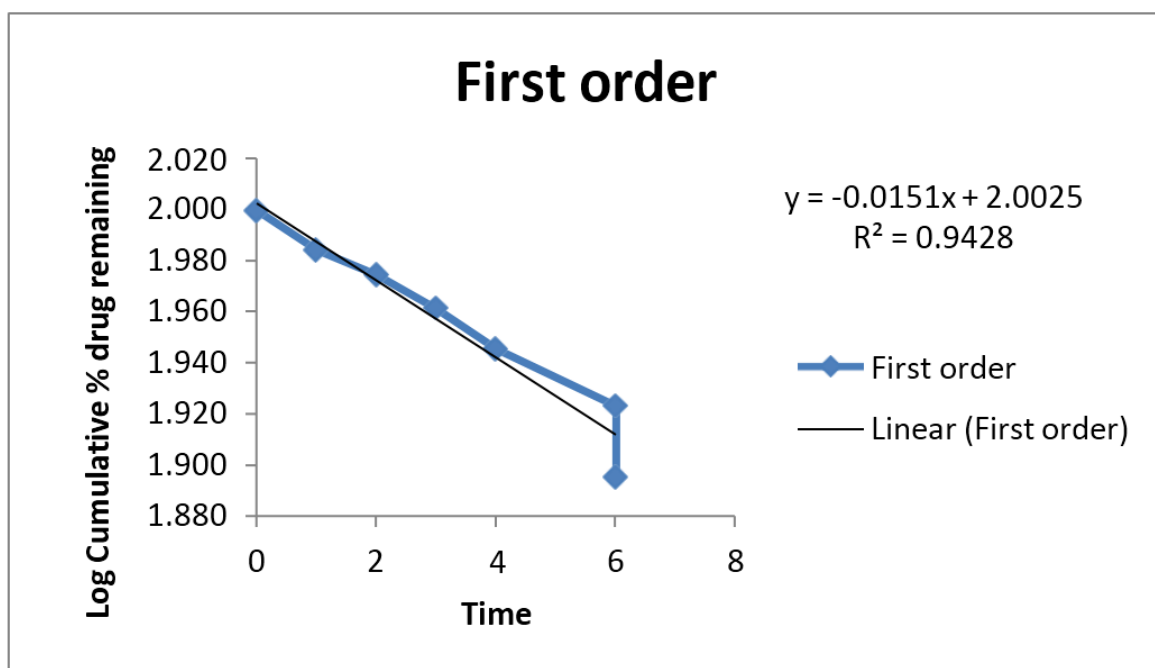


Figure No. 6.49: Time vs Log cumulative % drug release

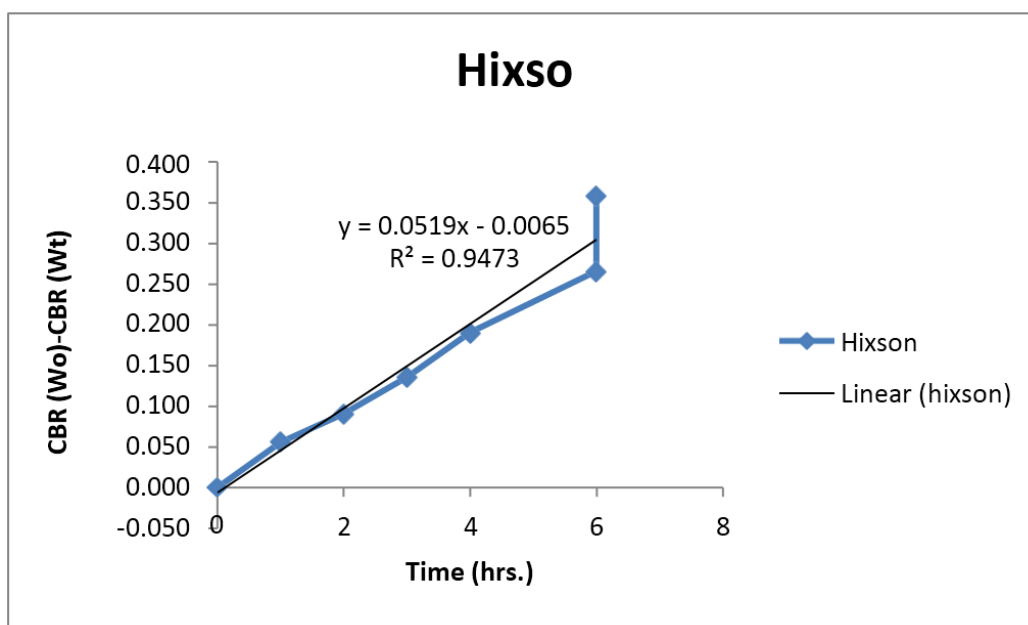


Figure No. 6.50: Time vs Drug remain

Table 6.19: *In-vitro* drug release data for optimization of BL5

Time (Hr)	cumulative % drug released	% drug remaining	Sqare root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642



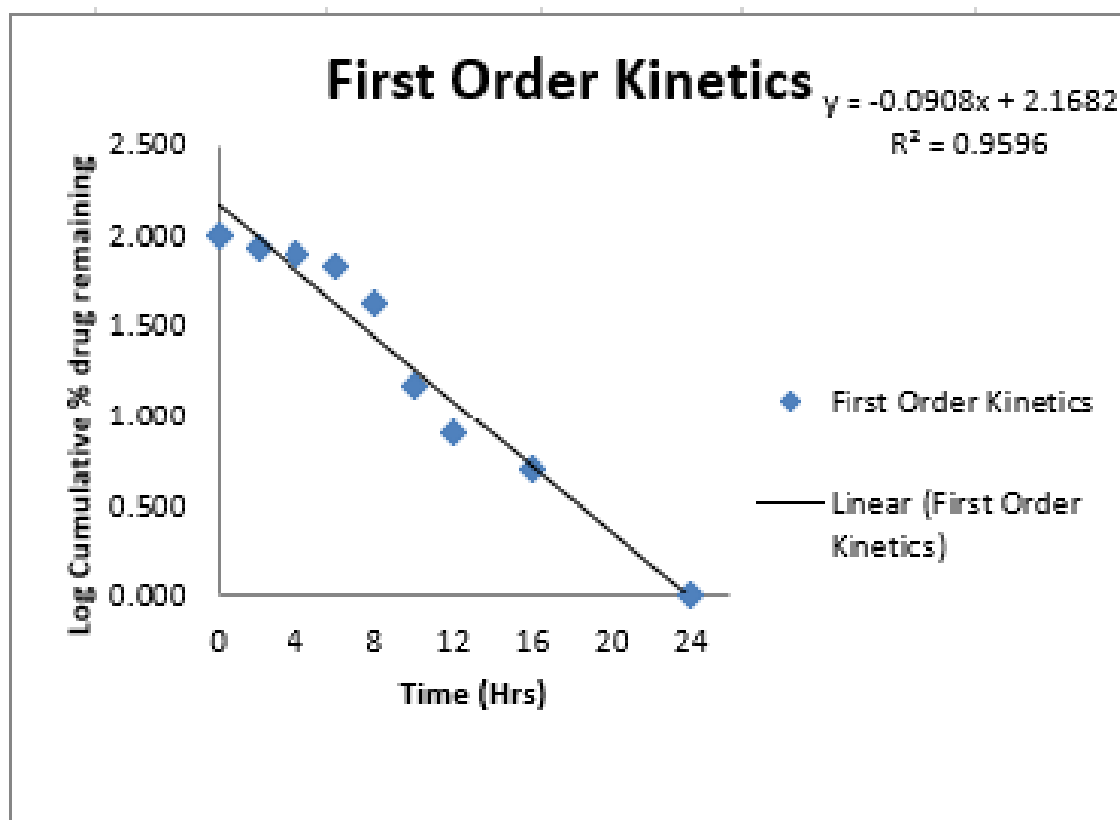


Figure No. 6.51: Time vs Log cumulative % drug release

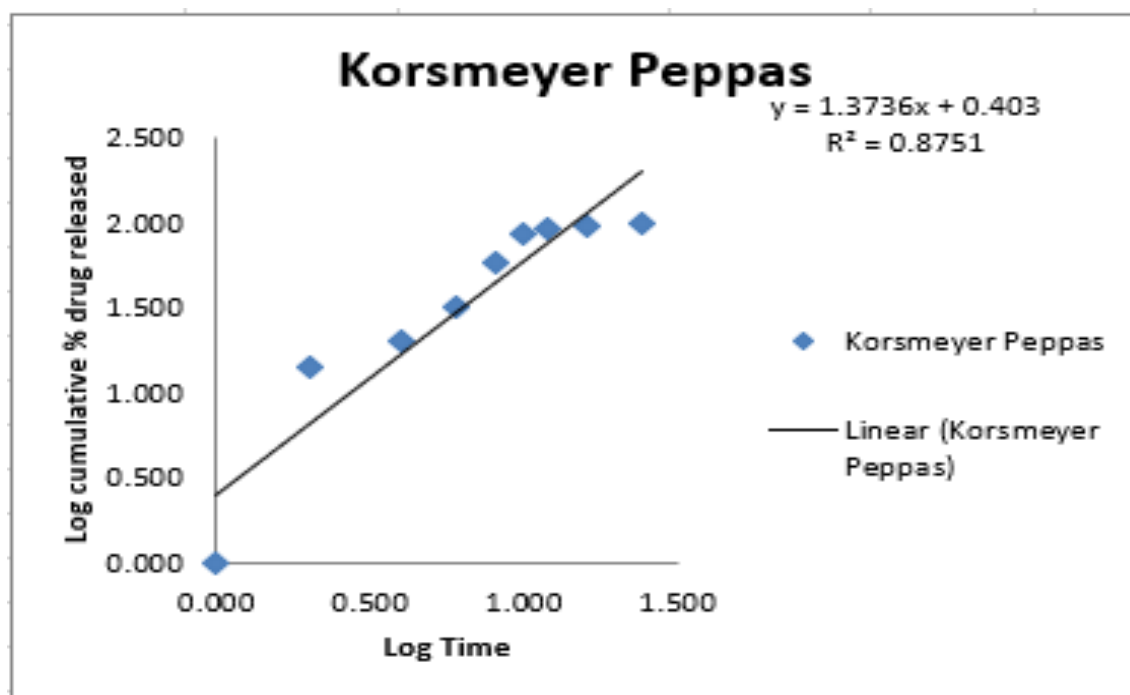


Figure No. 6.52: Log time vs Log cumulative % drug released

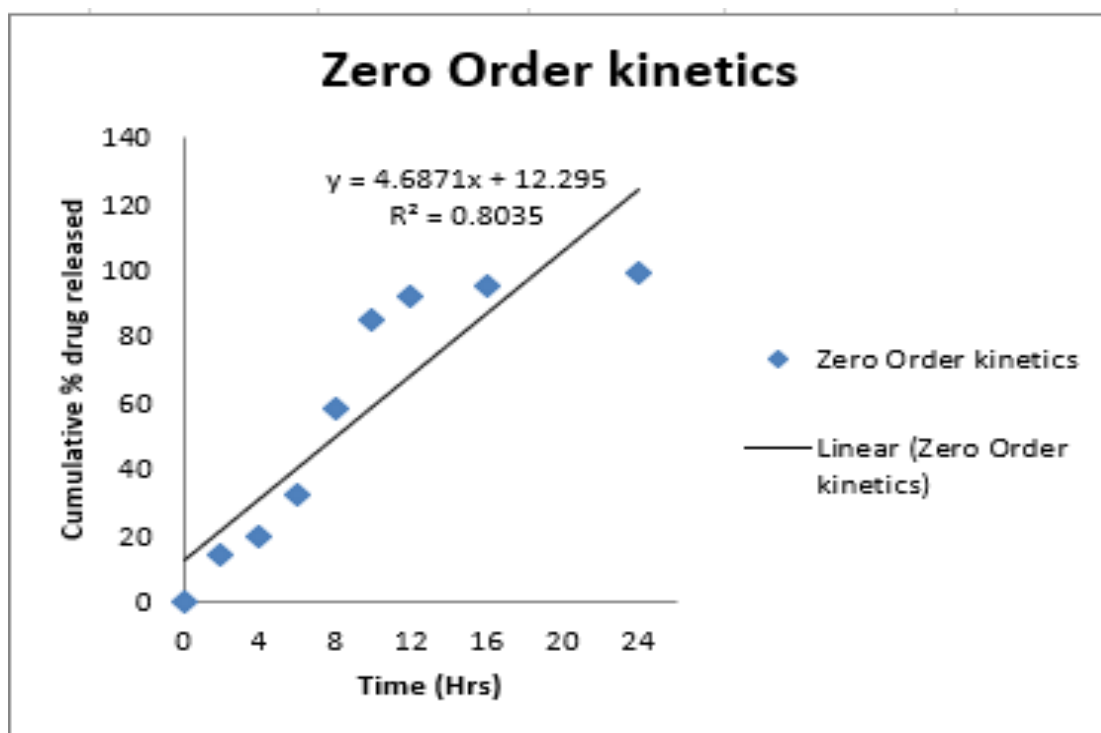


Figure No. 6.53: Time vs cumulative % drug release

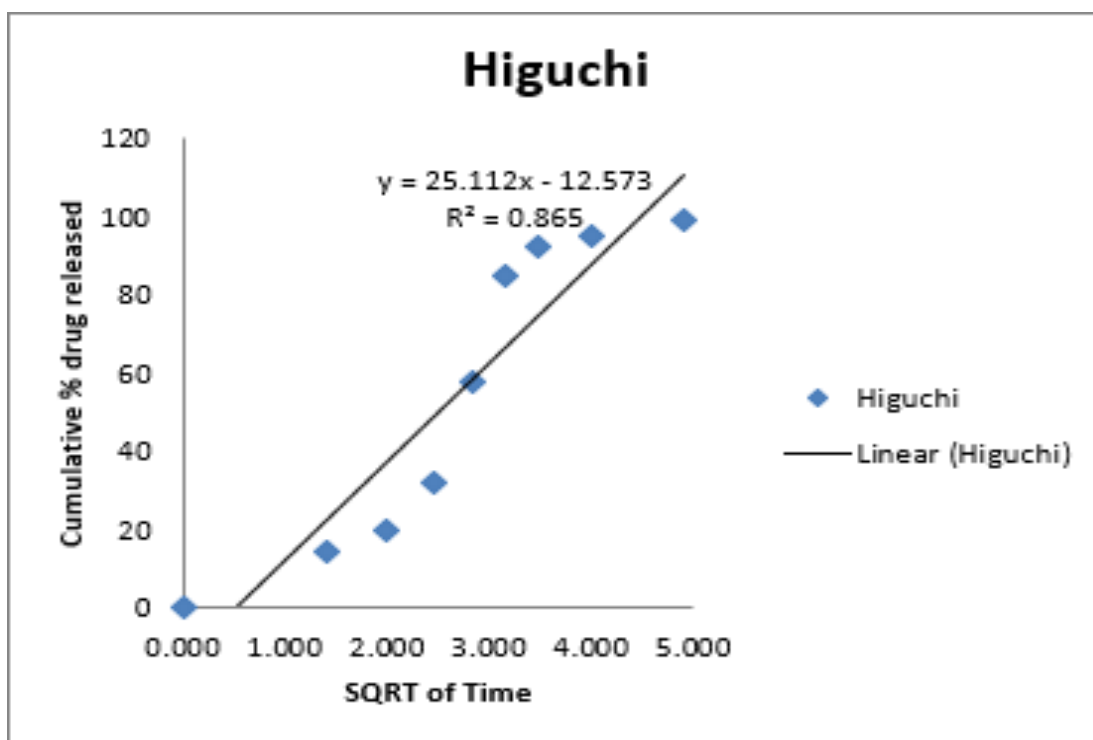
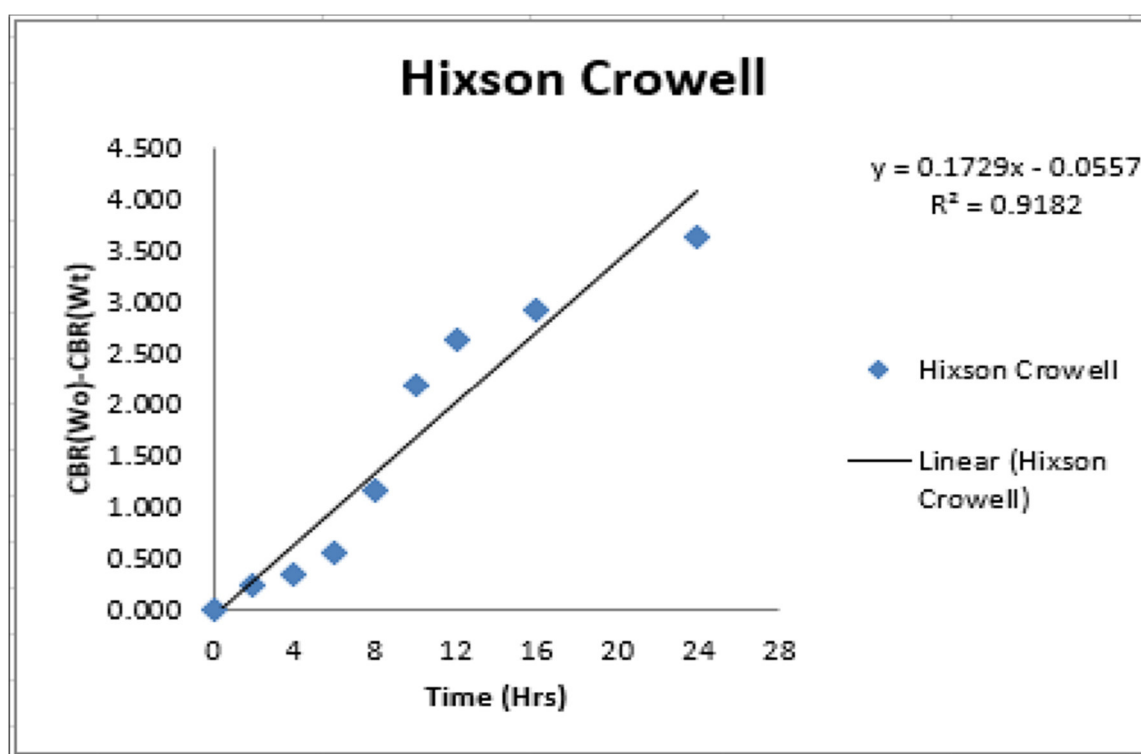


Figure No. 6.54: Time vs Cumulative % drug released



**Figure No. 6.55: Time vs Drug remained**

The instrument of drug proclamation from a dosage form is interpreted mostly through the use of mathematical models. Comprehending the drug release kinetics of a dosage form is a crucial instrument. Higuchi square root model ( $r^2 = 0.865$  for BL4) appeared to have the greatest match to the medication release data. This suggests that the drug release is a time-dependent, diffusion-controlled mechanism with a square root. The dissolution data was also shown in accordance with the Hixson-Crowell model ( $r^2 = 0.9182$  for BL4), which illustrates how the formulation's outward area and diameter changed as the dissolving progressed completed time. The kind of diffusing is additionally defined by the typical Korsmeyer-Peppas power law equation; this was determined by evaluating the quantity of  $n$  (Release exponent), which is more than 0.875, indicating that the release of medicine from the apparatus follows highly case II transfer.

## GOAT SKIN DRUG RELEASE OF FORMULATION BL5

Table 6.20: Log cumulative drug remaining data for BL5

Time (Hr)	log Cumu % drug remaining		
0	2	2	2
1	1.984	1.992	1.991
2	1.975	1.984	1.984
3	1.961	1.975	1.975
4	1.946	1.965	1.965
5	1.923	1.949	1.95
6	1.895	1.928	1.931
7	1.863	1.903	1.909

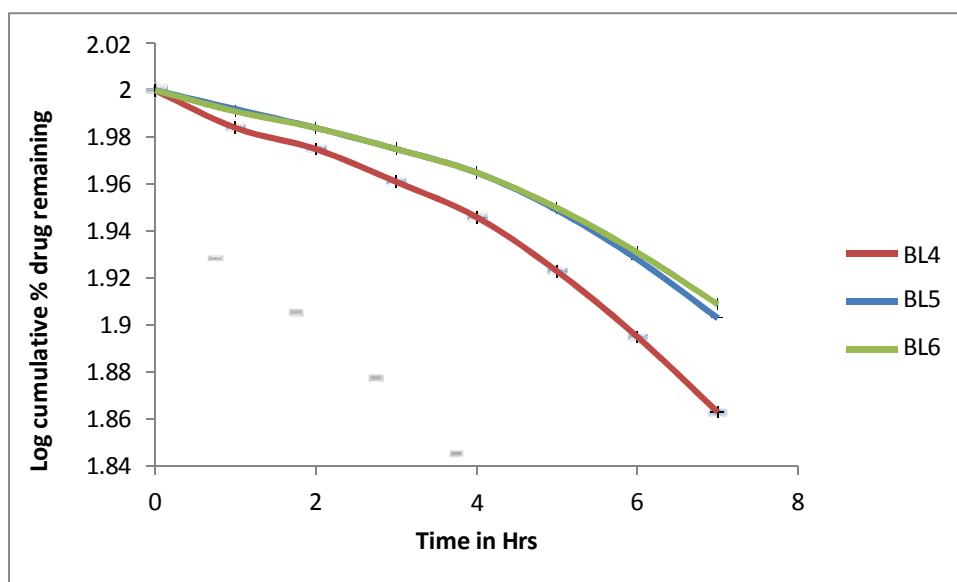


Figure No. 6.56: Time vs Log cumulative % drug remaining

Table 6.21: Cumulative drug release data for BL5 wrt to SQRT

Square root time	Cumulative % drug released		
0	0	0	0
1	3.5374	1.83195	2.1102
1.414	5.68143	3.6278	3.6078
1.732	8.48515	5.625225	5.6238
2	11.7653	7.76925	7.8126
2.449	16.1817	11.1777	10.942
2.449	21.4043	15.19088	14.609
2.646	27.1034	20.01035	18.929

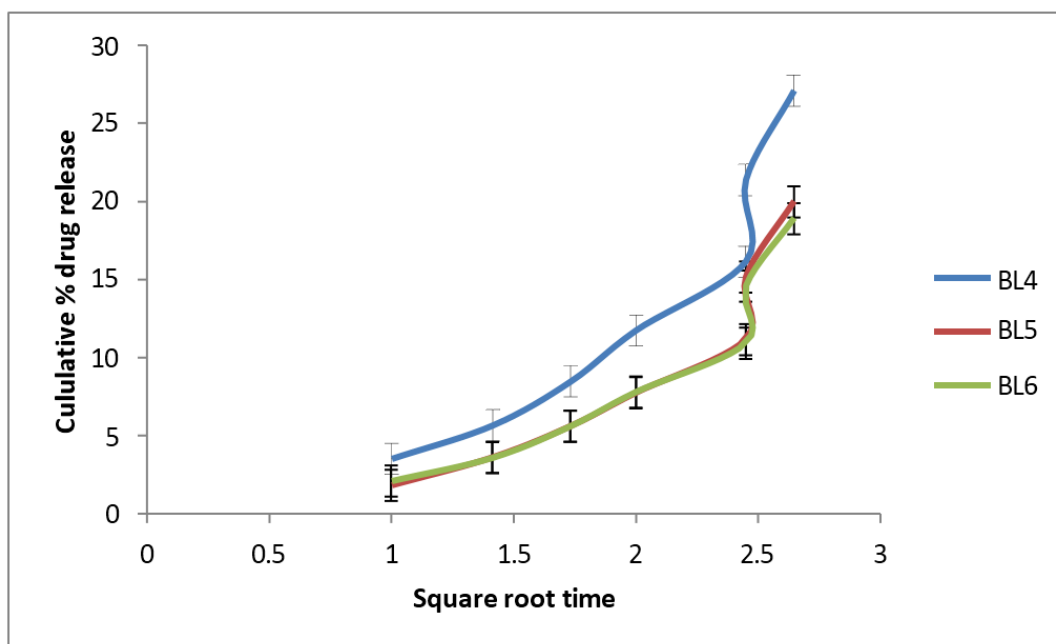


Figure No. 6.57: Sq root time vs Cumulative % drug release

Table 6.22: Log cumulative drug released data for BL5 wrt Log time

Log time	Log cumulative % drug released		
0	0	0	0
0	0.549	0.263	0.324
0.301	0.754	0.56	0.557
0.477	0.929	0.75	0.75
0.602	1.071	0.89	0.893
0.778	1.209	1.048	1.039
0.778	1.331	1.182	1.165
0.845	1.433	1.301	1.277

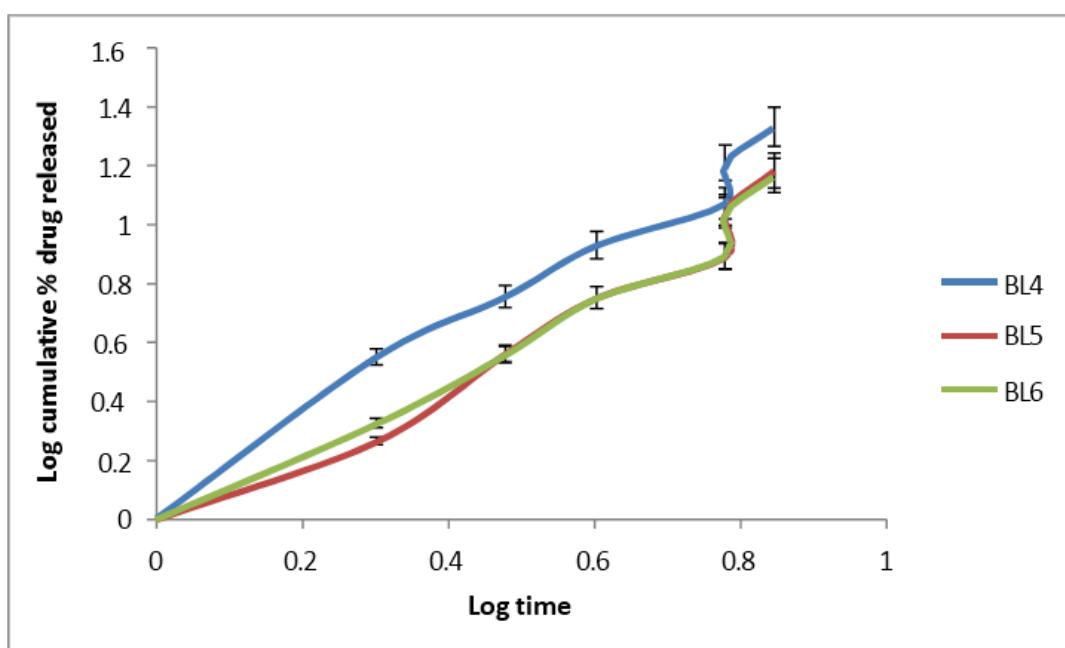


Figure No. 6.58: Log time vs log cumulative % drug released

Table 6.23: *In-vitro* drug release data for optimization of BL5

Time (Hr.)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remanning	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt.)	Wo- Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	1.83195	98.16805	1.000	1.992	0.000	0.263	1.83195	4.613	0.029
2	3.6278	96.3722	1.414	1.984	0.301	0.560	1.79585	4.585	0.057
3	5.625225	94.37478	1.732	1.975	0.477	0.750	1.997425	4.553	0.089
4	7.76925	92.23075	2.000	1.965	0.602	0.890	2.144025	4.518	0.124
5	11.1777	88.8223	2.236	1.949	0.699	1.048	3.40845	4.462	0.180
6	15.19088	84.80913	2.449	1.928	0.778	1.182	4.013175	4.394	0.248
7	20.01035	79.98965	2.646	1.903	0.845	1.301	4.819475	4.309	0.333

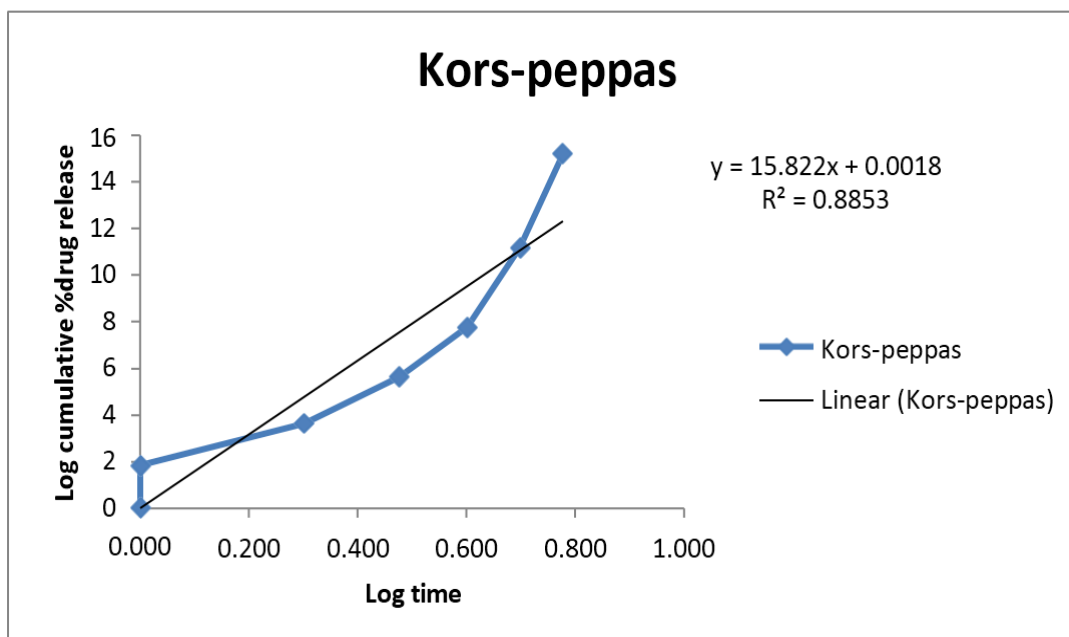


Figure No. 6.59: Log time vs Log cumulative % drug release

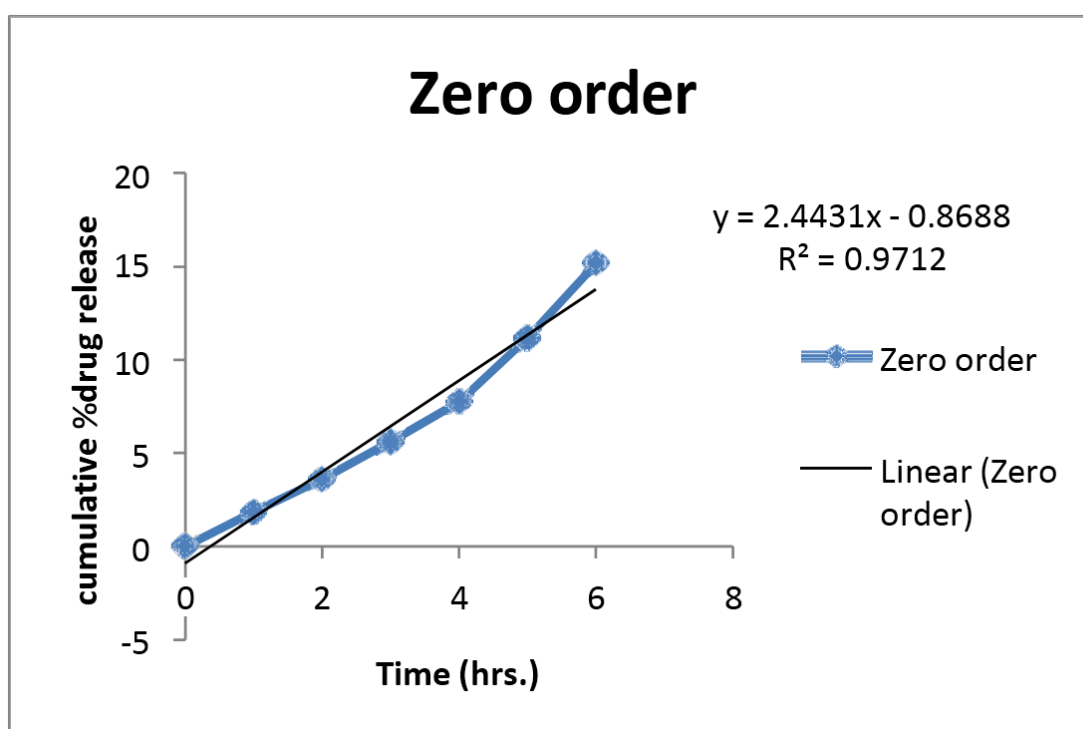


Figure No. 6.60: Time vs Cumulative % drug release



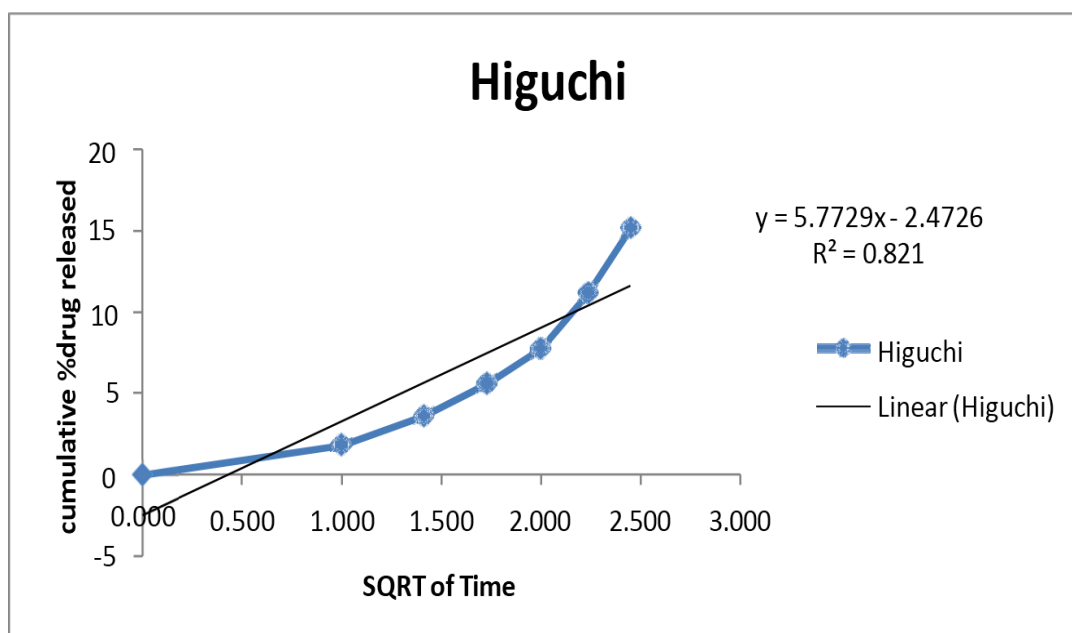


Figure No. 6.61: Sq root of time vs cumulative % drug released

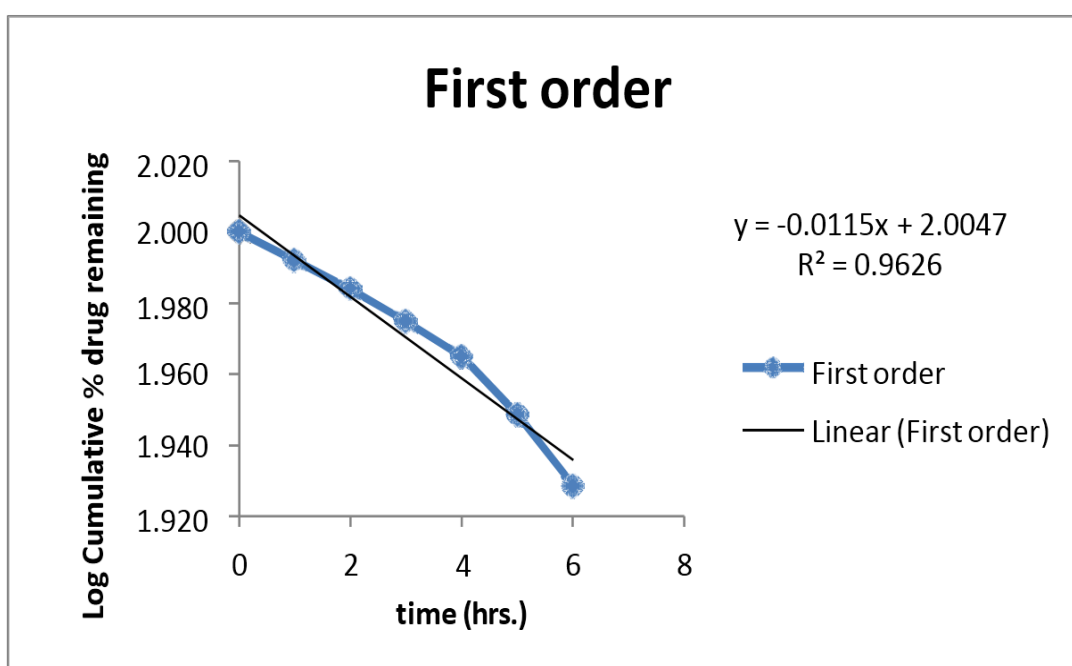


Figure No. 6.62: Time vs Log cumulative % drug remaining

Table 6.24: *In-vitro* drug remain data for BL5

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	W <sub>0</sub> - W <sub>t</sub>
0	0	100	0.000	2.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	1.146	14	4.414	0.228
4	20	80	2.000	1.903	1.301	6	4.309	0.333
6	32	68	2.449	1.833	1.505	12	4.082	0.560
8	58	42	2.828	1.623	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.996	4	1.000	3.642

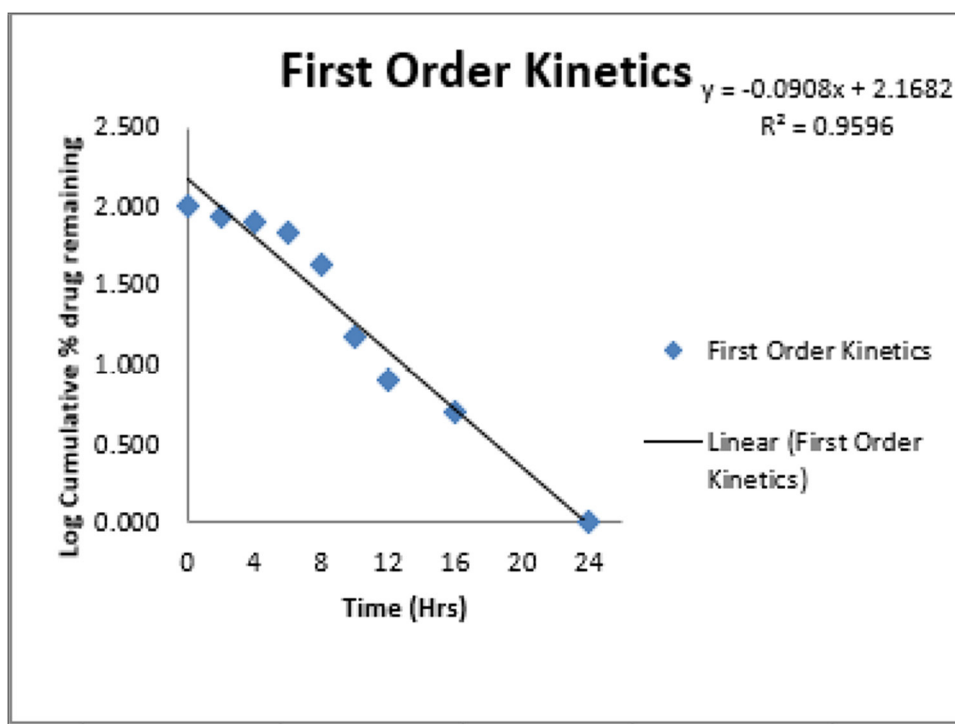


Figure No. 6.63: Time vs Log cumulative % drug remaining

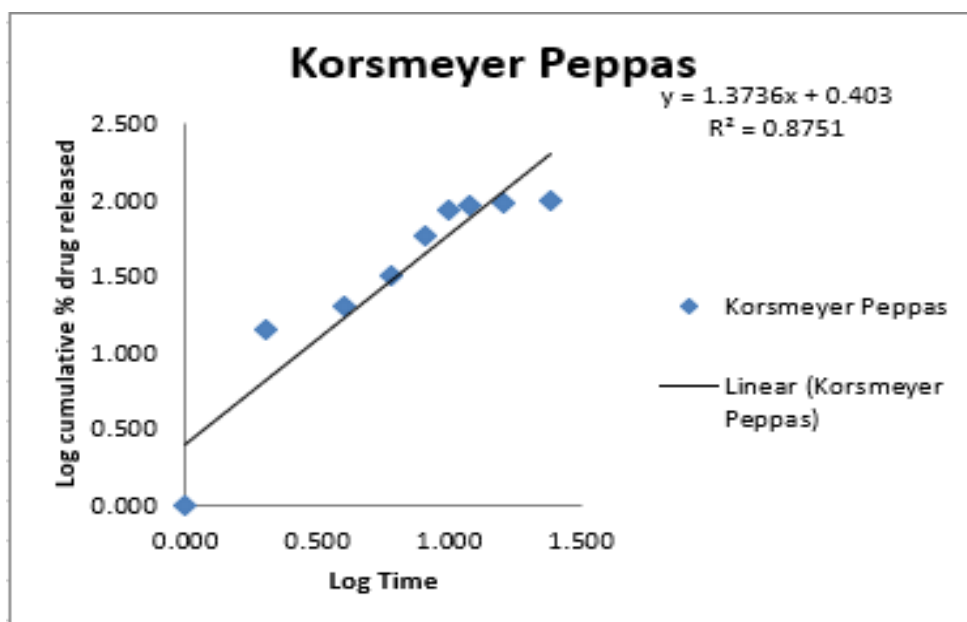


Figure No. 6.64: Log time vs Log cumulative % drug released

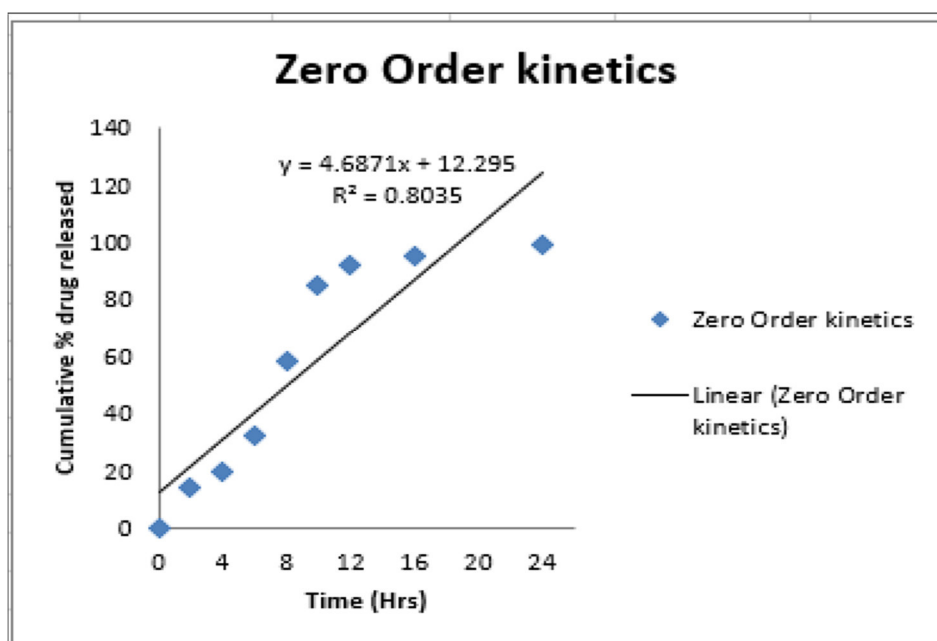


Figure No. 6.65: Time vs cumulative % drug released

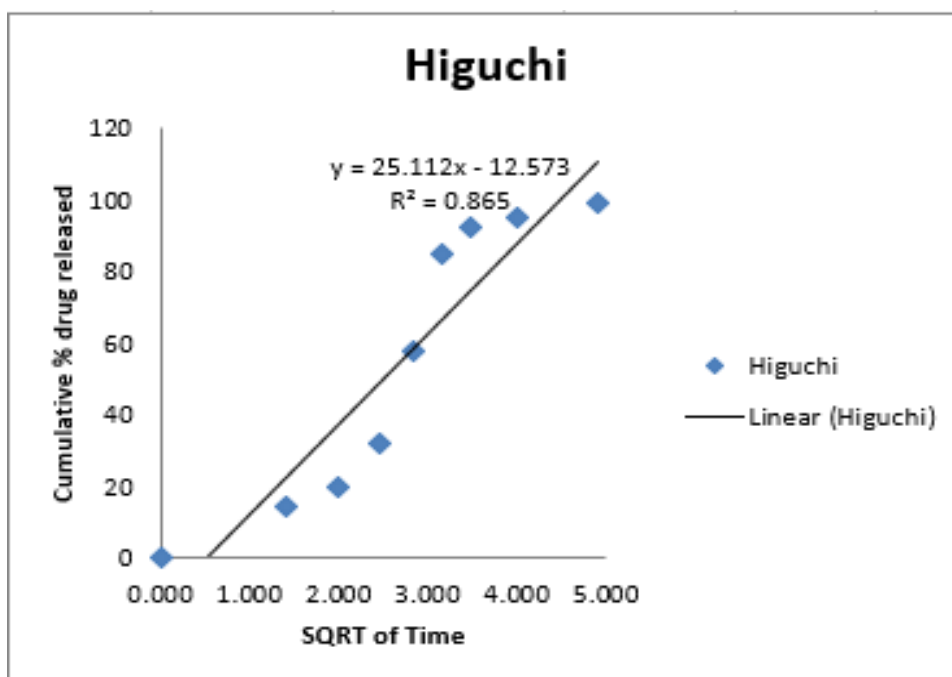


Figure No. 6.66: Sq root of time vs cumulative % drug released

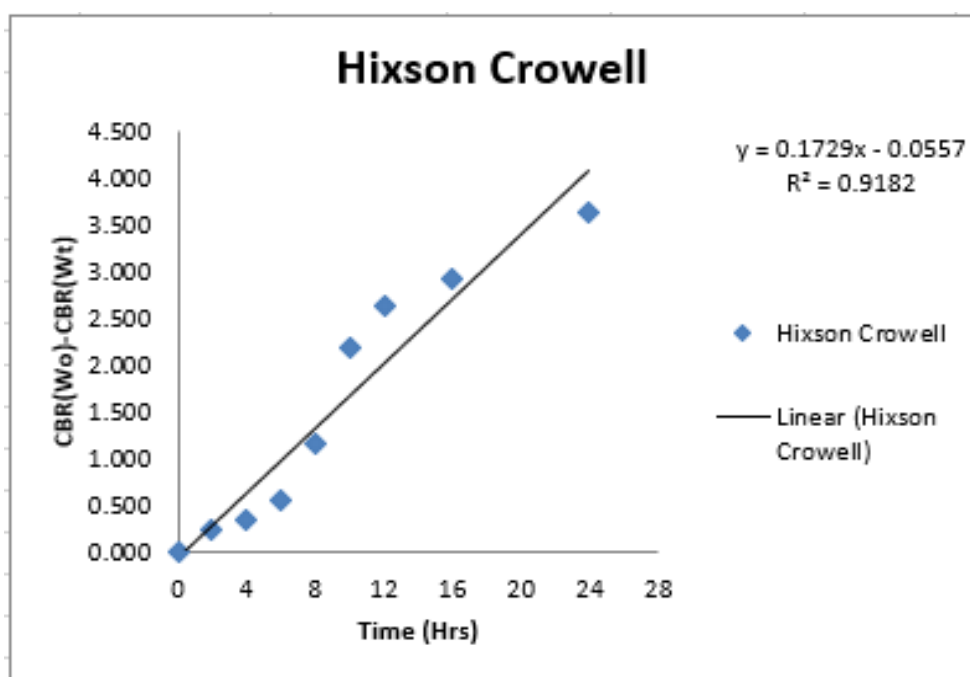


Figure No. 6.67: Time vs cube root of drug remaining

## GOAT SKIN DRUG RELEASE OF FORMULATION BL6

Table 6.25: *In-vitro* drug release data for optimization of BL6

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	W/o-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	2.1102	97.8898	1.000	1.991	0.000	0.324	2.1102	4.609	0.033
2	3.6078	96.3922	1.414	1.984	0.301	0.557	1.4976	4.585	0.057
3	5.6238	94.3762	1.732	1.975	0.477	0.750	2.016	4.553	0.089
4	7.8126	92.1874	2.000	1.965	0.602	0.893	2.1888	4.517	0.125
5	10.9422	89.0578	2.236	1.950	0.699	1.039	3.1296	4.466	0.176
6	14.6094	85.3906	2.449	1.931	0.778	1.165	3.6672	4.404	0.238
7	18.9294	81.0706	2.646	1.909	0.845	1.277	4.32	4.328	0.314

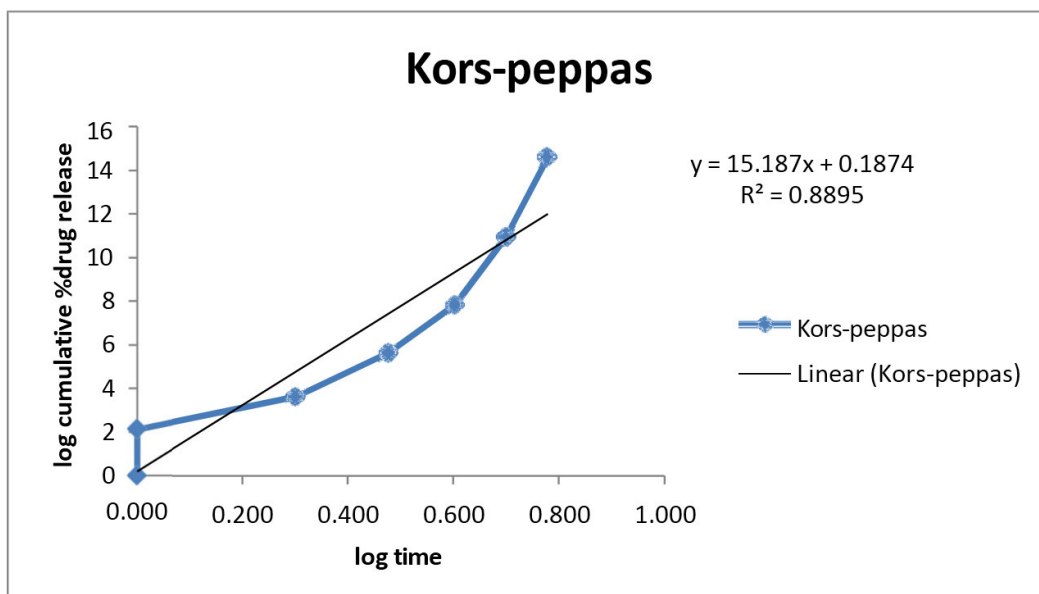


Figure No. 6.68: Log time vs log cumulative % drug release

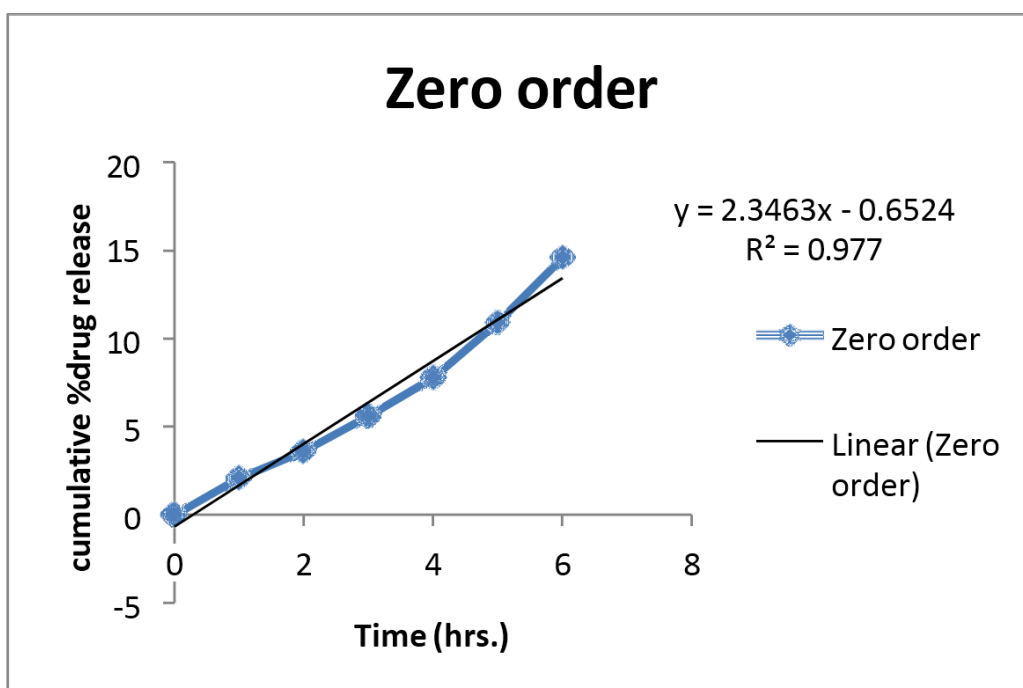


Figure No. 6.69: Time vs Cumulative % drug release

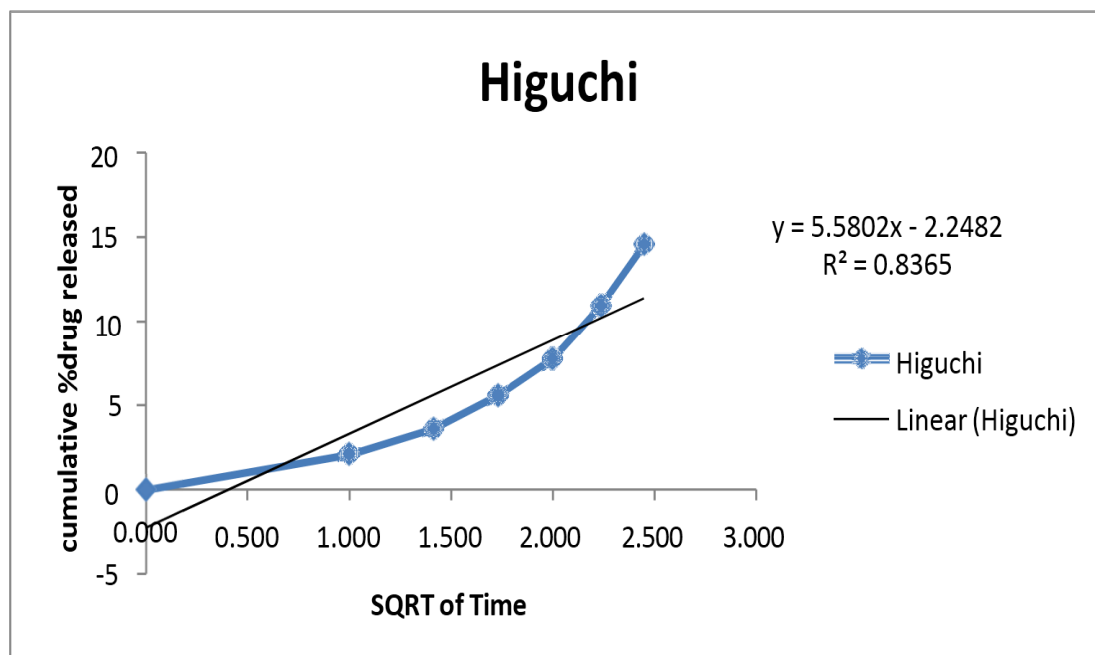


Figure No. 6.70: Sq root time vs cumulative % drug release

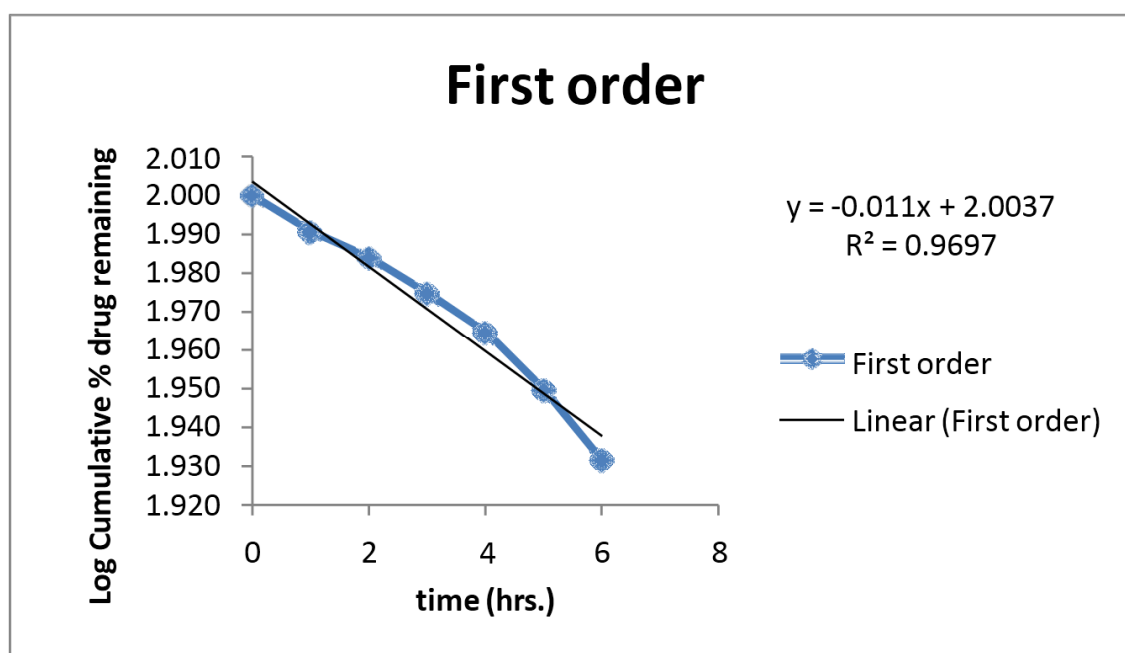


Figure No. 6.71: Time vs Log cumulative % drug remaining



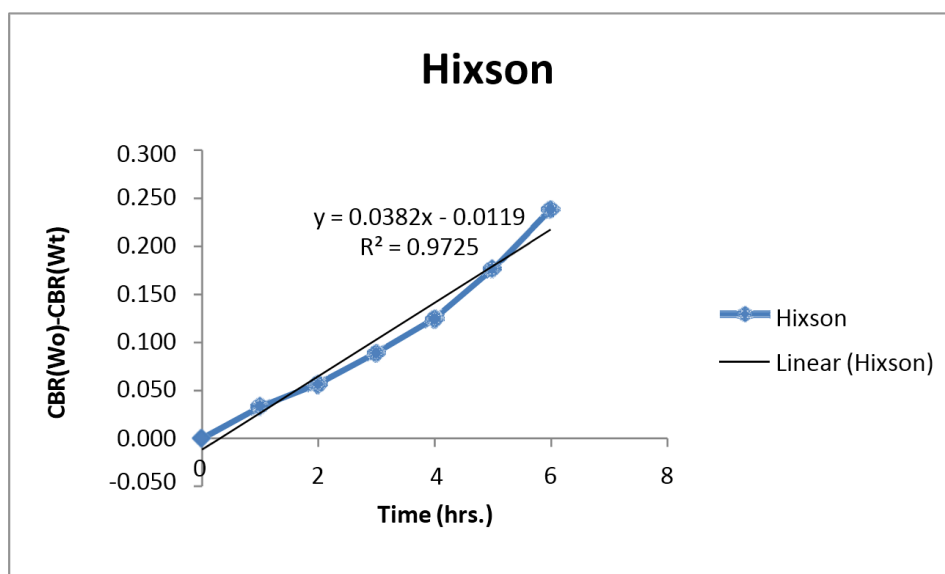


Figure No. 6.72: Time vs Cube root drug remaining

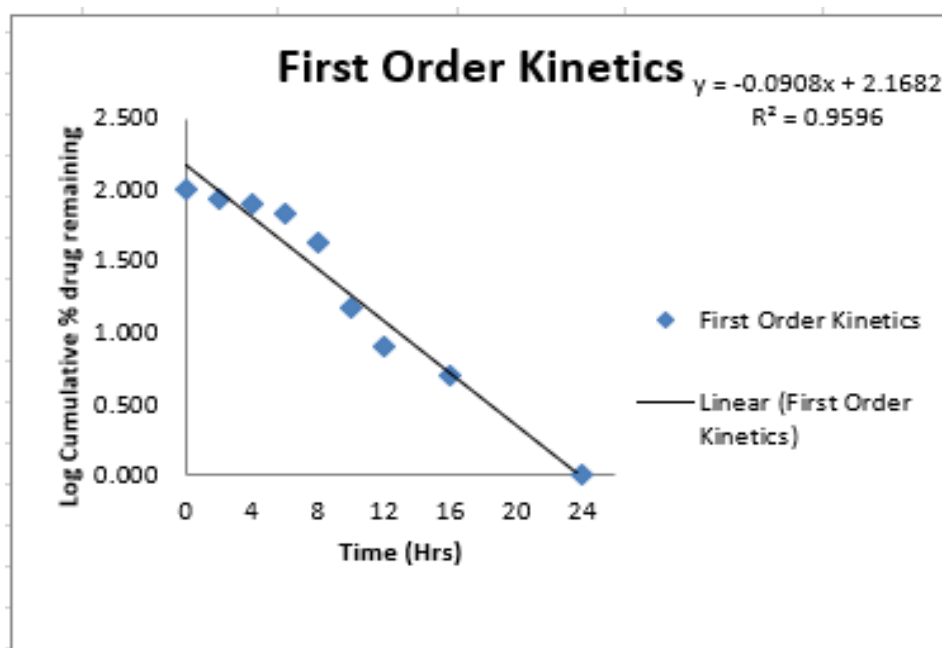


Figure No. 6.73: Time vs cumulative % drug remaining

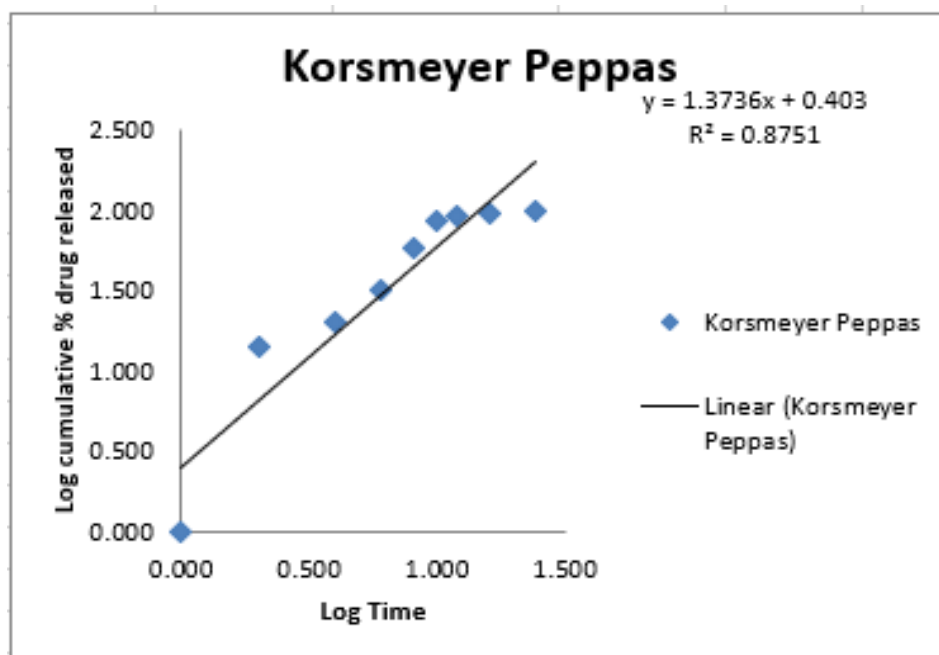


Figure No. 6.74: Log time vs Log cumulative % drug released

Table 6.26: *In-vitro* drug remain data for BL6

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

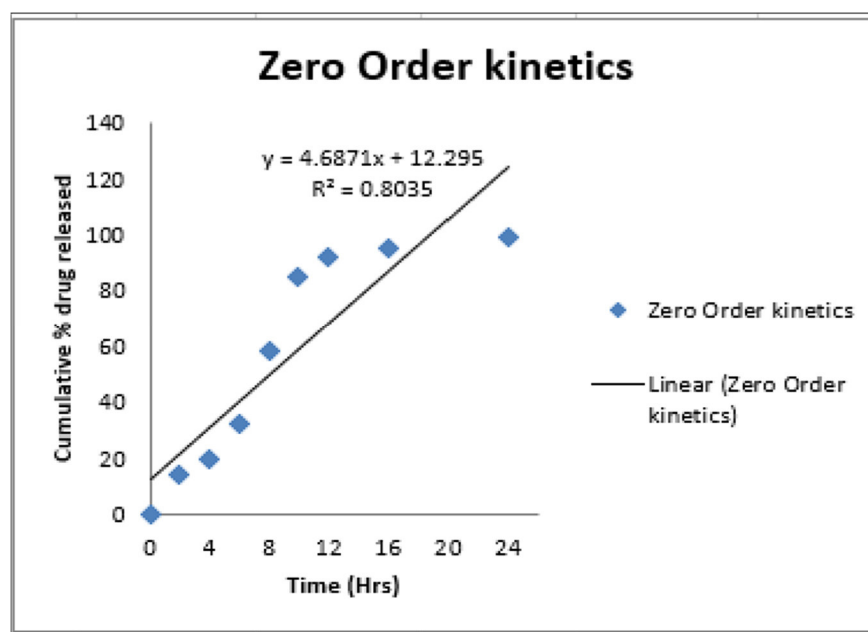


Figure No. 6.75: Time vs Cumulative % drug released

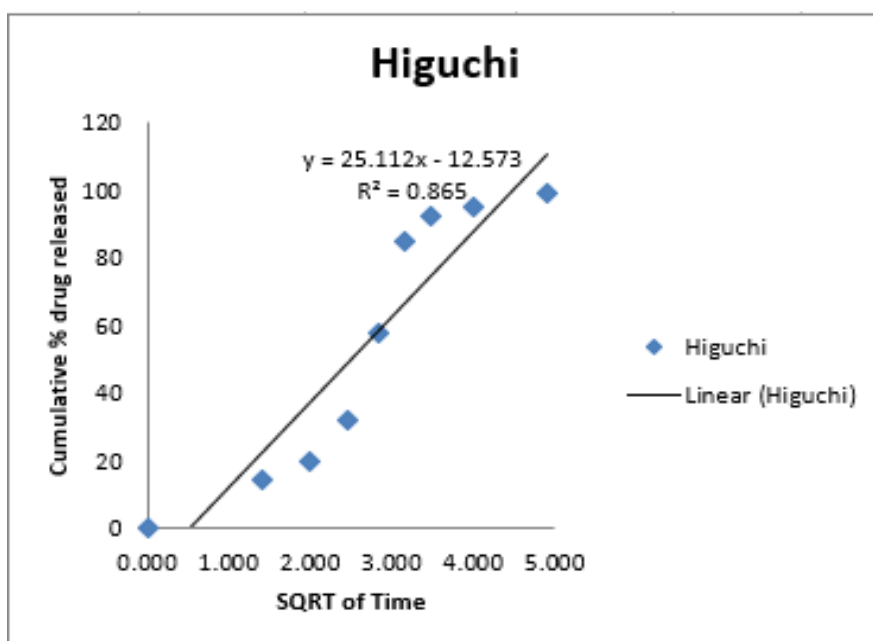


Figure No. 6.76: Sq root time vs Cumulative %drug released

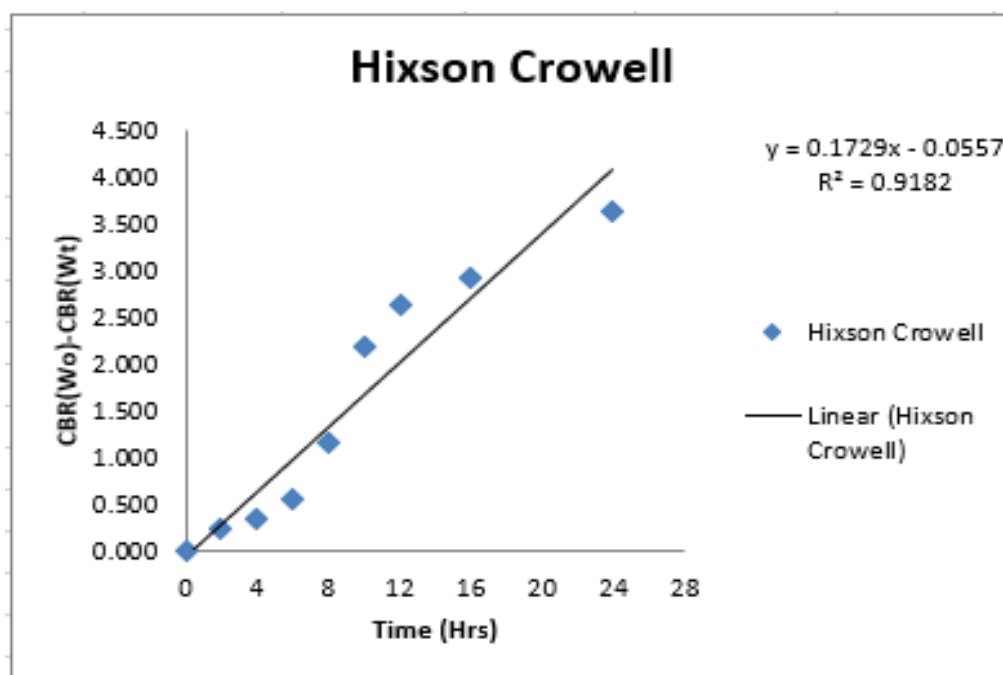


Figure No. 6.77: Time vs Cube root of drug remain

The machinery of drug release from a dosage form is interpreted mostly through the use of mathematical models. Comprehending the drug release kinetics of a dosage form is a crucial instrument. Higuchi square root model ( $r^2 = 0.865$  for BL5 and  $r^2 = 0.8365$  for BL6) was determined to best fit the drug release data. This suggests that drug release is a time-dependent, diffusion-controlled process with a square root. The dissolving data was also shown in accordance with the Hixson-Crowell model, which shows how the formulation's surface area and diameter changed as a function of time ( $r^2 = 0.9182$  for BL5 and  $r^2 = 0.9725$  for BL6). The kind of diffusion is also stated by the model Korsmeyer-Peppas power law equation; this was determined by evaluating the value of  $n$  (Release exponent), which is more than 0.875, indicating that the drug release from the system follows Super case II transport. The permeability is studied using goatskin rather than ratskin, and the outcomes are compared. In goatskin, the penetration rate is doubled. A comparative analysis reveals that the proportion of permeation has increased by twofold.

## GOAT SKIN DRUG RELEASE OF FORMULATION SCO4

Table 6.27: Cumulative % drug release data wrt to Time

Time (Hr)	cumulative % drug released		
0	0	0	0
1	6.93145	5.392025	15.26
2	11.347775	15.1226	27.849
3	16.881925	28.35325	43.627
4	25.8795	48.7673	61.549
5	42.11545	72.0034	80.057
6	62.621125	95.587675	100.51
7	85.28915	--	--

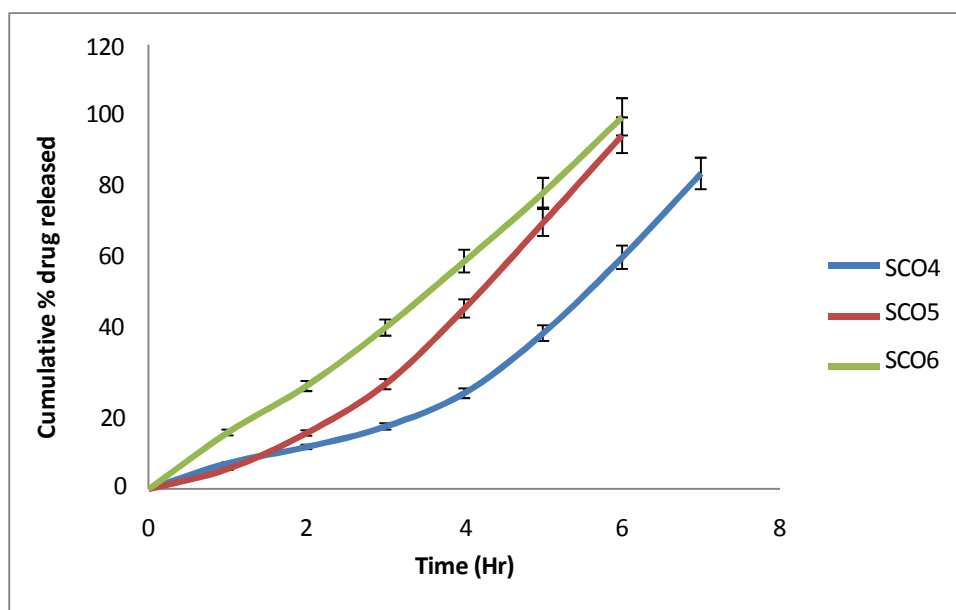


Figure No. 6.78: Time vs cumulative % drug released

Table 6.28: Log cum % drug release wrt to Time

Time (Hr)	L og Cumu % drug remaining		
0	2	2	2
1	1.969	1.976	1.928
2	1.948	1.929	1.858
3	1.92	1.855	1.751
4	1.87	1.71	1.585
5	1.763	1.447	1.3
6	1.573	0.645	--
7	1.168	--	---

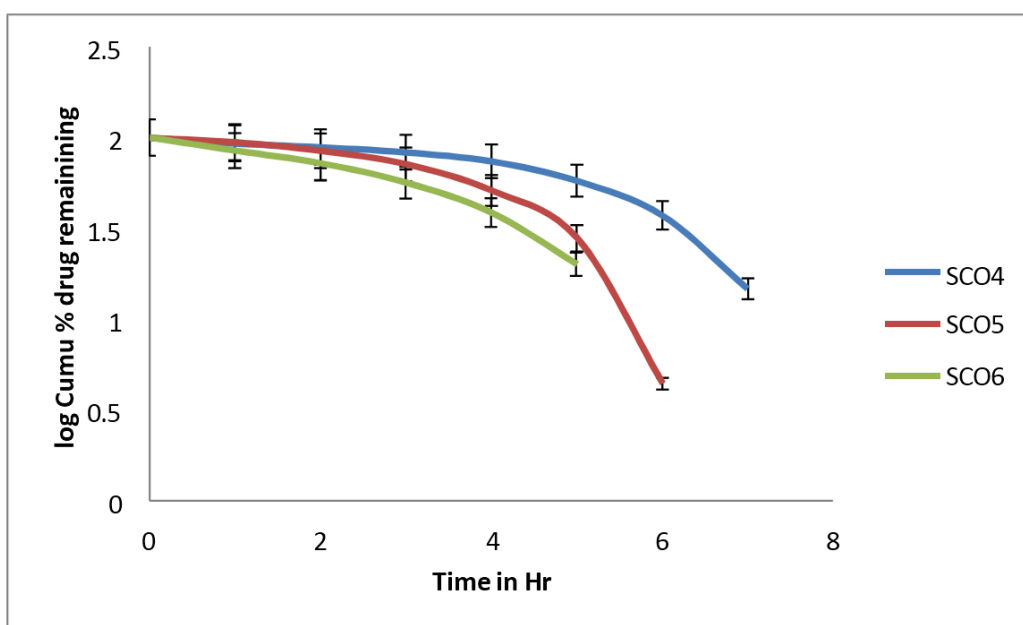


Figure No. 6.79: Time vs log cumulative % drug remaining.

Table 6.29: Cumulative % drug released data wrt to SQRT

Square root time	cumulative % drug released		
0	0	0	0
1	6.93145	5.392025	15.26
1.414	11.34778	15.1226	27.849
1.732	16.88193	28.35325	43.627
2	25.8795	48.7673	61.549
2.236	42.11545	72.0034	80.057
2.449	62.62113	95.58768	100.51
2.646	85.28915	--	--

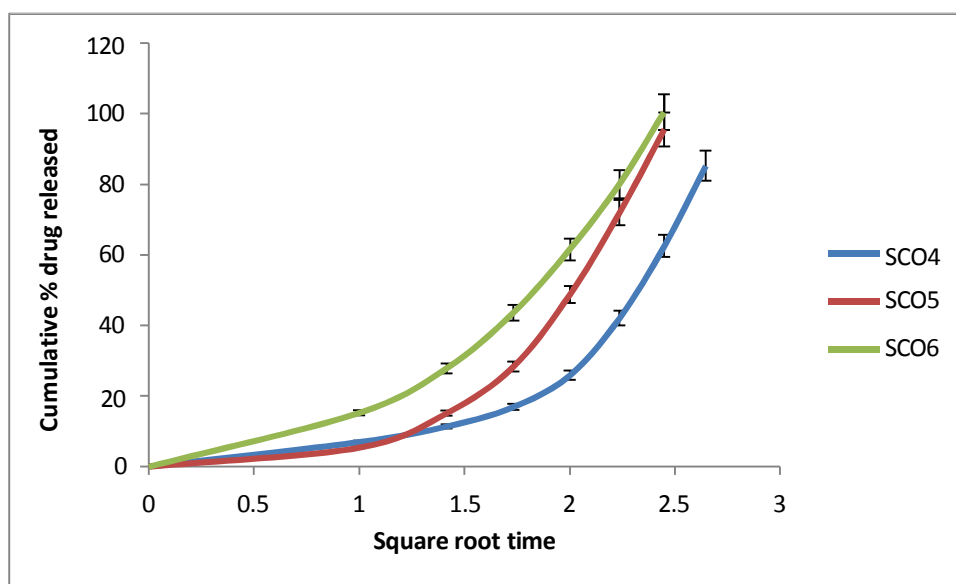


Figure No. 6.80: Sq root time vs cumulative % drug released



Table 6.30: Log cumulative % drug released wrt to log time

Log time	log Cumu % drug released		
0	0	0	0
0	0.841	0.732	1.184
0.301	1.055	1.18	1.445
0.477	1.227	1.453	1.64
0.602	1.413	1.688	1.789
0.699	1.624	1.857	1.903
0.778	1.797	1.98	2.002
0.845	1.931	--	--

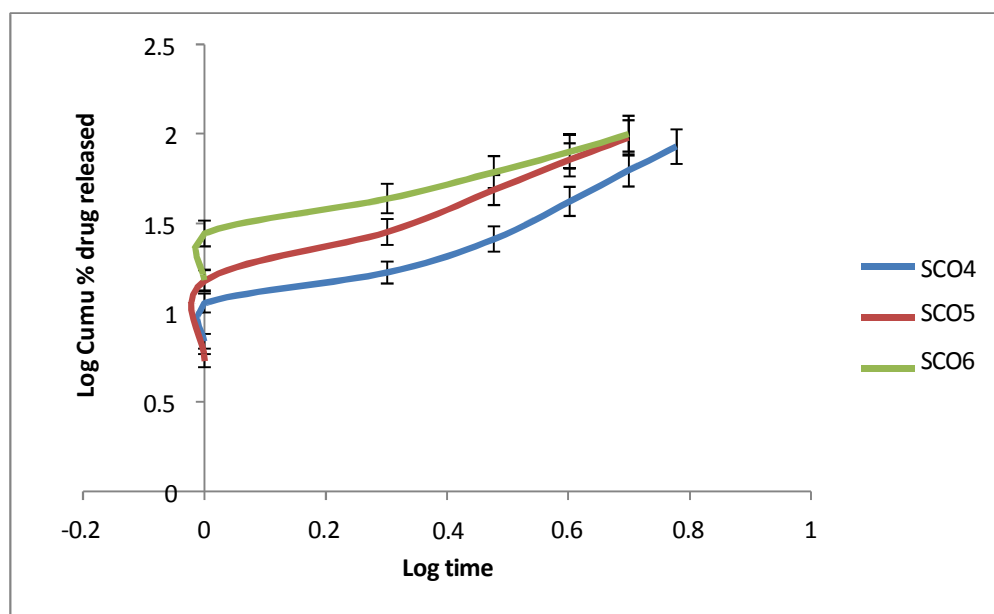


Figure No. 6.81: Log time vs log cumulative % drug released

Table 6.31: *In-vitro* drug release data for optimization of SCO4

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	W <sub>0</sub> -W <sub>t</sub>
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	6.93145	93.06855	1.000	1.969	0.000	0.841	6.93145	4.532	0.110
2	11.34778	88.65223	1.414	1.948	0.301	1.055	4.416325	4.459	0.183
3	16.88193	83.11808	1.732	1.920	0.477	1.227	5.53415	4.364	0.278
4	25.8795	74.1205	2.000	1.870	0.602	1.413	8.997575	4.201	0.441
5	42.11545	57.88455	2.236	1.763	0.699	1.624	16.23595	3.868	0.774
6	62.62113	37.37888	2.449	1.573	0.778	1.797	20.50568	3.344	1.298
7	85.28915	14.71085	2.646	1.168	0.845	1.931	22.66803	2.450	2.192

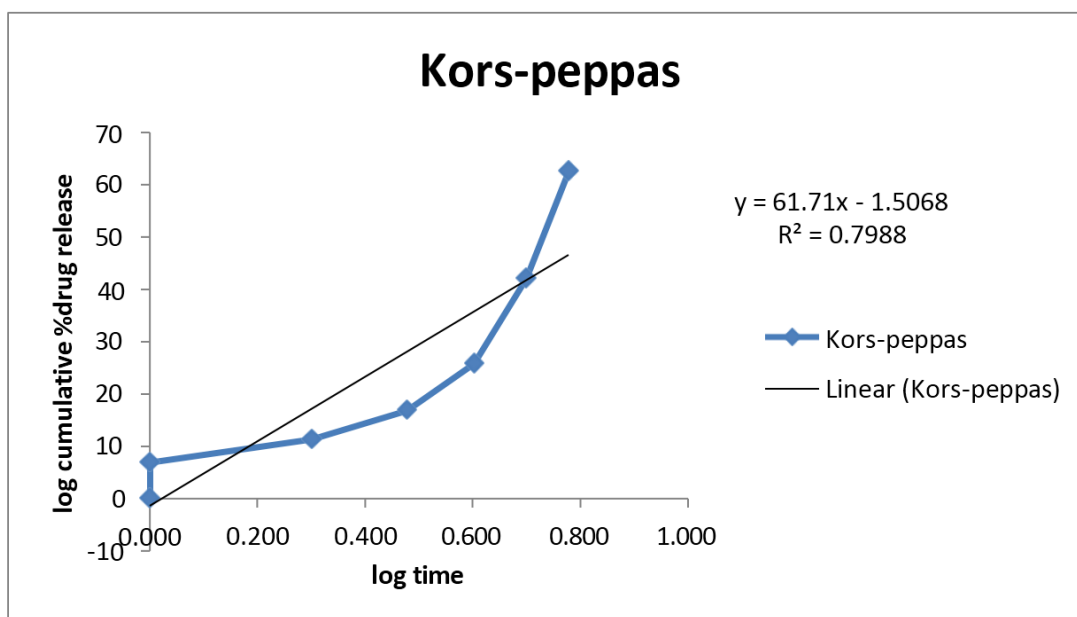


Figure No. 6.82: Log time vs log cumulative % drug release

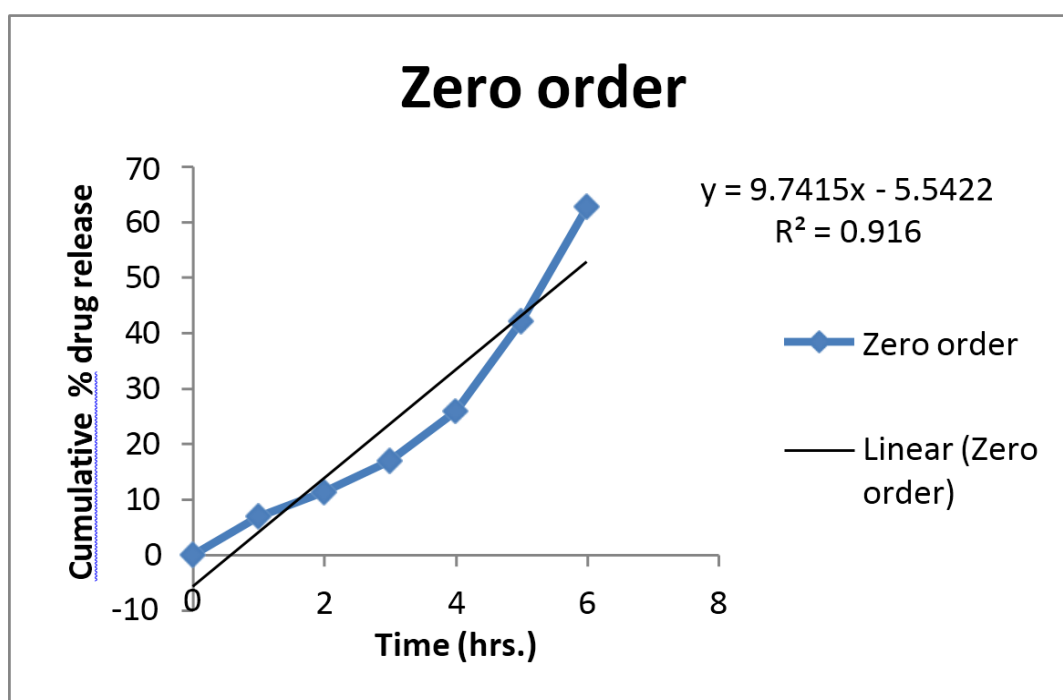


Figure No. 6.83: Time vs cumulative % drug release

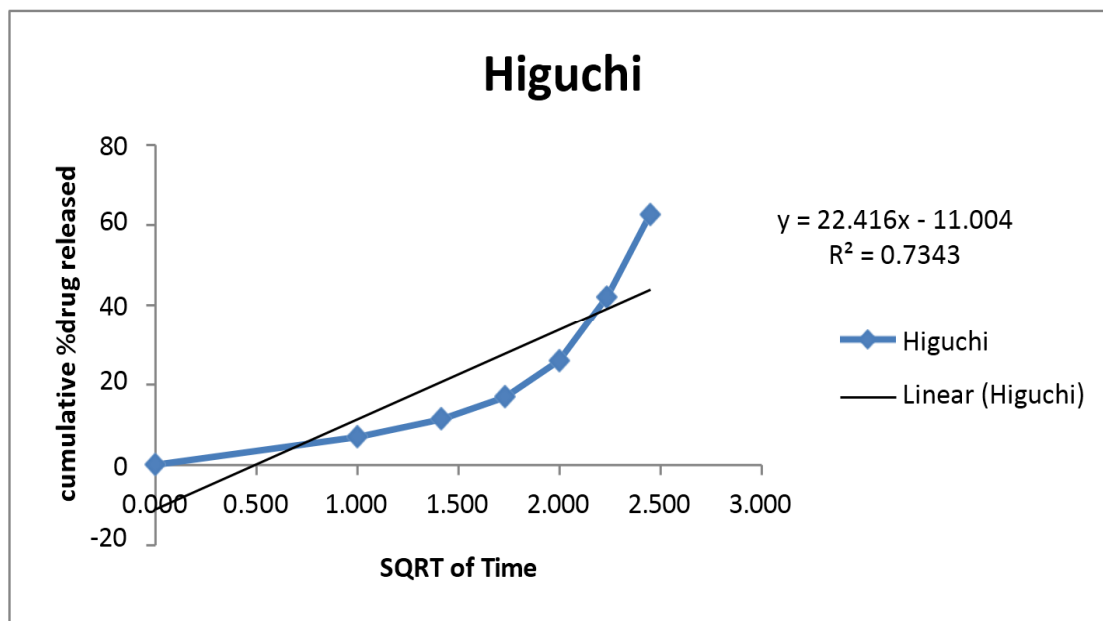


Figure No. 6.84: Sq root time vs cumulative % drug released

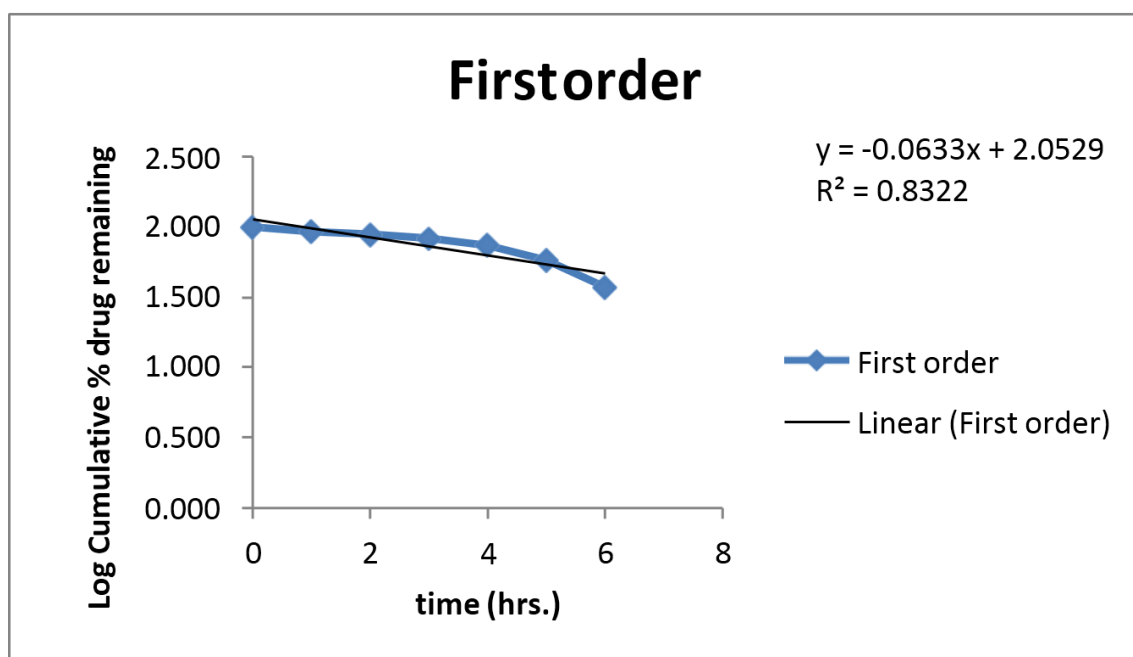
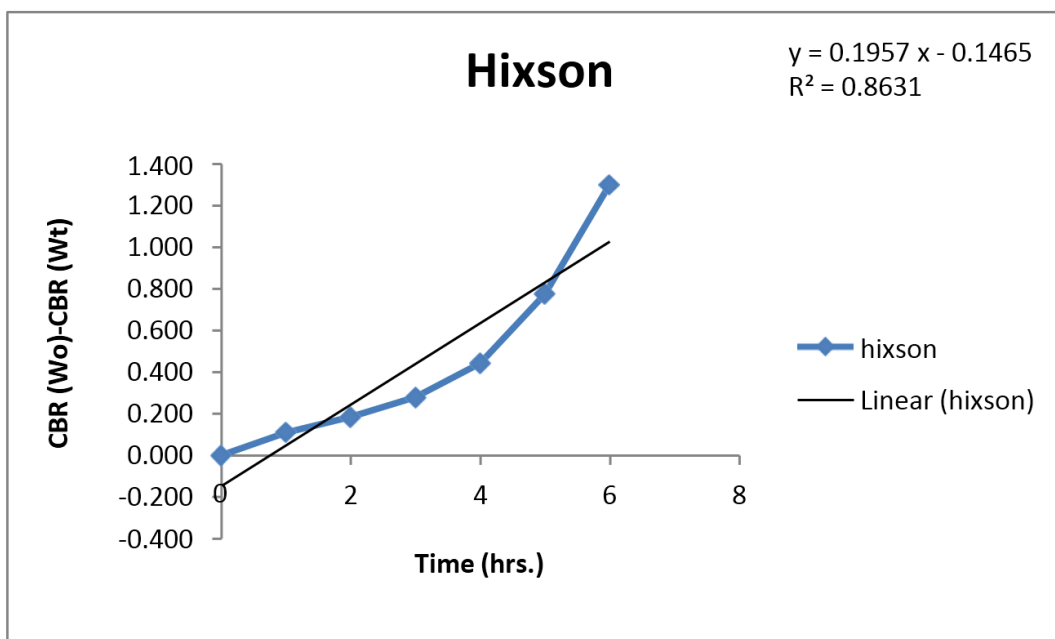


Figure No. 6.85: Time vs Log cumulative % drug remaining



**Figure No. 6.86: Time vs cube root drug remained**

Table 6.32: *In-vitro* drug remain data for SCO4

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	W <sub>0</sub> -W <sub>t</sub>
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

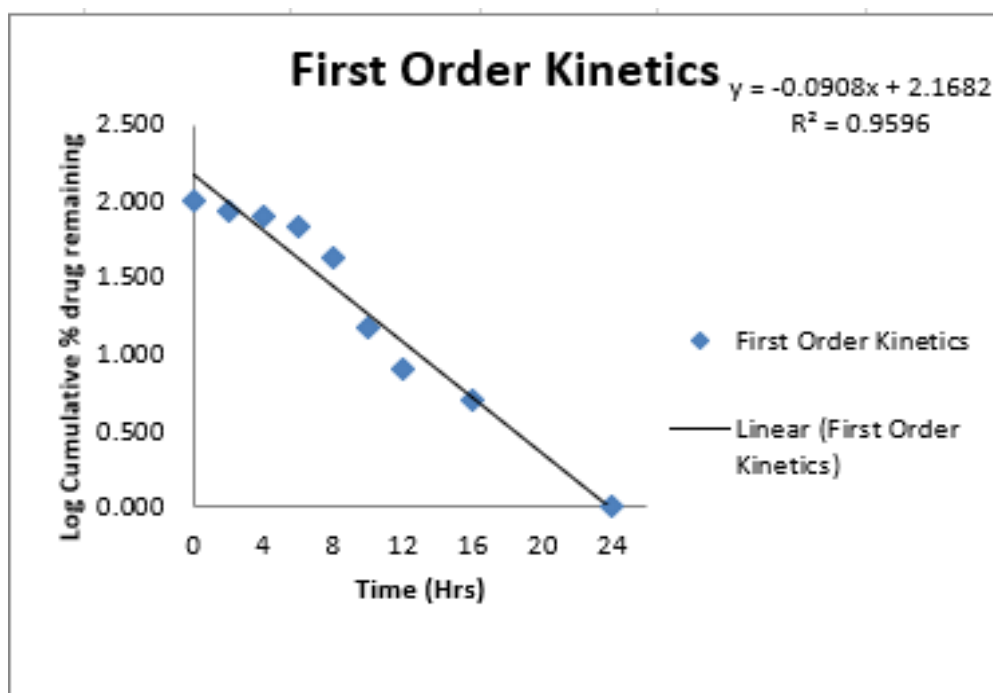


Figure No. 6.87: Time vs log cumulative % drug remaining

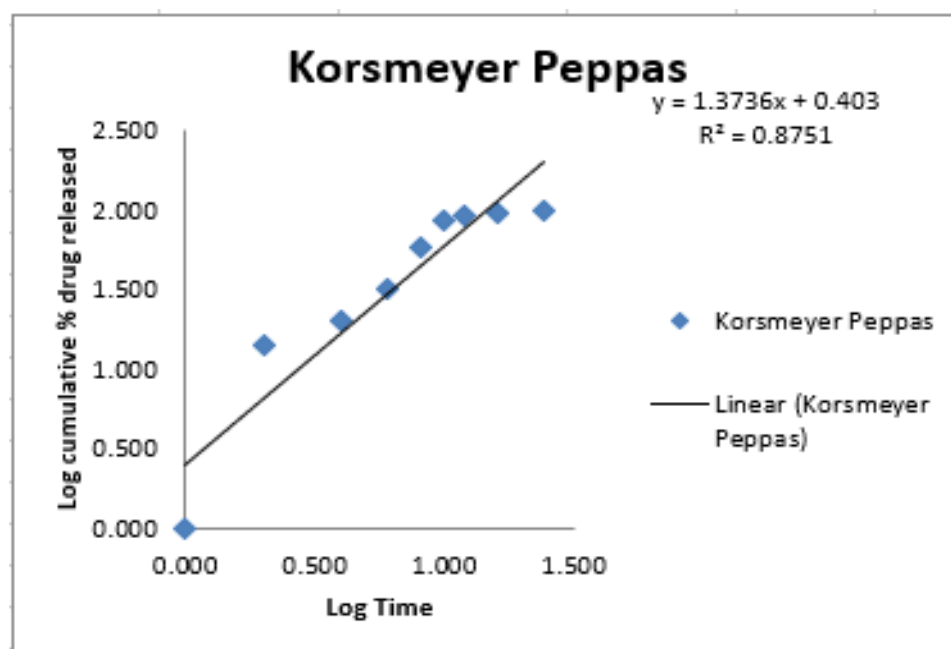


Figure No. 6.88: Log time vs &lt;Log cumulative % drug released

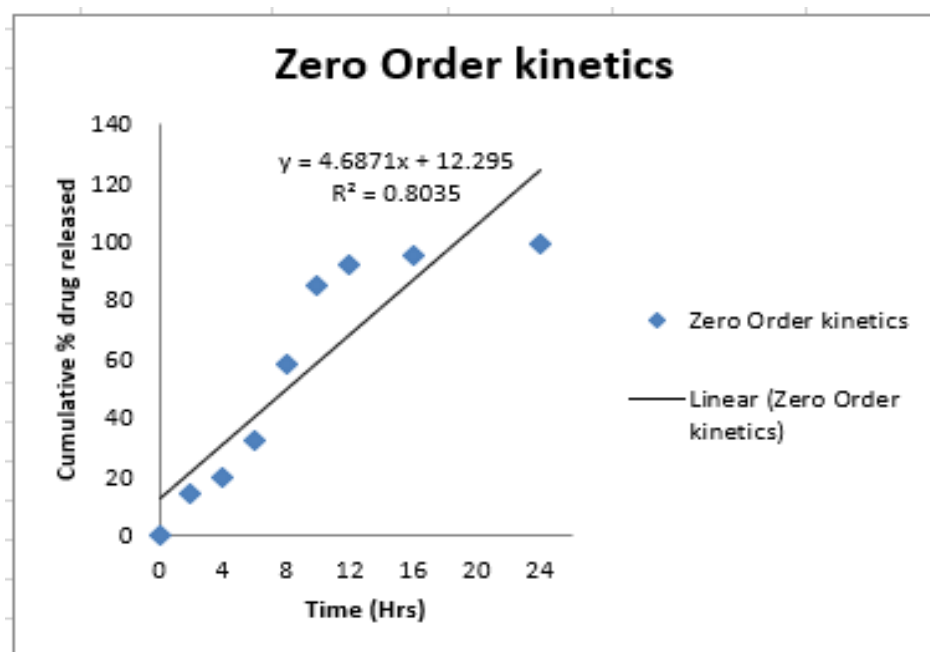


Figure No. 6.89: Time vs cumulative % drug released

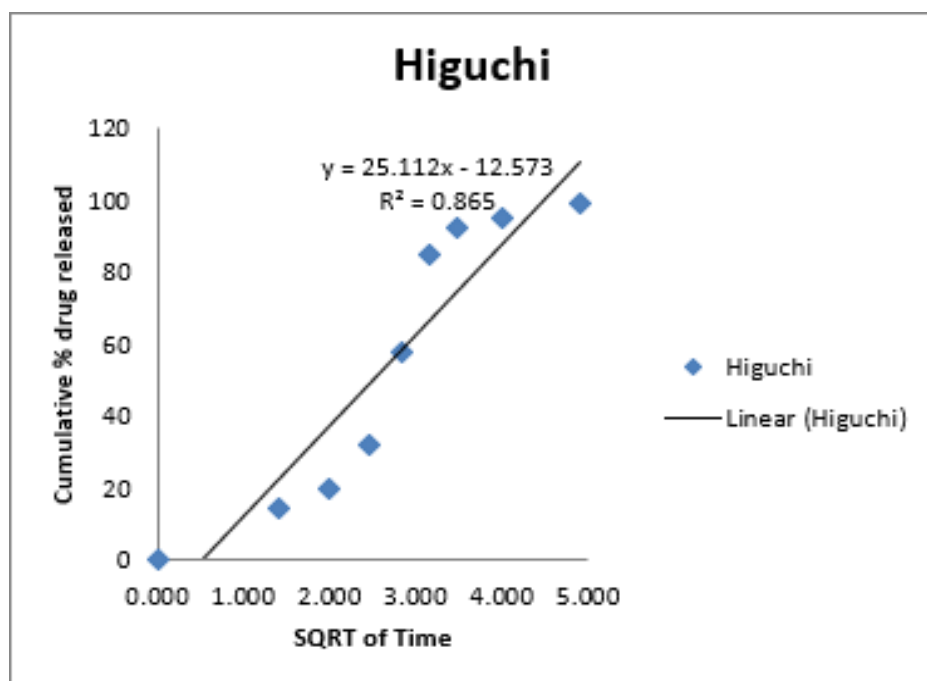


Figure No. 6.90: Sq root time vs cumulative % drug released



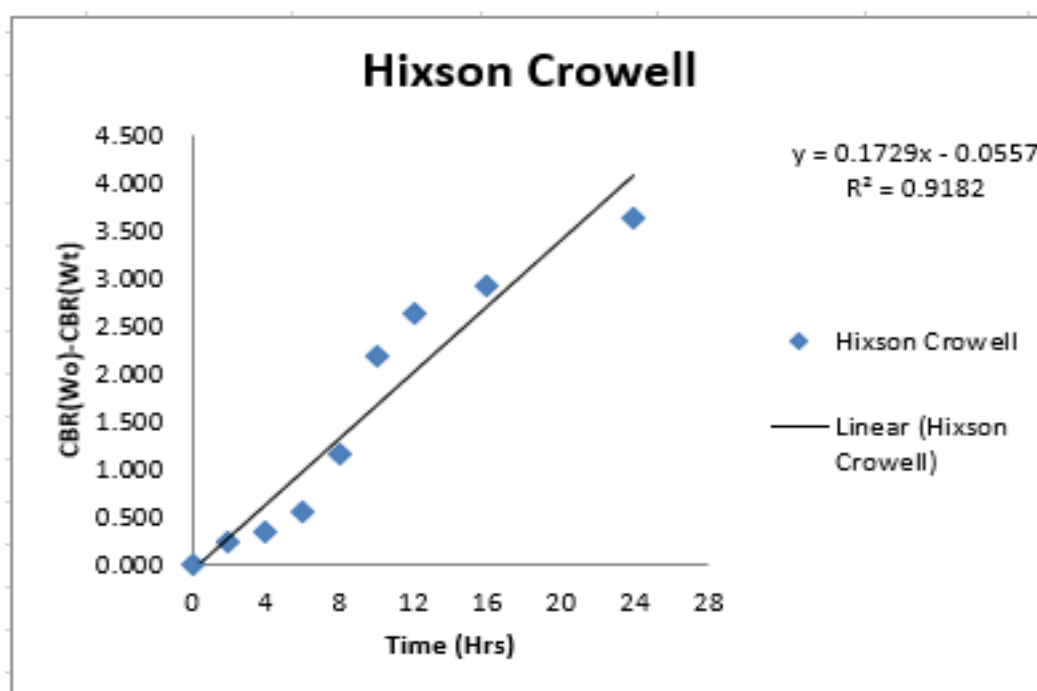


Figure No. 6.91: Time vs cube root of drug remain

## GOAT SKIN DRUG RELEASE OF FORMULATION SCO5

Table 6.33: *In-vitro* drug release data for optimization of SCO5

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	W <sub>0</sub> -Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	5.392025	94.60798	1.000	1.976	0.000	0.732	5.392025	4.557	0.085
2	15.1226	84.8774	1.414	1.929	0.301	1.180	9.730575	4.395	0.247
3	28.35325	71.64675	1.732	1.855	0.477	1.453	13.23065	4.153	0.489
4	48.7673	51.2327	2.000	1.710	0.602	1.688	20.41405	3.714	0.928
5	72.0034	27.9966	2.236	1.447	0.699	1.857	23.2361	3.036	1.606
6	95.58768	4.412325	2.449	0.645	0.778	1.980	23.58428	1.640	3.002

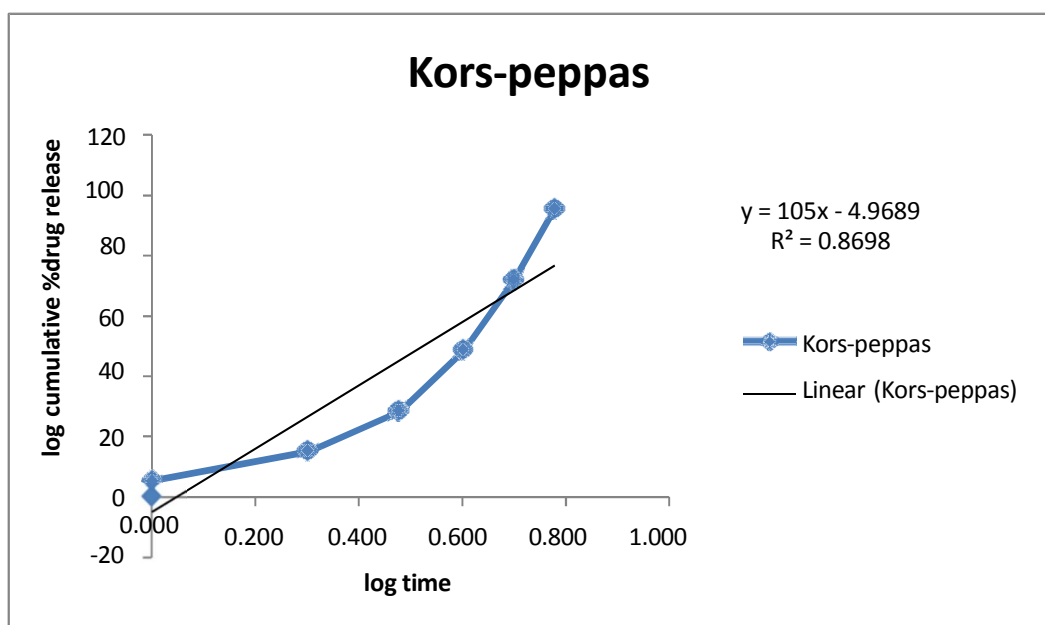


Figure No. 6.92: Log time vs log cumulative % drug release

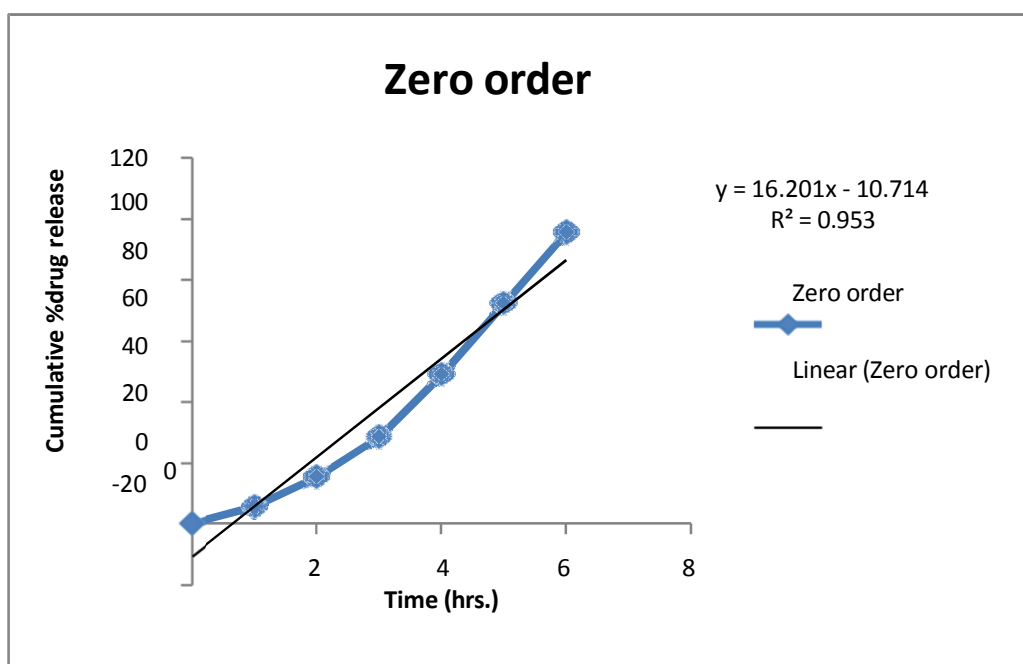


Figure No. 6.93: Time vs cumulative % drug release

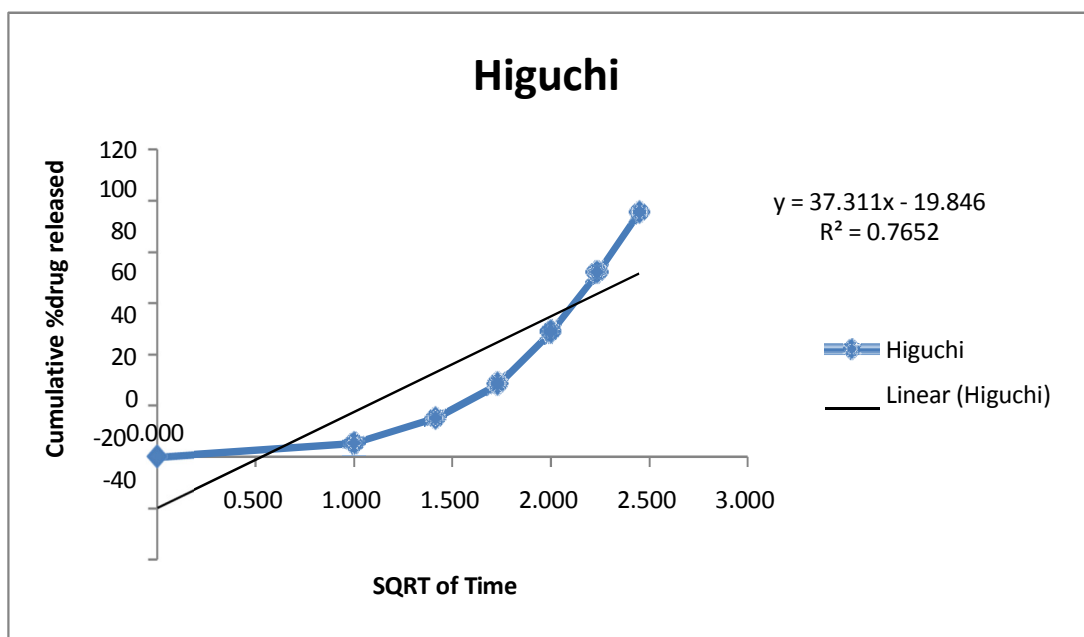


Figure No. 6.94: Sq root time vs cumulative % drug released

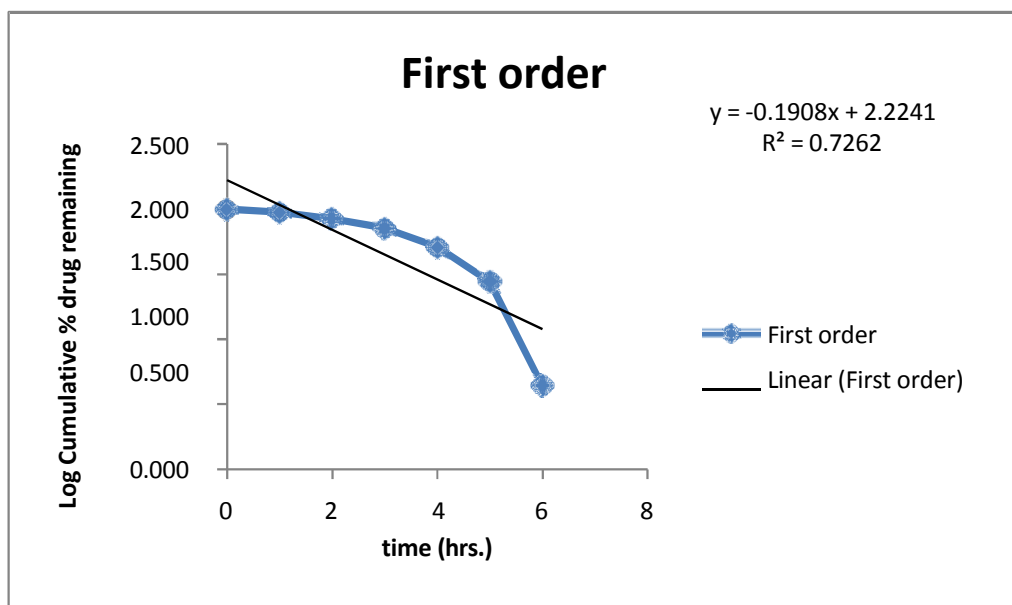
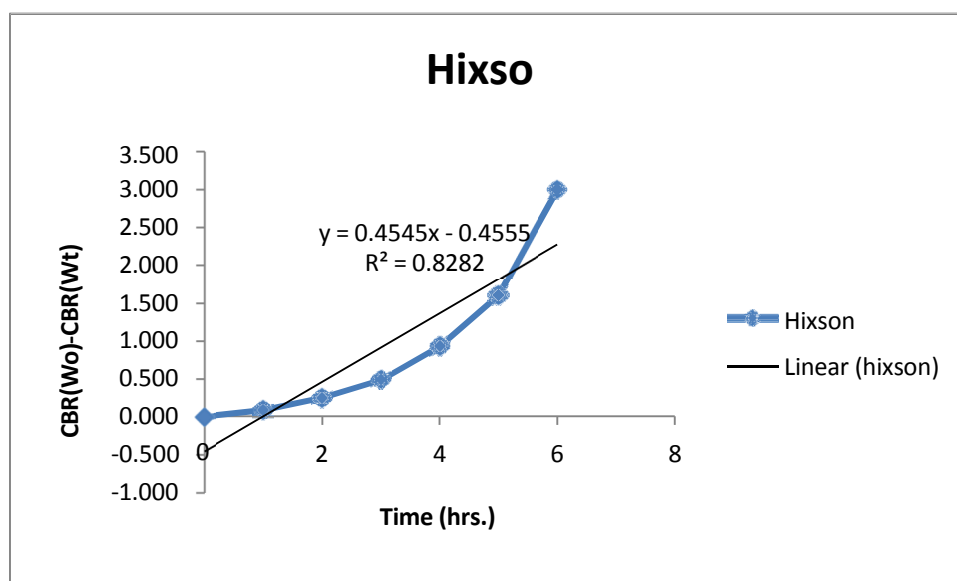


Figure No. 6.95: Time vs Log cumulative % drug remaining



**Figure No. 6.96: Time vs Cube root drug remain**

Table 6.34: *In-vitro* drug remaining data for SCO5

Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

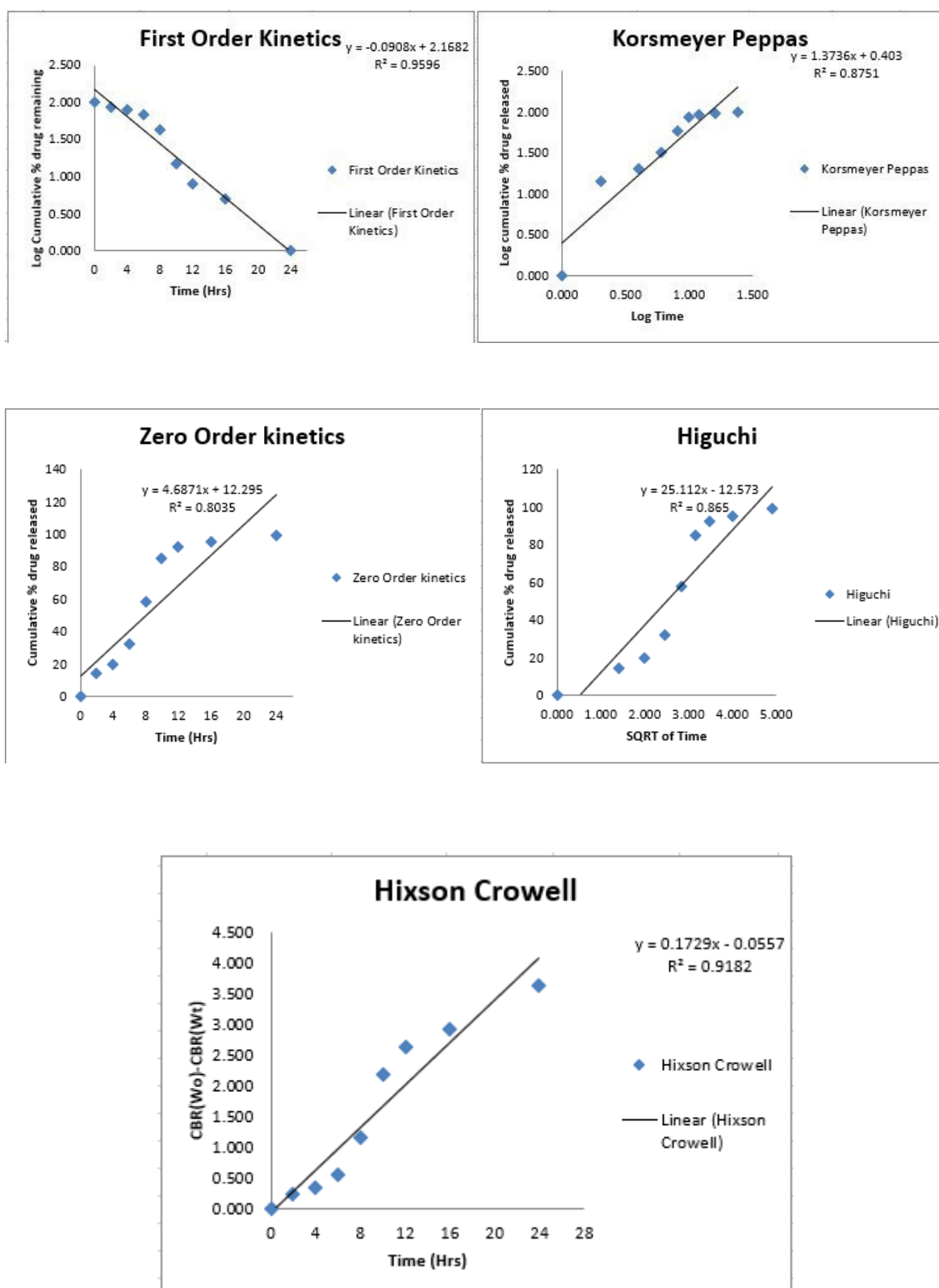


Figure No. 6.97: Time vs cube root drug remain.

## GOAT SKIN DRUG RELEASE OF FORMULATION SCO6

Table 6.35: *In-vitro* drug release data for optimization of SCO6

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	15.2597	84.7403	1.000	1.928	0.000	1.184	15.2597	4.392	0.250
2	27.84898	72.15103	1.414	1.858	0.301	1.445	12.58928	4.163	0.479
3	43.6268	56.3732	1.732	1.751	0.477	1.640	15.77783	3.834	0.808
4	61.54865	38.45135	2.000	1.585	0.602	1.789	17.92185	3.375	1.267
5	80.0569	19.9431	2.236	1.300	0.699	1.903	18.50825	2.712	1.930
6	100.5076	-0.5076	2.449	#NUM!	0.778	2.002	20.4507	-0.798	5.440



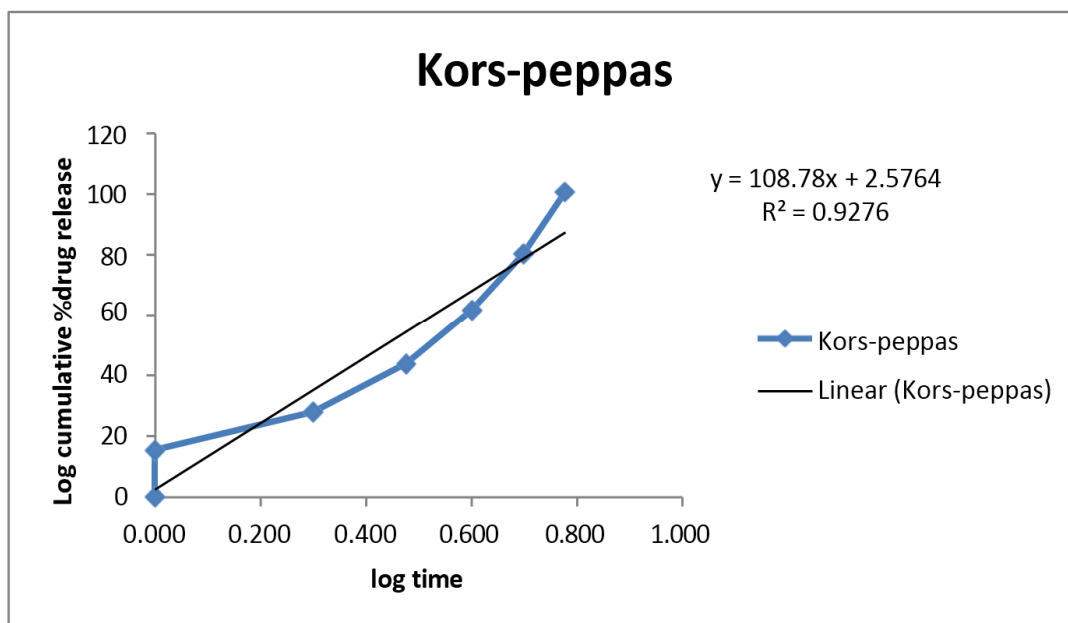


Figure No. 6.98: Log time vs Log cumulative % drug release

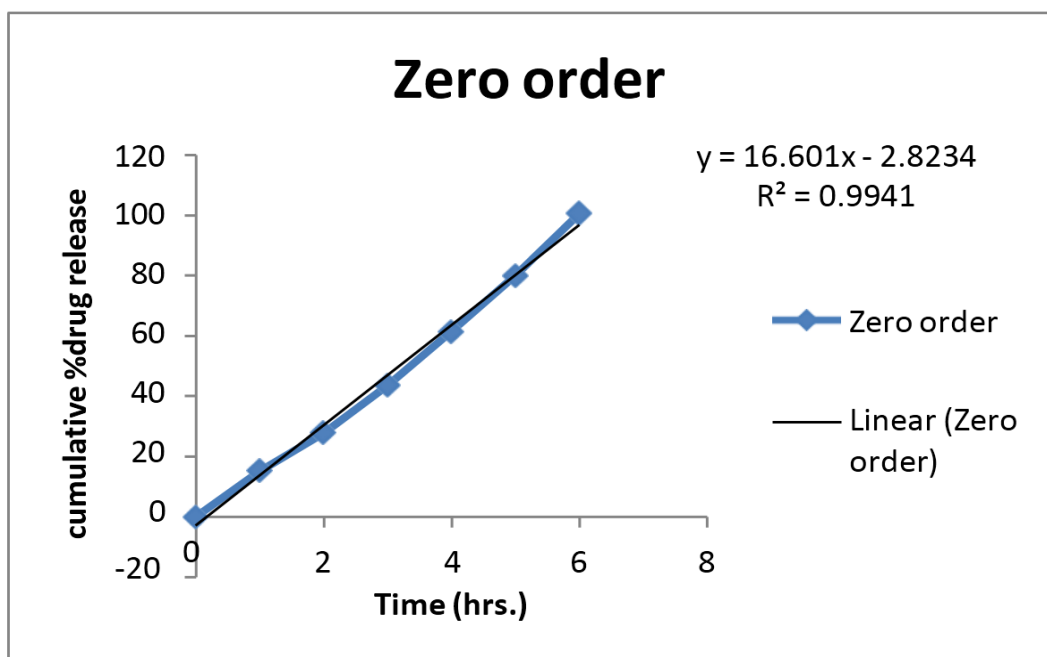


Figure No. 6.99: Time vs Cumulative % drug release

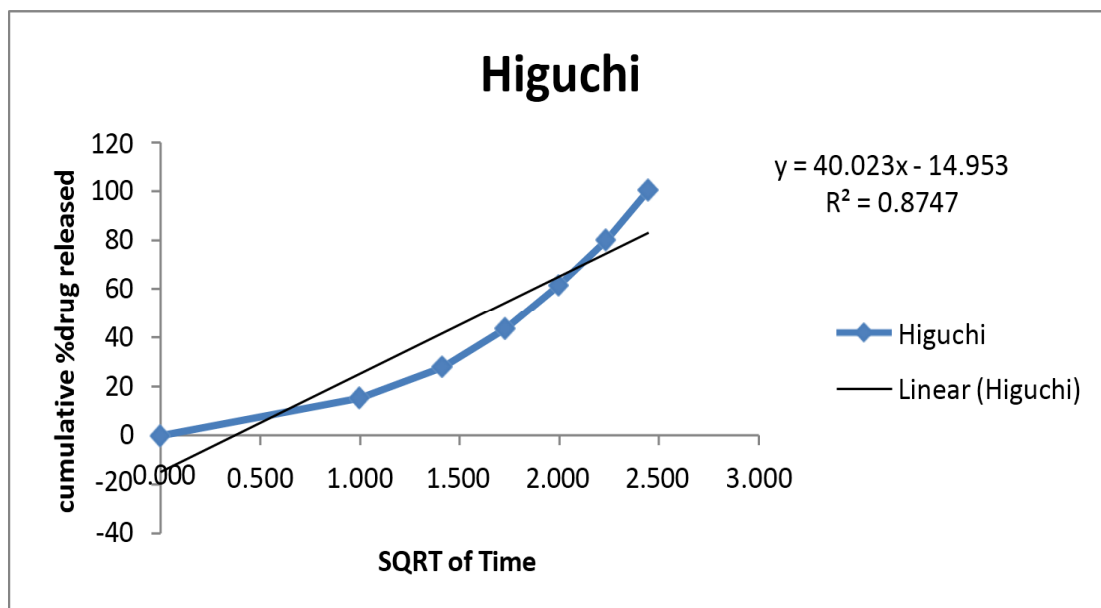


Figure No. 6.100: Sq root time vs cumulative % drug released

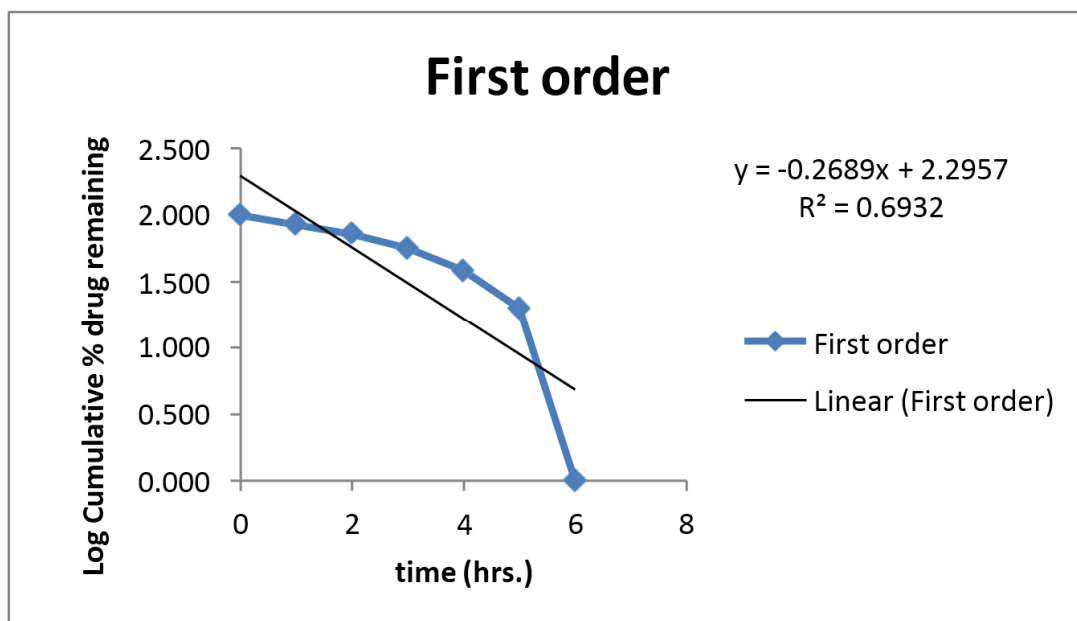


Figure No. 6.101: Time vs log cumulative % drug remaining

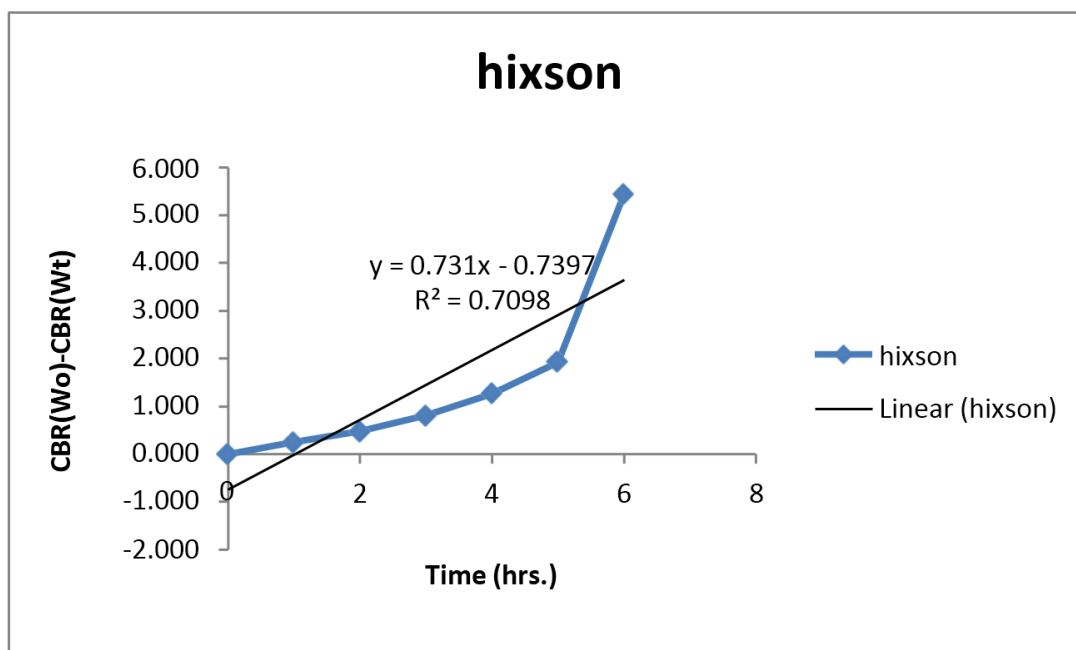


Figure No. 6.102: Time vs cube root drug remain

Table 6.36: *In-vitro* drug remaining data for SCO6

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	W <sub>0</sub> -W <sub>t</sub>
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

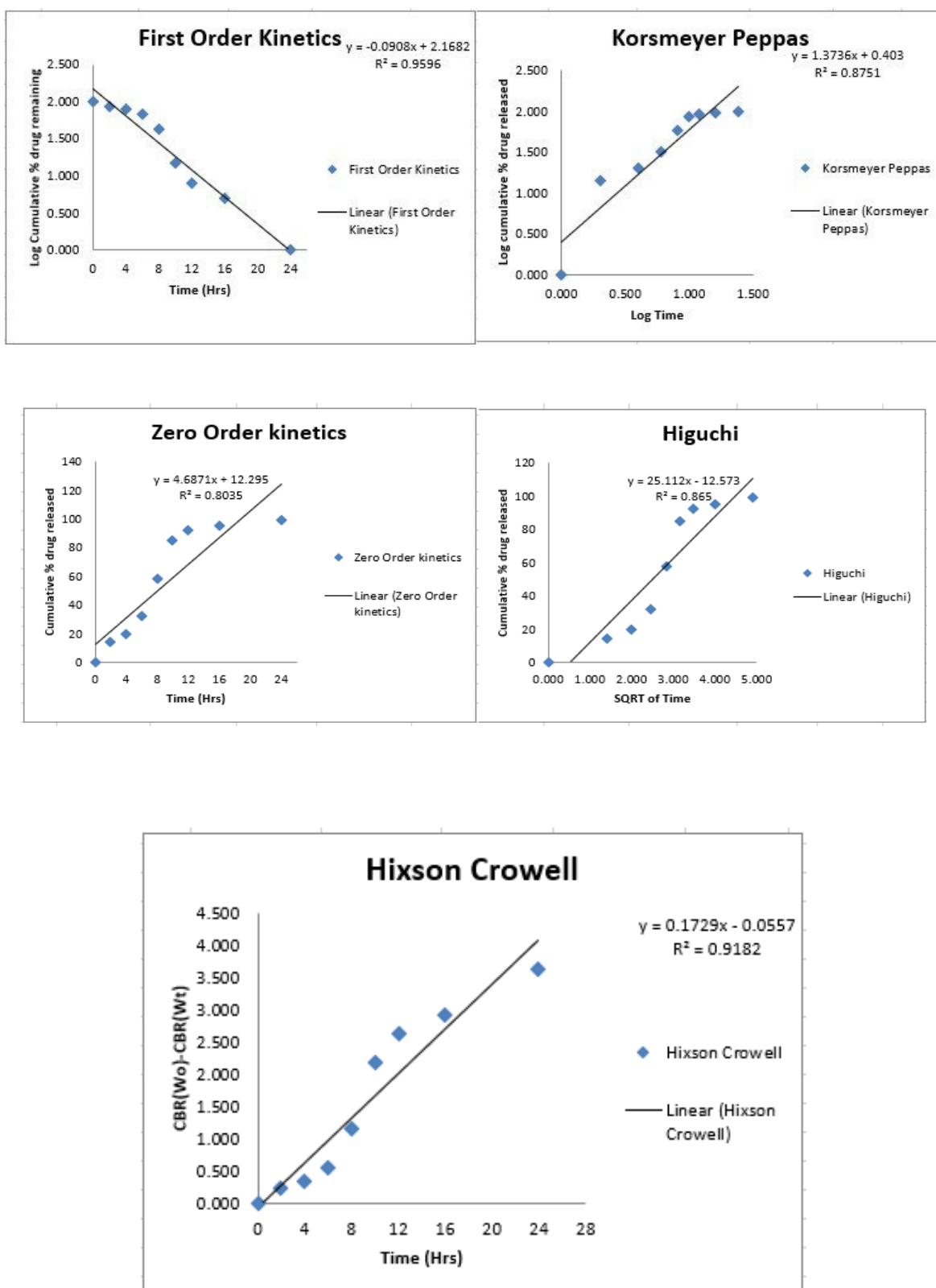


Figure No. 6.103: Time vs cube root of drug remain

When interpreting the process of drug release from a dosage form, mathematical models are essential. Understanding a dosage form's drug release kinetics is a crucial tool. The Higuchi square root model was determined to be the best fit for the drug release;  $r^2 = 0.7343$  for SCO4,  $r^2 = 0.865$  for SCO5, and  $r^2 = 0.7652$  for SCO6 indicate that the drug release is regulated by diffusion and is a time-dependent process. The dissolving data was also plotted in accordance with the Hixson–Crowell method, which shows how the formulation's surface area and diameter changed as a function of time for SCO4, SCO5, and SCO6 ( $r^2 = 0.8631$  and  $r^2 = 0.8282$  and  $r^2 = 0.9182$  respectively). Furthermore, the type of diffusion is indicated by the model Korsmeyer-Peppas power law equation, which was evaluated by the value of  $n$  (Release exponent), which is higher than 0.79, indicating that the drug release from the system follows Super case II transport.

## DRUG RELEASE OF FORMULATION BL4 THROUGH SNAKE SKIN

Table 6.37: Cumulative % drug release wrt to time

Time (Hr)	Cumulative % drug released		
0	0	0	0
1	2.685625	0.658475	0.5574
2	4.82965	1.281525	1.1071
3	7.633375	2.1428	1.8584
4	10.91355	3.169	2.848
5	15.329875	4.8549	4.4789
6	20.5525	7.218825	6.2564
7	26.251575	15.22685	9.5183

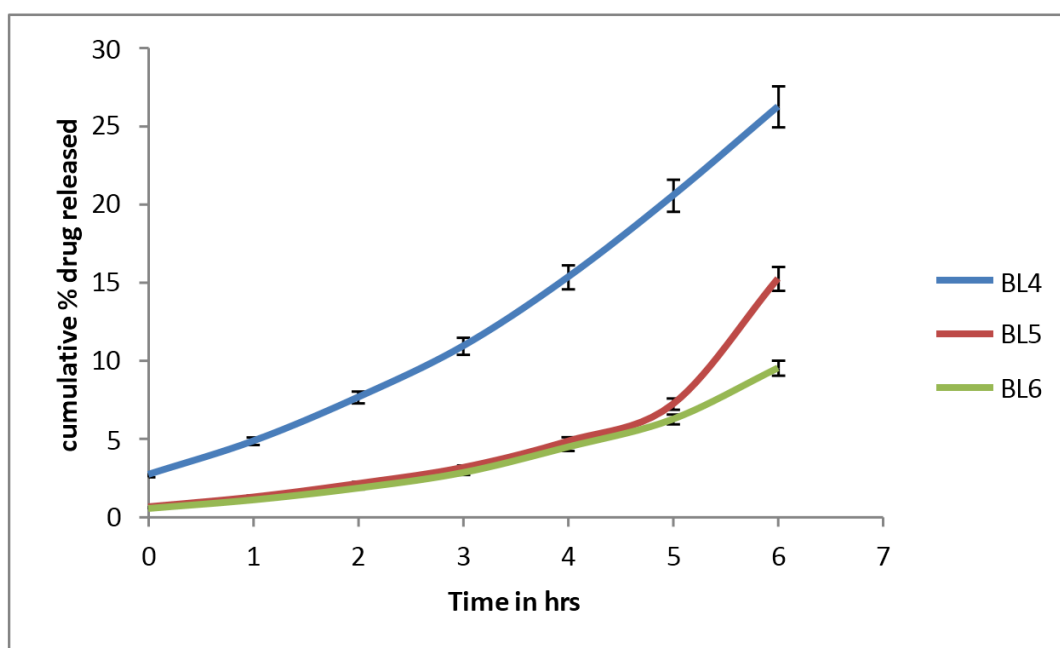


Figure No. 6.104: Time vs cumulative % drug released

Table 6.38: Log cumulative % drug remaining wrt to Time

Time (Hr)	Log Cumu % drug remainining		
0	2	2	2
1	1.988	1.997	1.998
2	1.979	1.994	1.995
3	1.966	1.991	1.992
4	1.95	1.986	1.987
5	1.928	1.978	1.98
6	1.9	1.967	1.972
7	1.868	1.928	1.957

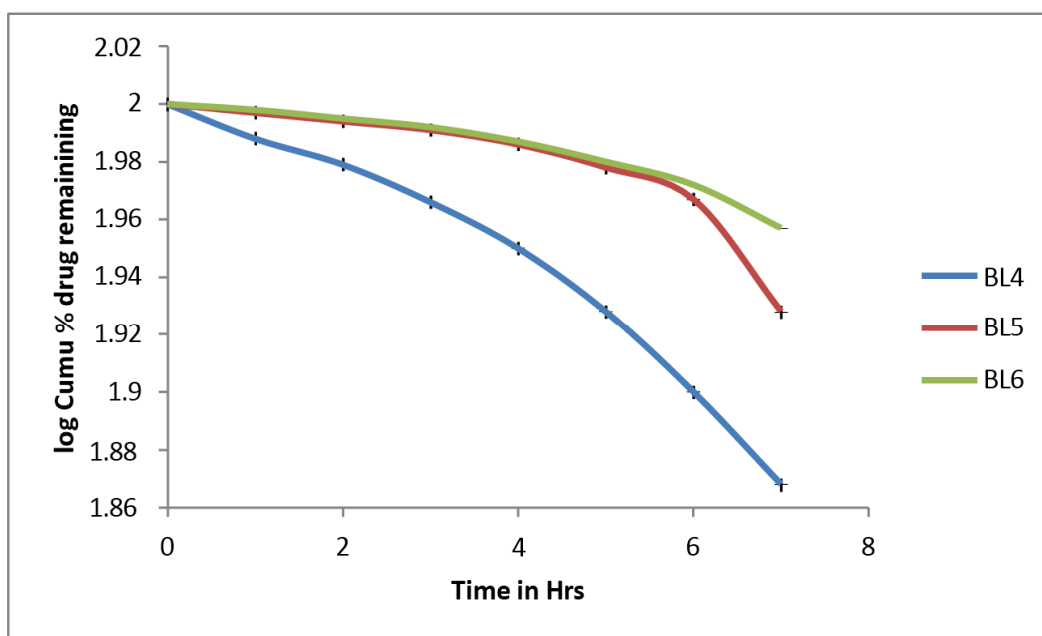


Figure No. 6.105: Time vs log cumulative % drug remaining



Table 6.39: Cumulative % drug released wrt to SQRT

Square root time	cumulative % drug released		
0	0	0	0
1	2.685625	0.658475	0.5574
1.414	4.82965	1.281525	1.1071
1.732	7.633375	2.1428	1.8584
2	10.91355	3.169	2.848
2.236	15.32988	4.8549	4.4789
2.449	20.5525	7.218825	6.2564
2.646	26.25158	15.22685	9.5183

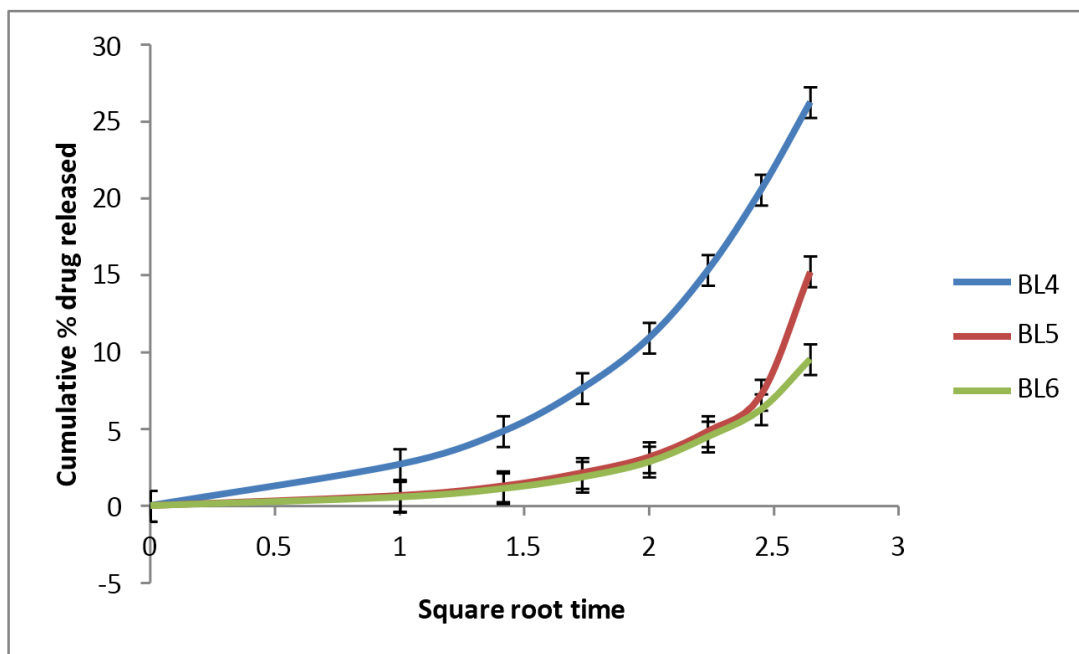


Figure No. 6.106: Sq root time vs cumulative % drug released

Table 6.40: Log cumulative % drug released wrt log time

Log time	Log cumulative % drug released		
0	0	0	0
0	0.429	-0.181	-0.254
0.301	0.684	0.108	0.044
0.477	0.883	0.331	0.269
0.602	1.038	0.501	0.455
0.699	1.186	0.686	0.651
0.778	1.313	0.858	0.796
0.845	1.419	1.183	0.979

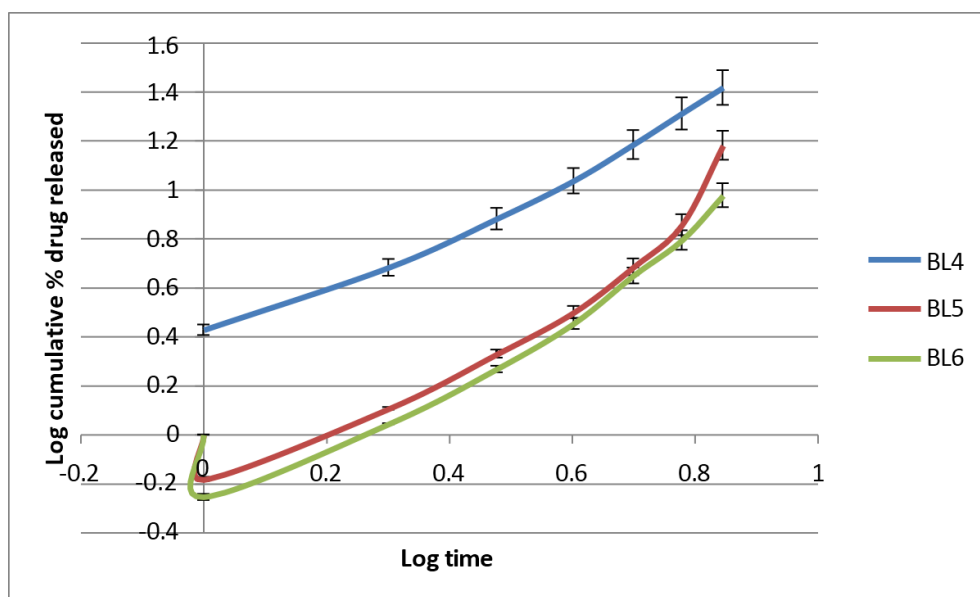


Figure No. 6.107: Log time vs log cumulative % drug released

To investigate the utilities of a shed snake skin as a model membrane for preclinical studies of transdermal drug delivery, in shed snake skin was greater than that reported in human skin, and shed snake skin had excellent drug release properties.

Table 6.41: *In-vitro* drug release data for optimization of BL4 (through snake skin)

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt)	W <sub>0</sub> -W <sub>t</sub>
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	2.685625	97.31438	1.000	1.988	0.000	0.429	2.685625	4.600	0.042
2	4.82965	95.17035	1.414	1.979	0.301	0.684	2.144025	4.566	0.076
3	7.633375	92.36663	1.732	1.966	0.477	0.883	2.803725	4.520	0.122
4	10.91355	89.08645	2.000	1.950	0.602	1.038	3.280175	4.466	0.176
5	15.32988	84.67013	2.236	1.928	0.699	1.186	4.416325	4.391	0.251
6	20.5525	79.4475	2.449	1.900	0.778	1.313	5.222625	4.299	0.343
7	26.25158	73.74843	2.646	1.868	0.845	1.419	5.699075	4.194	0.448

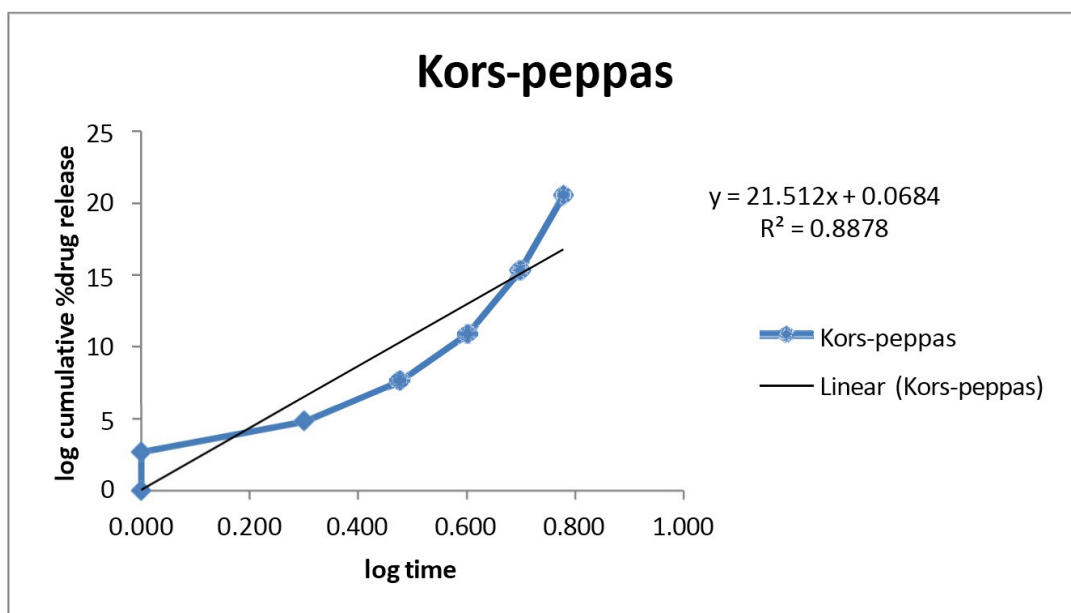


Figure No. 6.108: Log time vs Log cumulative % drug release

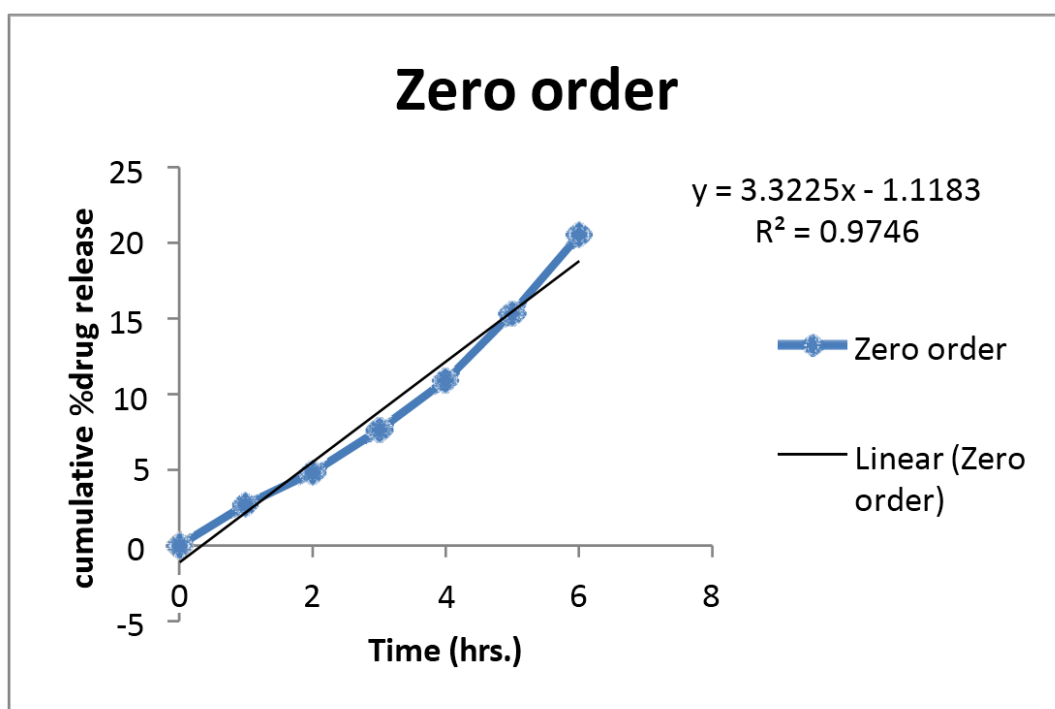


Figure No. 6.109: Time vs cumulative % drug release

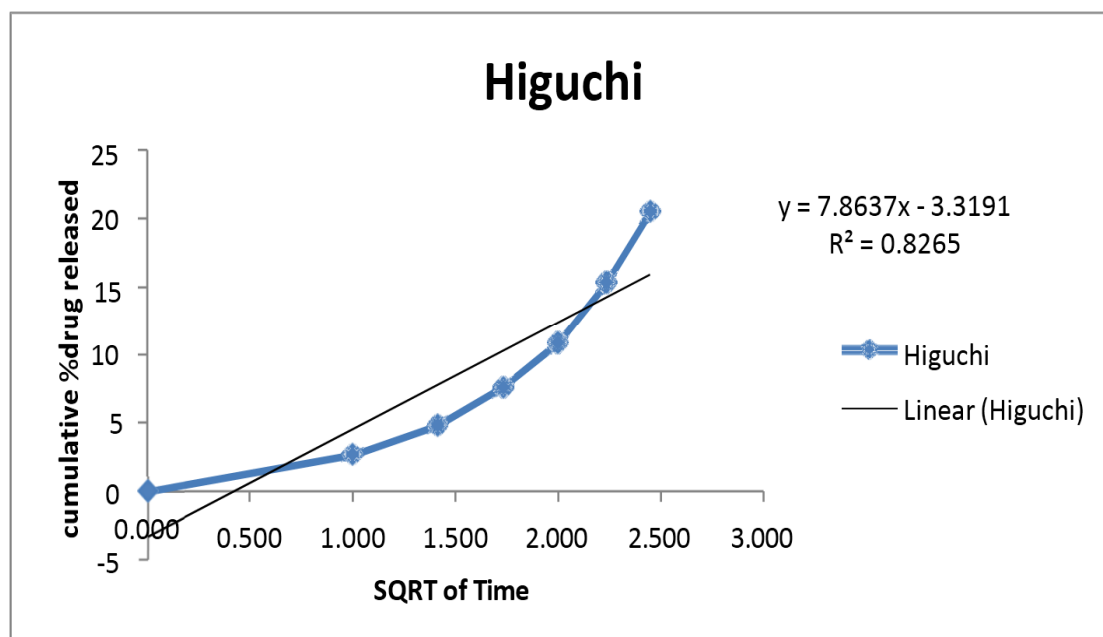


Figure No. 6.110: Sq root time vs cumulative % drug released

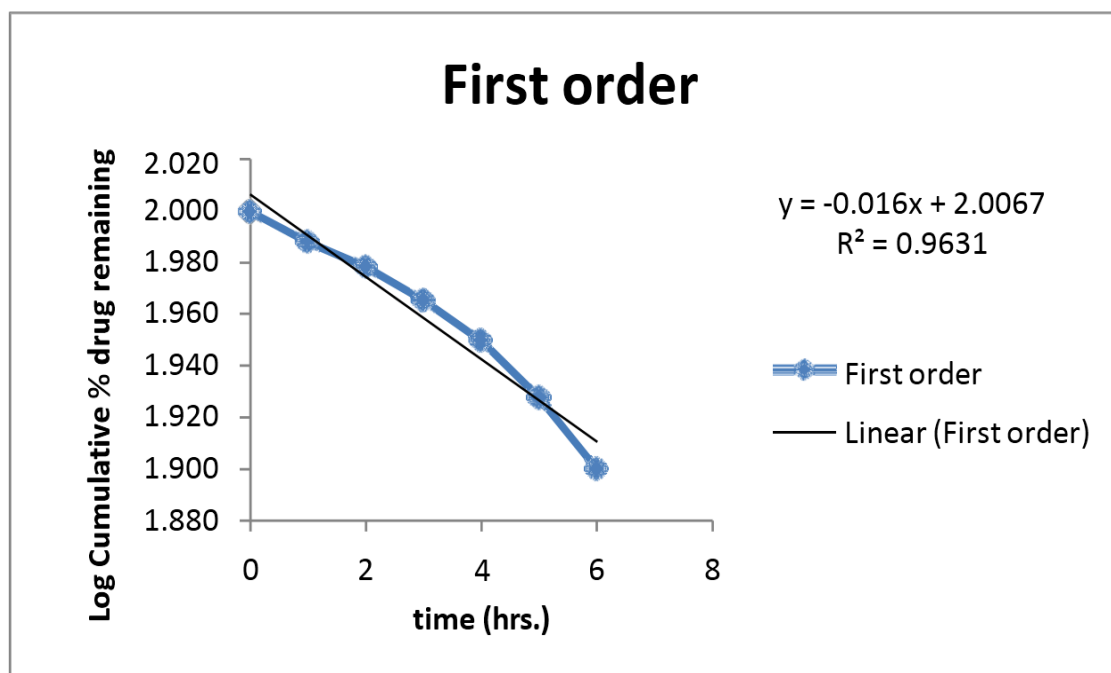
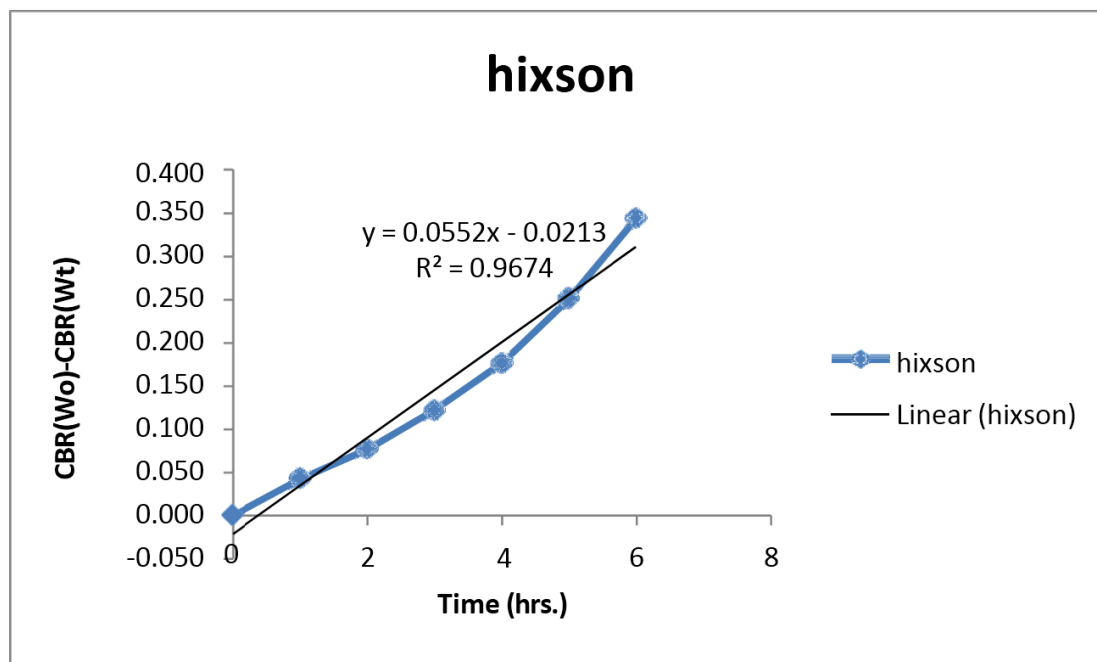


Figure No. 6.111: Time vs log cumulative % drug remaining



**Figure No. 6.112: Time vs Cube root of drug remain**

Table 6.42: *In-vitro* drug remain data for BL4 (through snake skin)

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

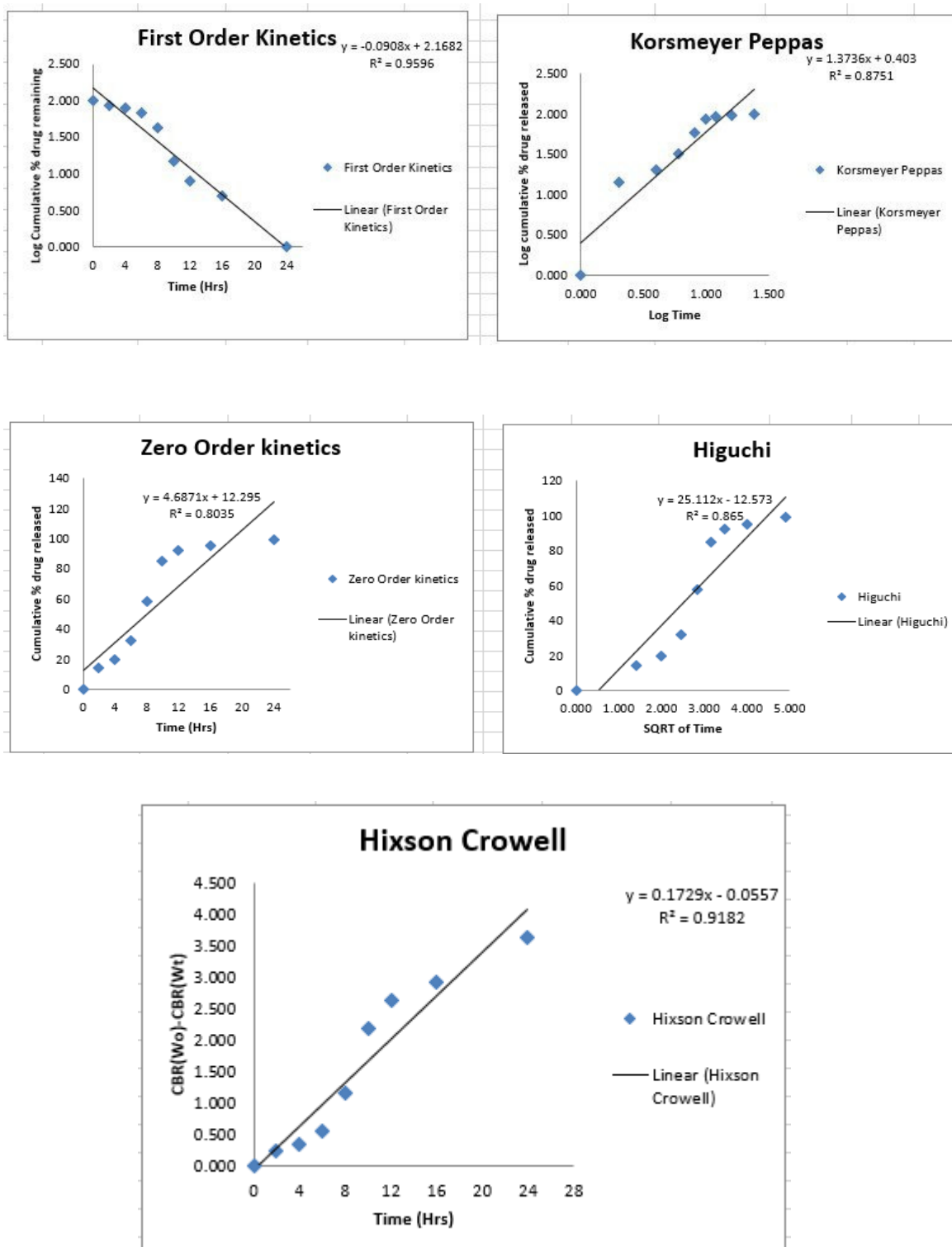


Figure No. 6.113: Time vs Cube root of drug remain



## SNAKE SKIN DRUG RELEASE OF FORMULATION BL5

Table 6.43: *In-vitro* drug release data for optimization of BL5

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	0.658475	99.34153	1.000	1.997	0.000	-0.181	0.658475	4.631	0.011
2	1.281525	98.71848	1.414	1.994	0.301	0.108	0.62305	4.622	0.020
3	2.1428	97.8572	1.732	1.991	0.477	0.331	0.861275	4.608	0.034
4	3.169	96.831	2.000	1.986	0.602	0.501	1.0262	4.592	0.050
5	4.8549	95.1451	2.236	1.978	0.699	0.686	1.6859	4.565	0.077
6	7.218825	92.78118	2.449	1.967	0.778	0.858	2.363925	4.527	0.115
7	15.22685	84.77315	2.646	1.928	0.845	1.183	8.008025	4.393	0.249

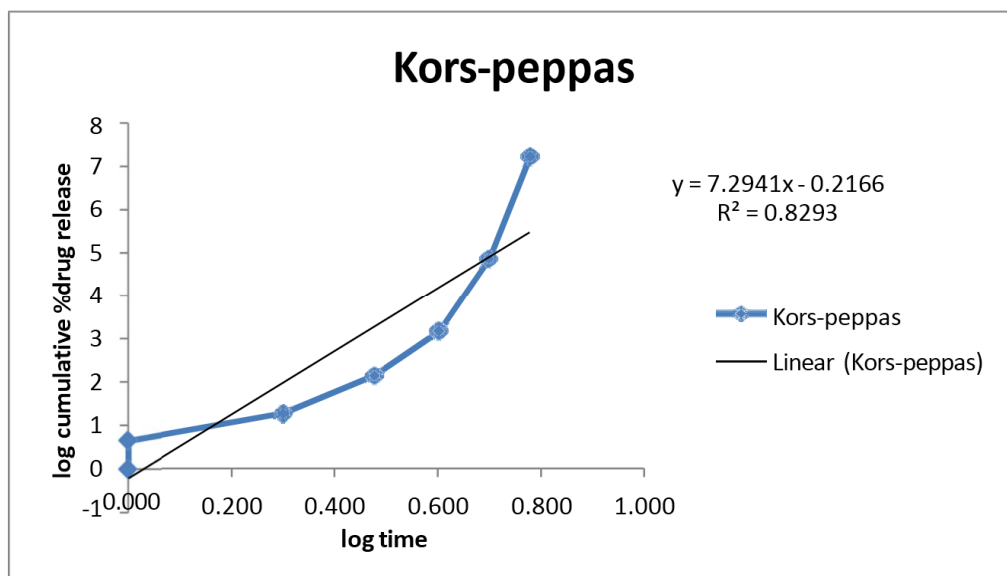


Figure No. 6.114: Log time vs log cumulative % drug release

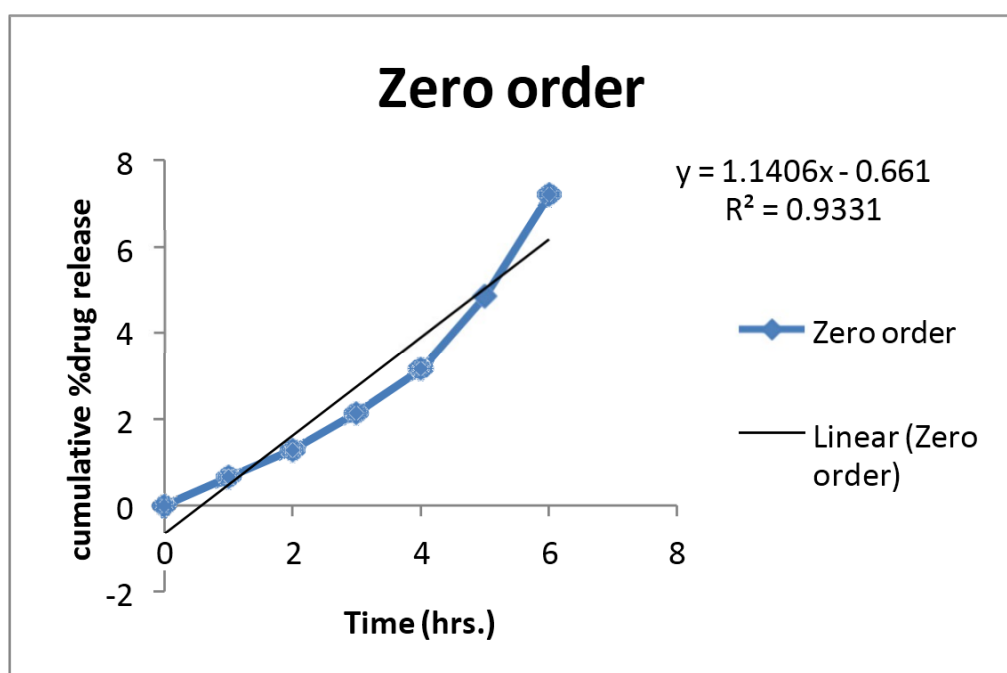


Figure No. 6.115: Time vs cumulative % drug release

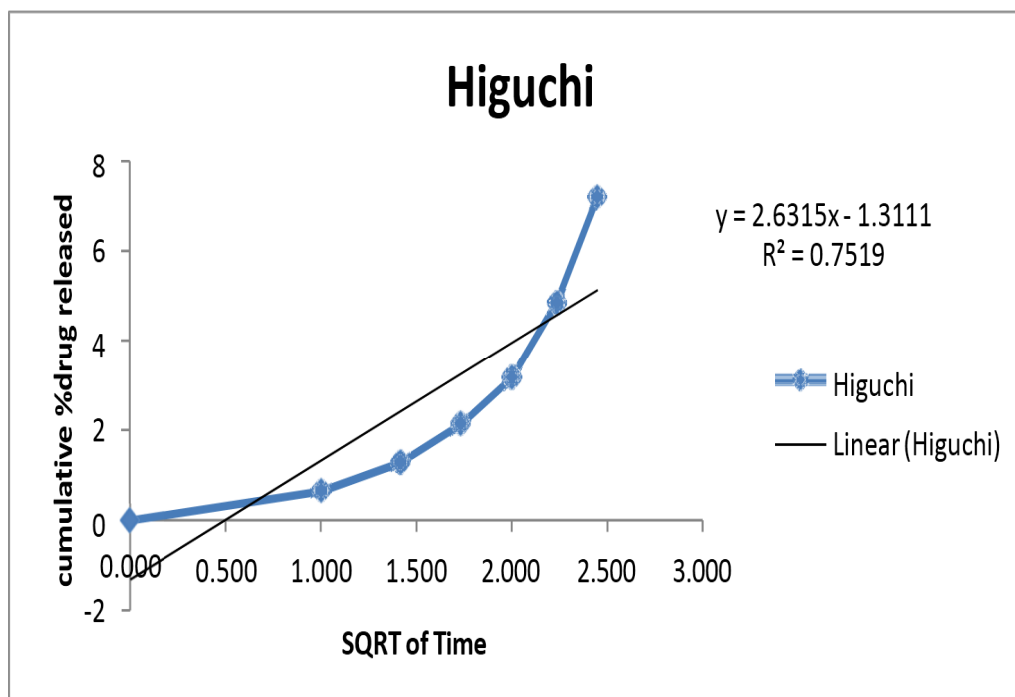


Figure No. 6.116: Sq root time vs cumulative % drug released

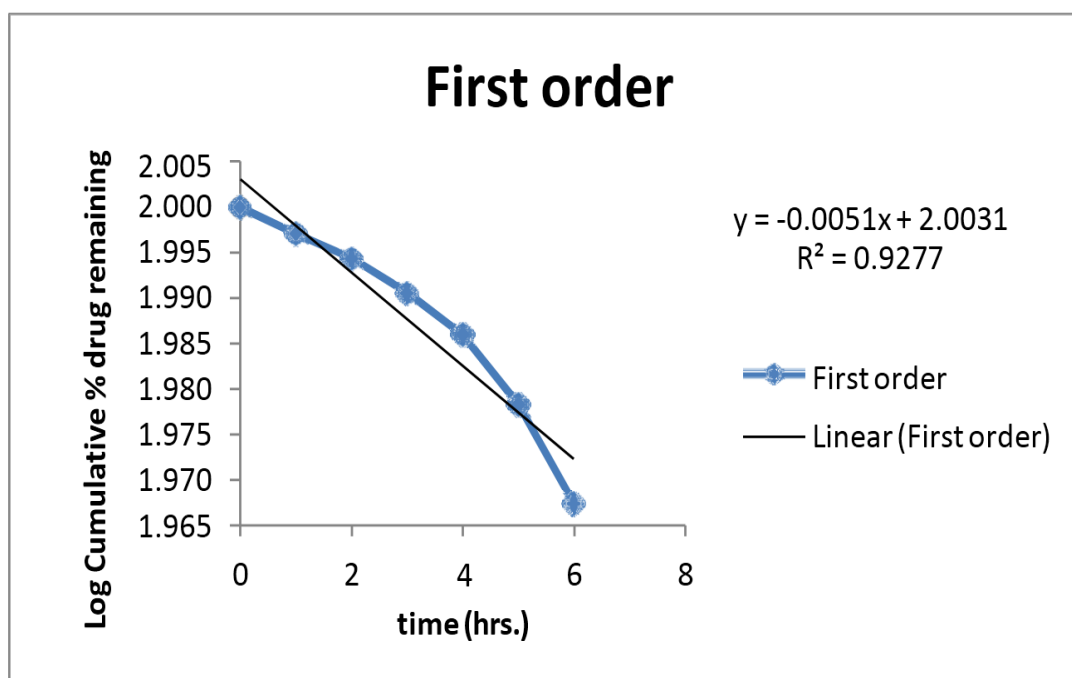
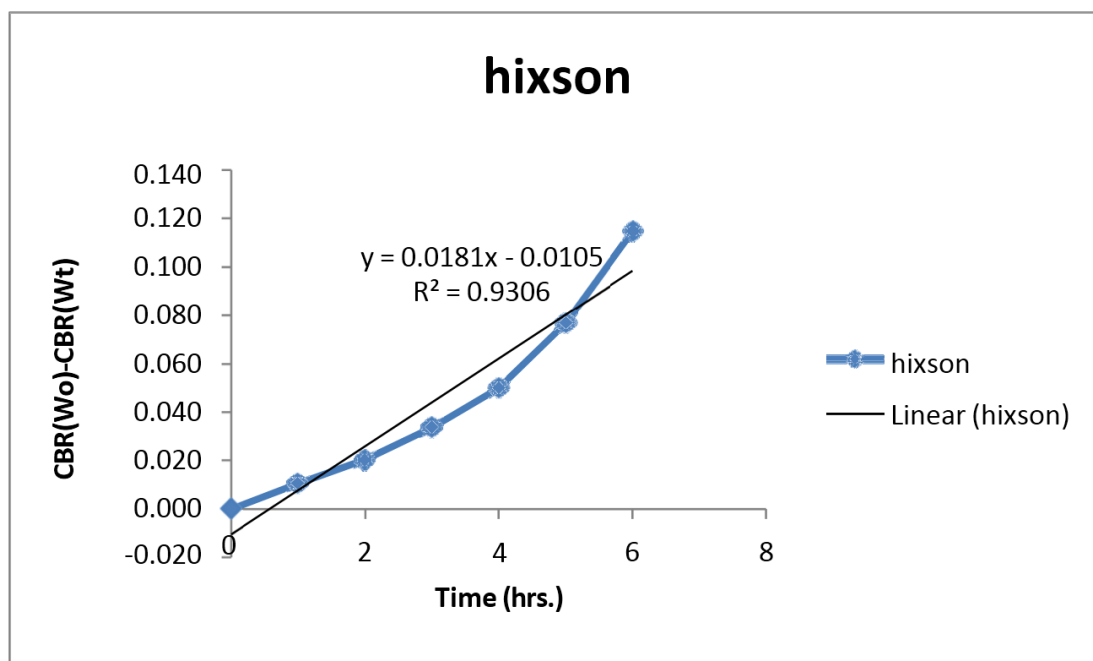


Figure No. 6.117: Time vs log cumulative % drug remaining



**Figure No. 6.118: Time vs cube root of drug remain**

Table 6.44: *In-vitro* drug remain data for BL5

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

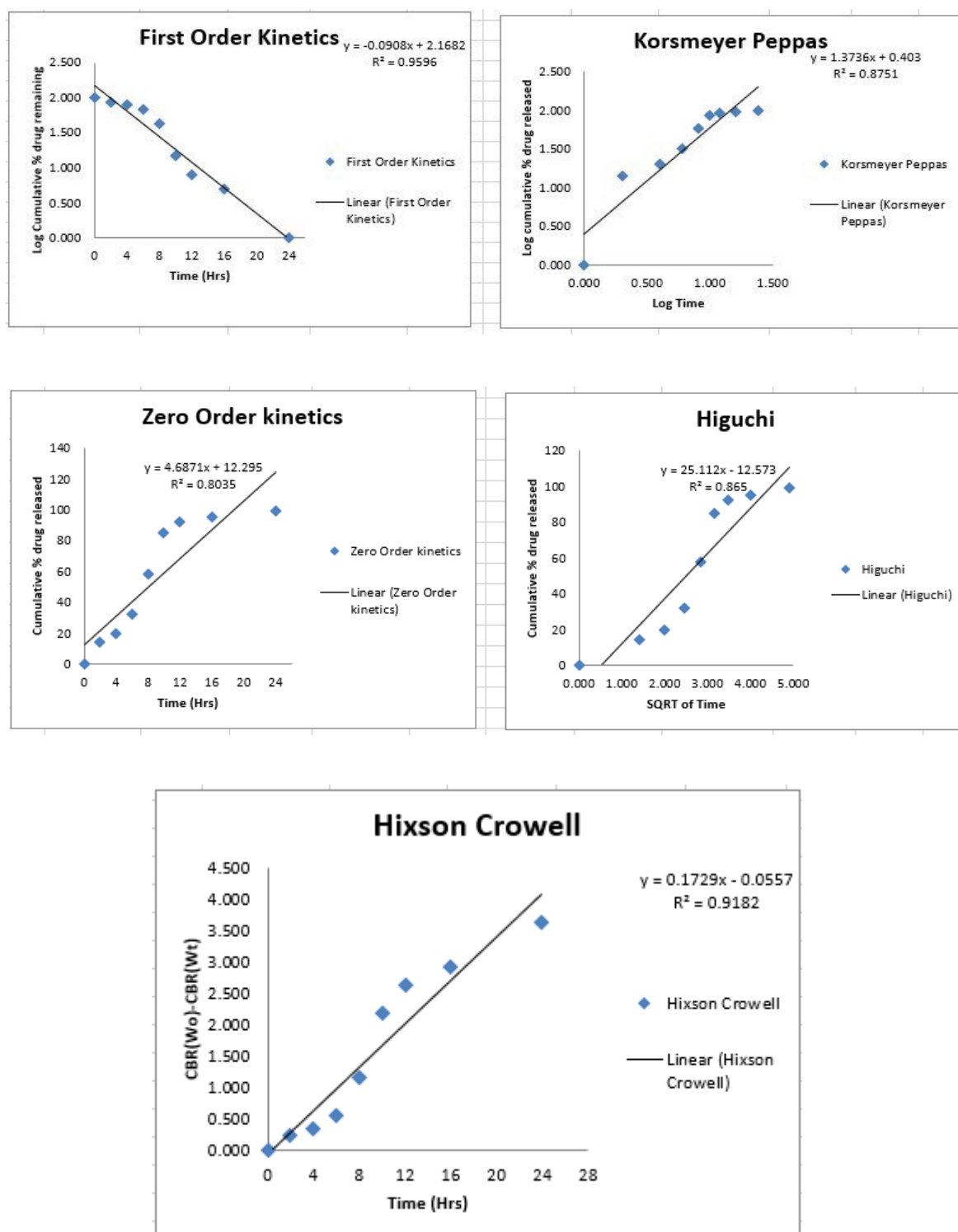


Figure No. 6.119: Time vs cube root of drug release

## SNAKE SKIN DRUG RELEASE OF FORMULATION BL6

Table 6.45: *In-vitro* drug remain data for BL5

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	0.55735	99.44265	1.000	1.998	0.000	-0.254	0.55735	4.633	0.009
2	1.1071	98.8929	1.414	1.995	0.301	0.044	0.54975	4.624	0.018
3	1.858425	98.14158	1.732	1.992	0.477	0.269	0.751325	4.613	0.029
4	2.847975	97.15203	2.000	1.987	0.602	0.455	0.98955	4.597	0.045
5	4.4789	95.5211	2.236	1.980	0.699	0.651	1.630925	4.571	0.071
6	6.256425	93.74358	2.449	1.972	0.778	0.796	1.777525	4.543	0.099
7	9.518275	90.48173	2.646	1.957	0.845	0.979	3.26185	4.489	0.153

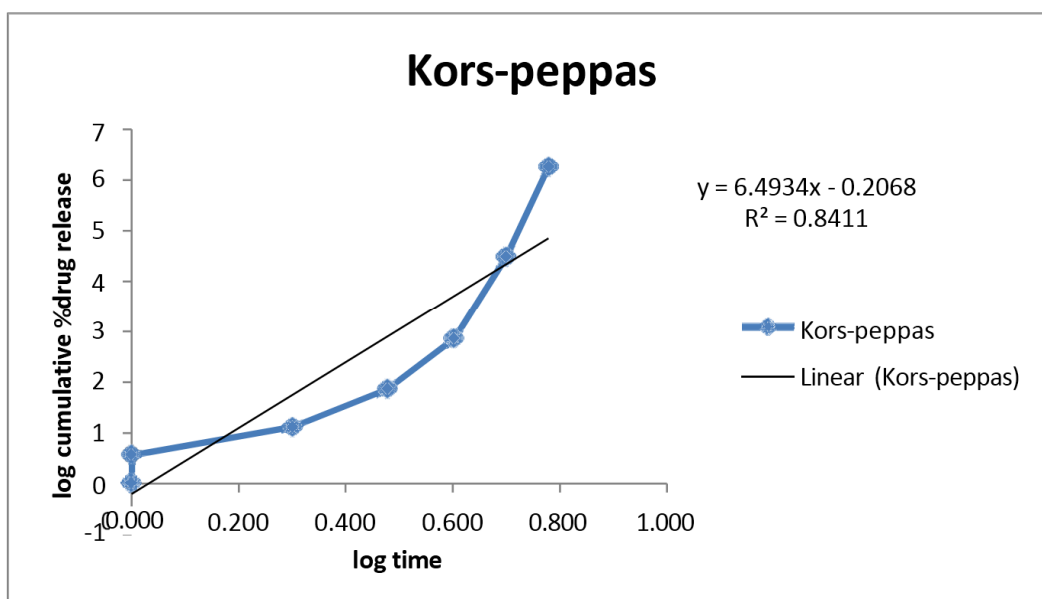


Figure No. 6.120: Log time vs log cumulative % drug release

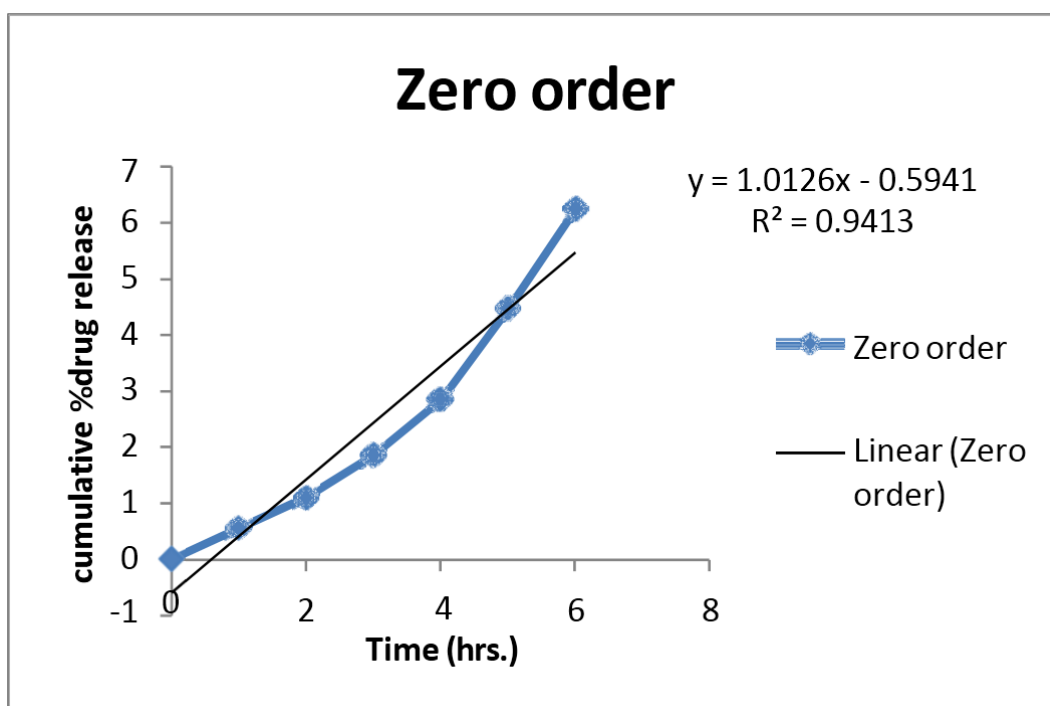


Figure No. 6.121: Time vs cumulative % drug release



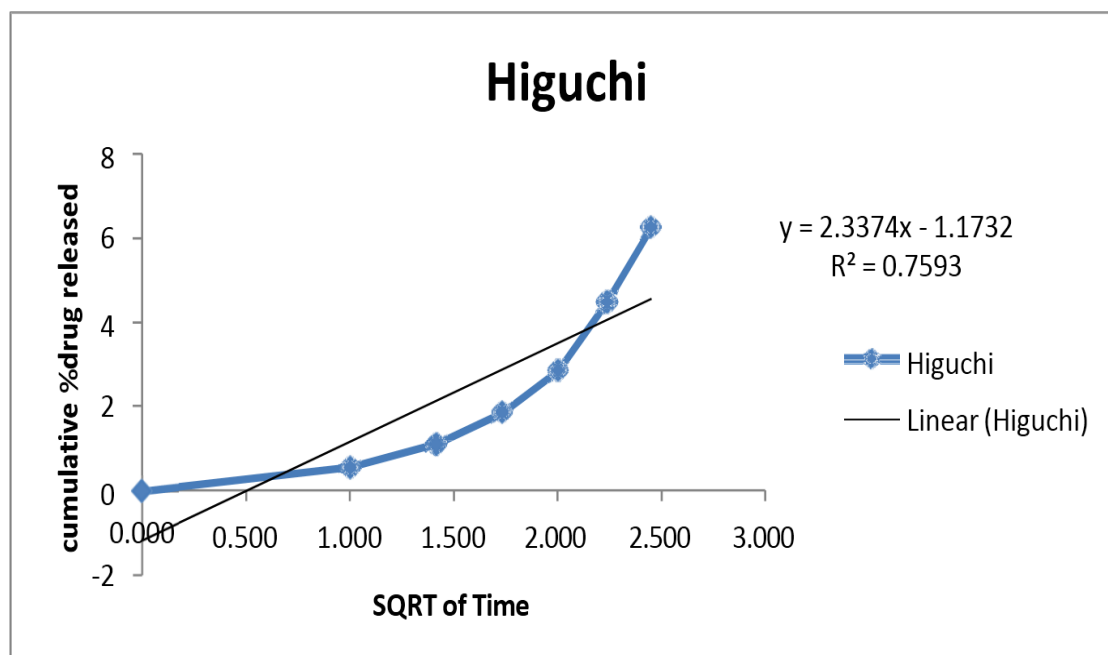


Figure No. 6.122: Sq root time vs cumulative % drug released

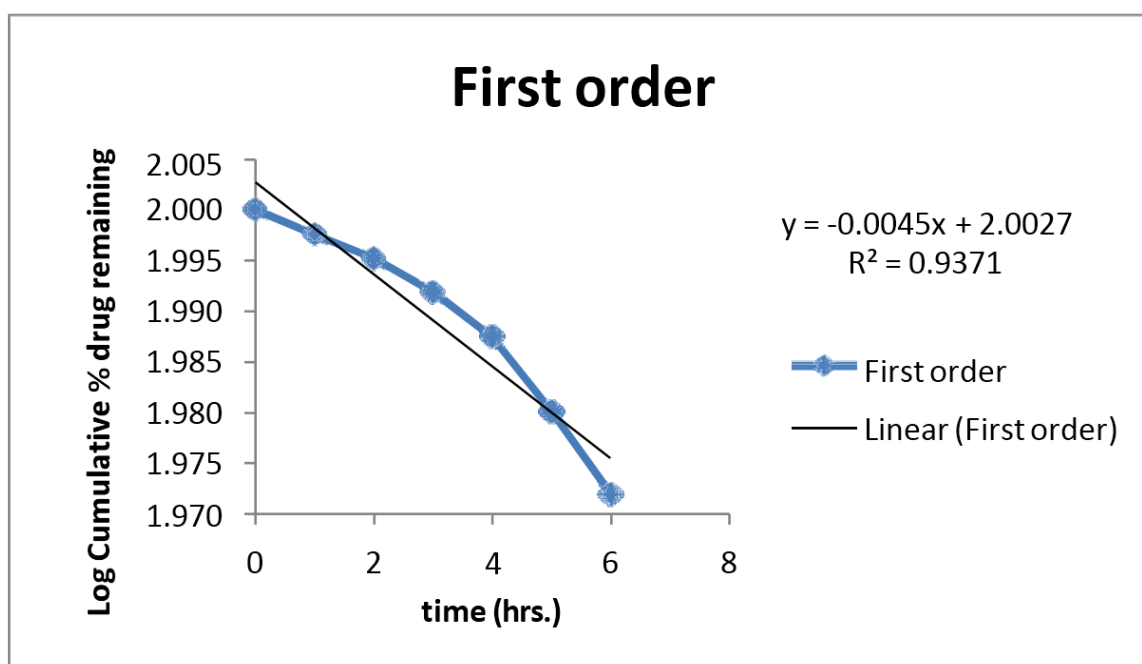
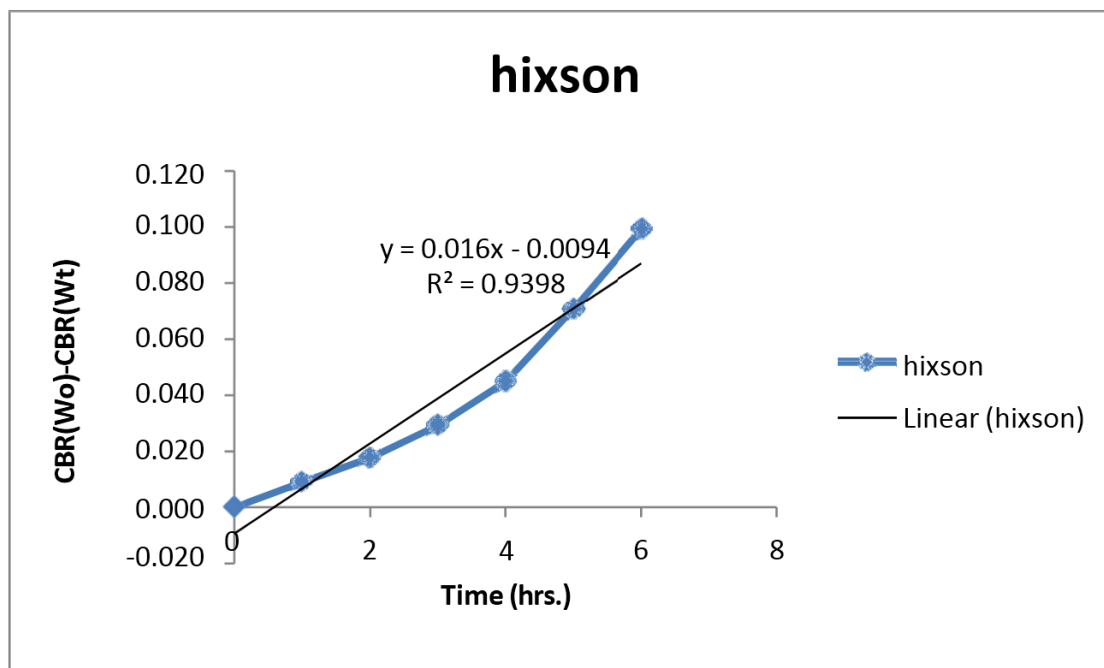


Figure No. 6.123: Time vs log cumulative % drug remaining



**Figure No. 6.124: Time vs Cube root drug remain**

Table 6.46: *In-vitro* drug remain data for BL6

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

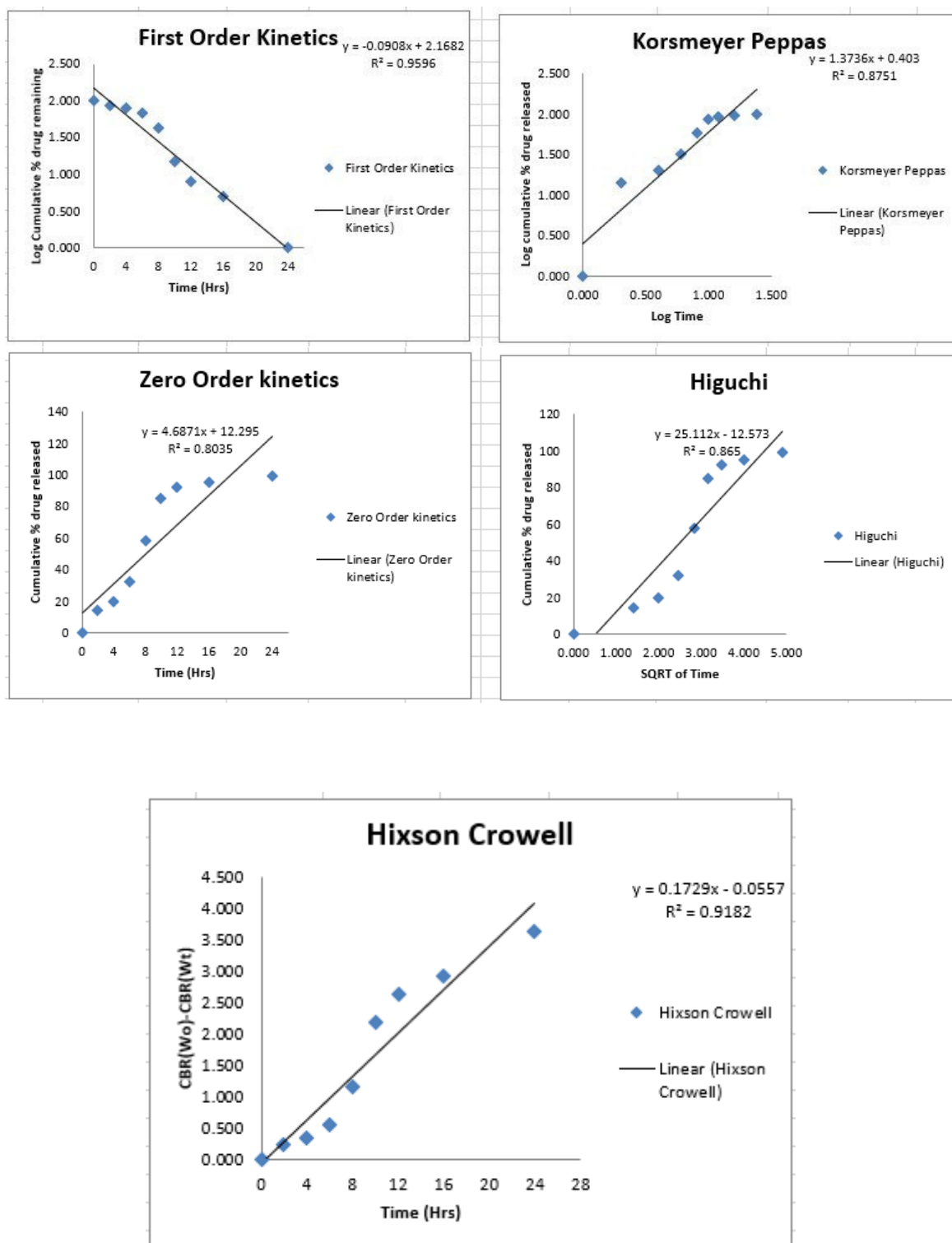


Figure No. 6.125: Time vs Cube root of drug remain

## SNAKE SKIN DRUG RELEASE OF FORMULATION SCO4

Table 6.47: Cumulative % drug released wrt Time

Time (Hr)	cumulative % drug released		
0	0	0	0
1	6.0885	4.101125	3.7365
2	10.101675	6.17185	5.6607
3	15.5442	8.389175	7.7314
4	22.342775	17.111875	14.713
5	32.4032	33.9159	28.677
6	54.411525	57.206975	48.889
7	78.453925	89.495625	71.081

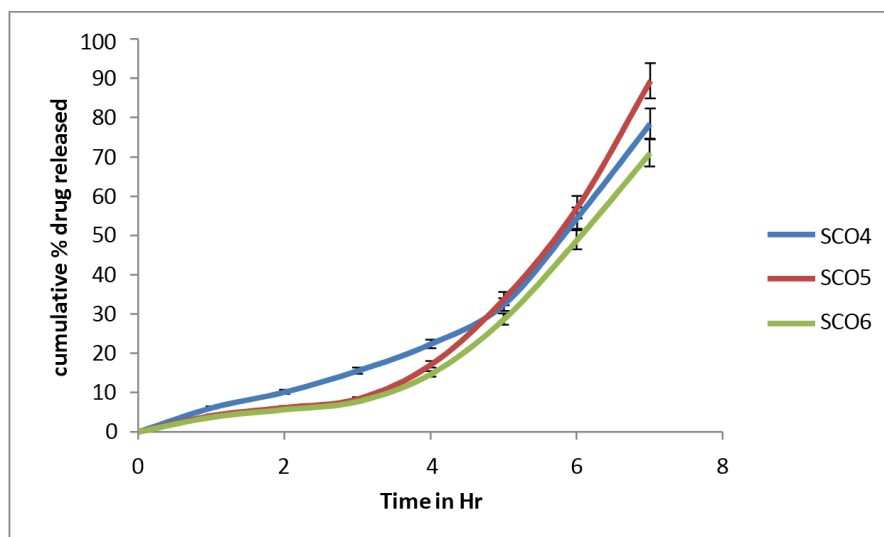


Figure No. 6.126: Time vs cumulative % drug released

Table 6.48: Log cumulative % drug remaining wrt to Time

Time (Hr)	log Cumu % drug remaining		
0	2	2	2
1	1.973	1.982	1.983
2	1.954	1.972	1.975
3	1.927	1.962	1.965
4	1.89	1.918	1.931
5	1.83	1.82	1.853
6	1.659	1.631	1.709
7	1.333	1.021	1.461

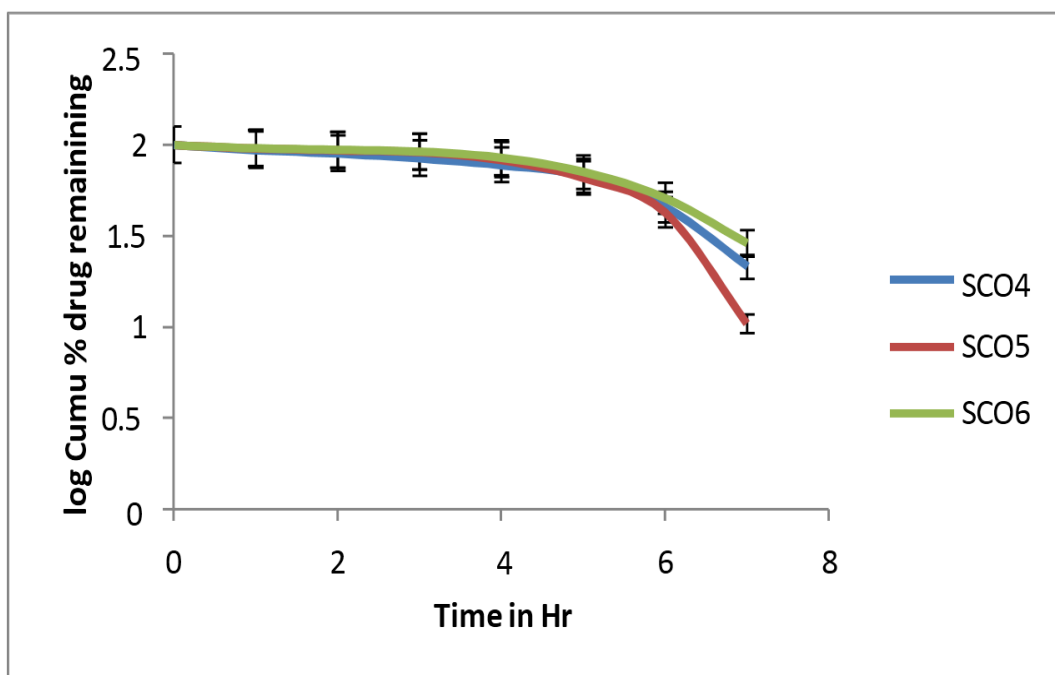


Figure No. 6.127: Time vs log cumulative % drug remaining

Table 49: Cumualtive % drug released wrt to SQRT

Square root time	cumulative % drug released		
0	0	0	0
1	6.0885	4.101125	3.7365
1.414	10.10168	6.17185	5.6607
1.732	15.5442	8.389175	7.7314
2	22.34278	17.11188	14.713
2.236	32.4032	33.9159	28.677
2.449	54.41153	57.20698	48.889
2.646	78.45393	89.49563	71.081

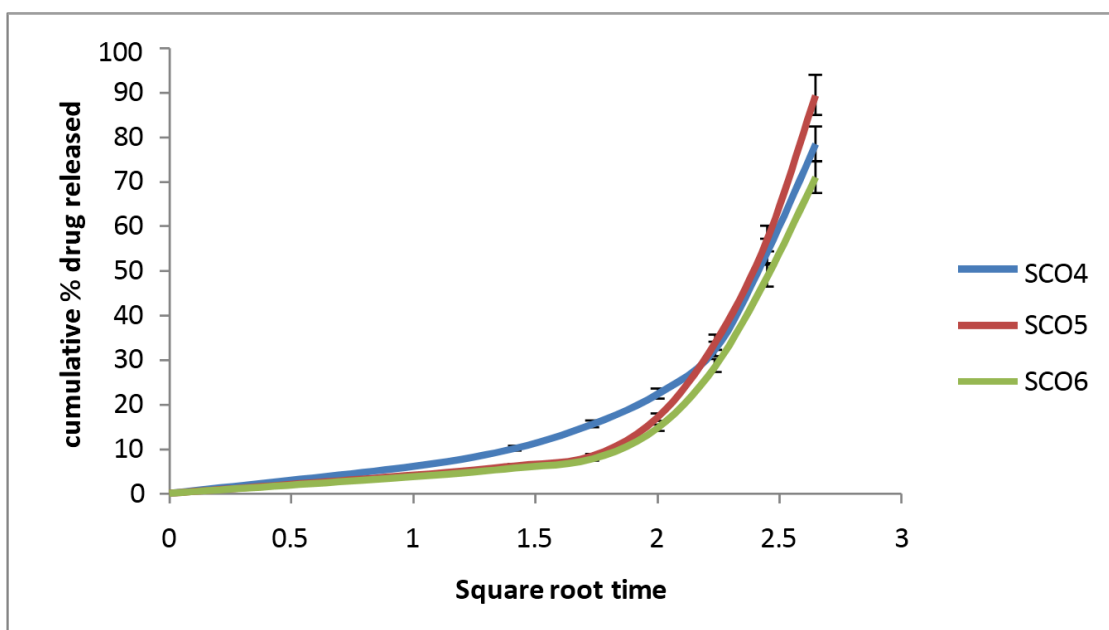


Figure No. 6.128: Sq root time vs cumulative % drug released

Table 50: Log cumulative % drug released wrt to Log time

Log time	log Cumu % drug released		
0	0	0	0
0	0.785	0.613	0.572
0.301	1.004	0.79	0.753
0.477	1.192	0.924	0.888
0.602	1.349	1.233	1.168
0.699	1.511	1.53	1.458
0.778	1.736	1.757	1.689
0.845	1.895	1.952	1.852

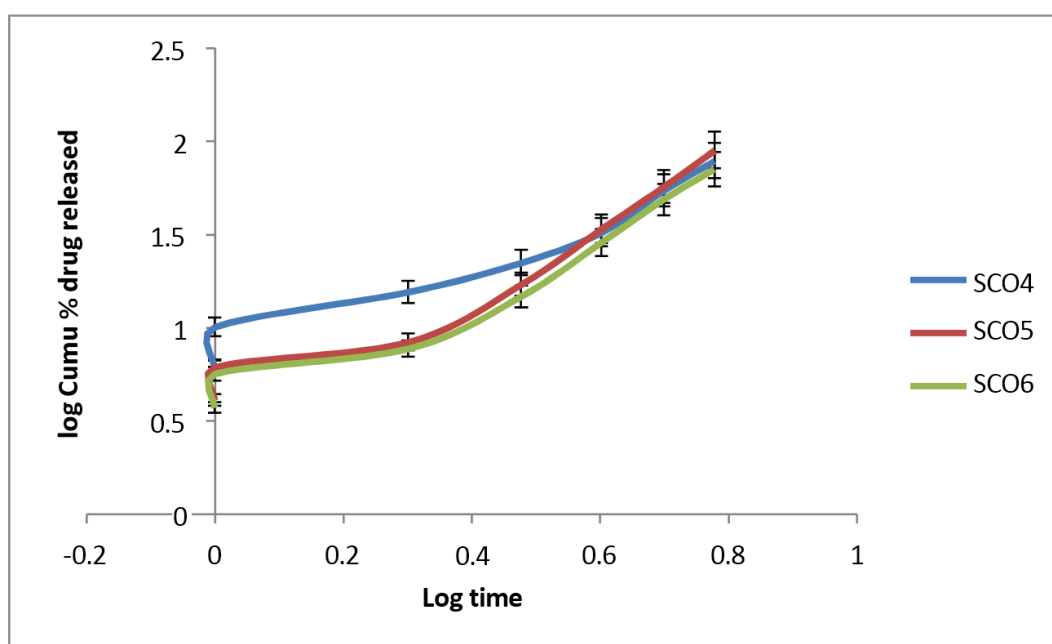


Figure No. 6.129: Log time vs log cumulative % drug released



Table 51: *In-vitro* drug release data for optimization of SCO4

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	6.0885	93.9115	1.000	1.973	0.000	0.785	6.0885	4.545	0.097
2	10.10168	89.89833	1.414	1.954	0.301	1.004	4.013175	4.480	0.162
3	15.5442	84.4558	1.732	1.927	0.477	1.192	5.442525	4.387	0.255
4	22.34278	77.65723	2.000	1.890	0.602	1.349	6.798575	4.266	0.376
5	32.4032	67.5968	2.236	1.830	0.699	1.511	10.06043	4.074	0.568
6	54.41153	45.58848	2.449	1.659	0.778	1.736	22.00833	3.572	1.070
7	78.45393	21.54608	2.646	1.333	0.845	1.895	24.0424	2.783	1.859

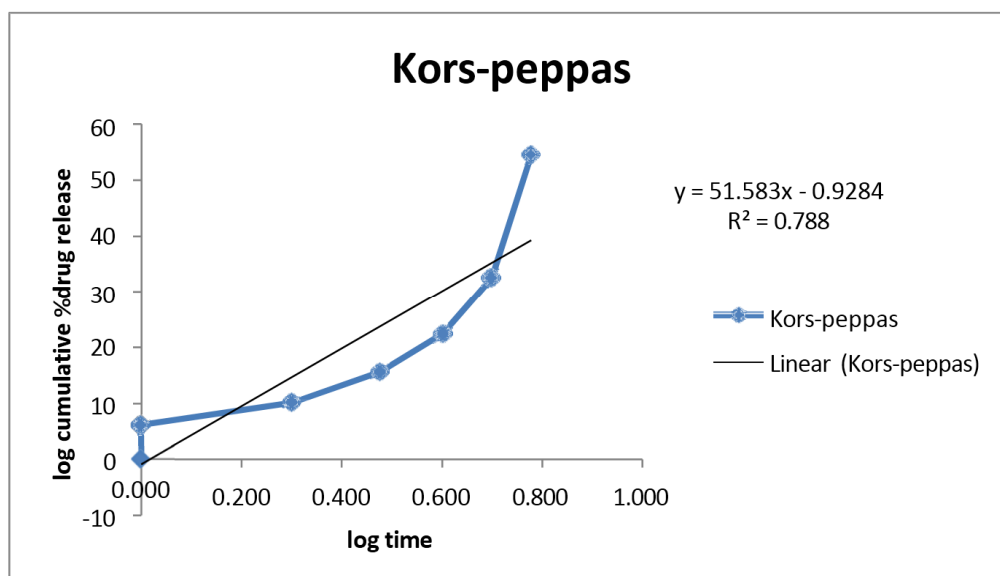


Figure No. 6.130: Log time vs log cumulative % drug release

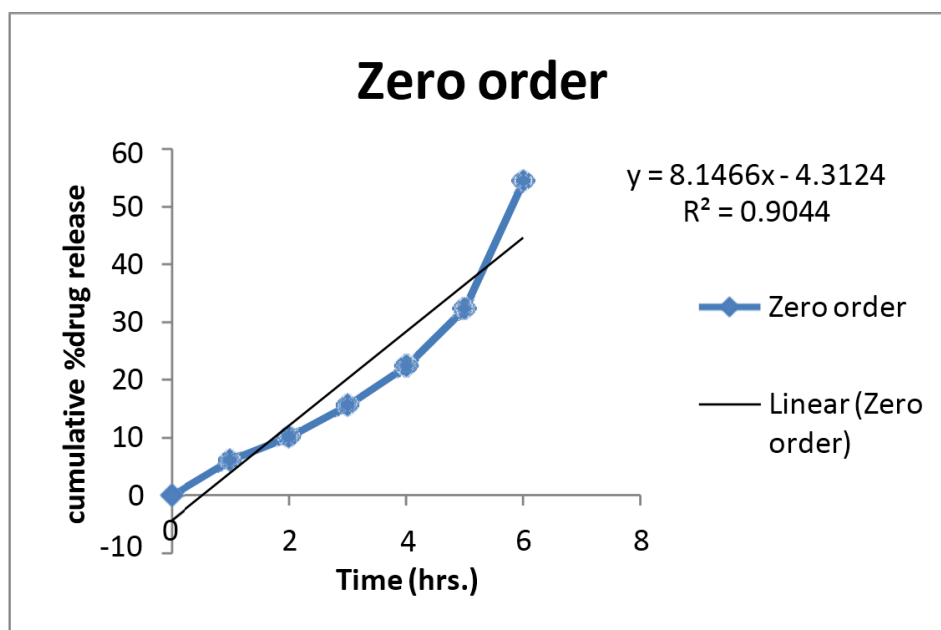


Figure No. 6.131: Time vs cumulative % drug release

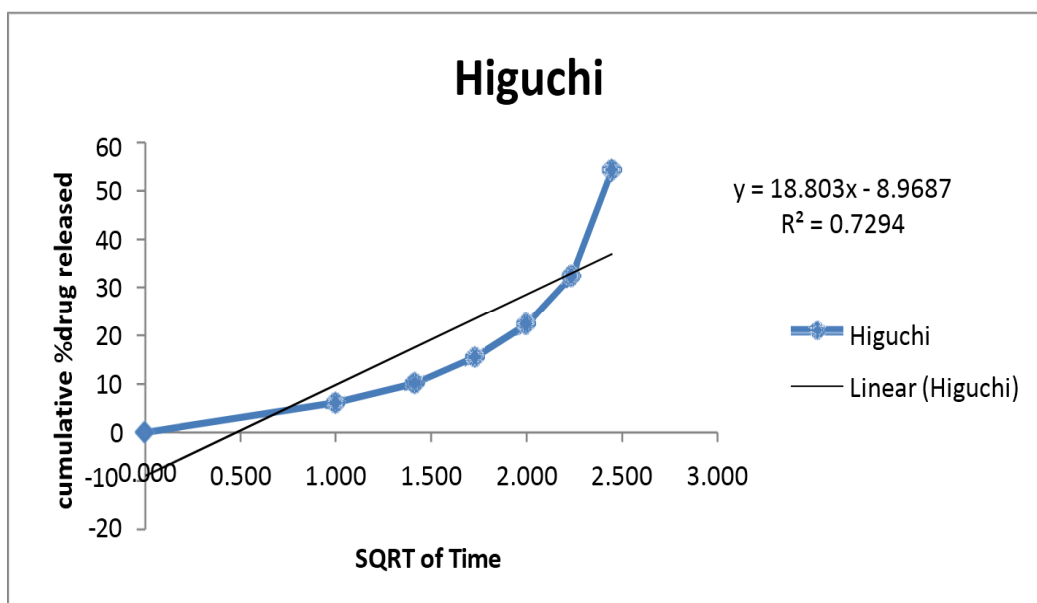


Figure No. 6.132: Sq root time vs cumulative % drug released

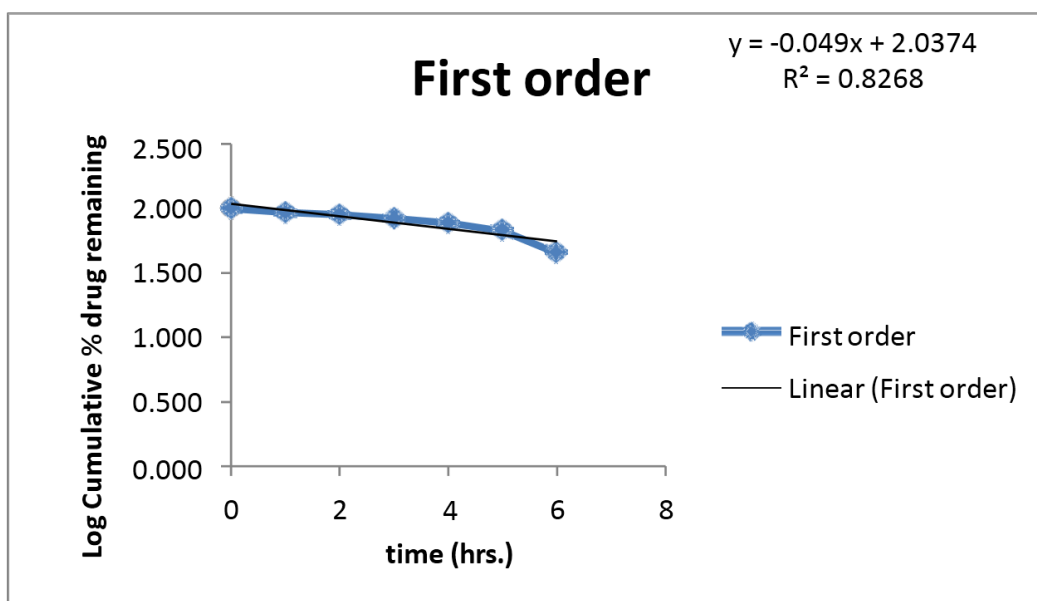
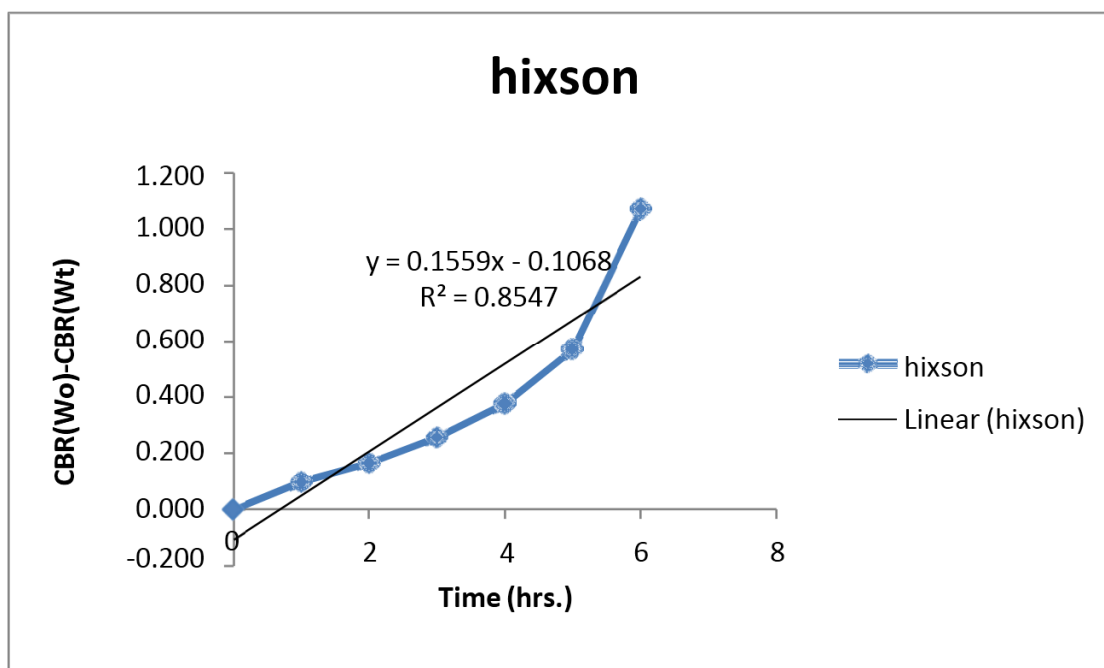


Figure No. 6.133: Time vs log cumulative % drug remaining



**Figure No. 6.134: Time vs cube root of drug remain**

Table 52: *In-vitro* drug remain data for SCO4

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

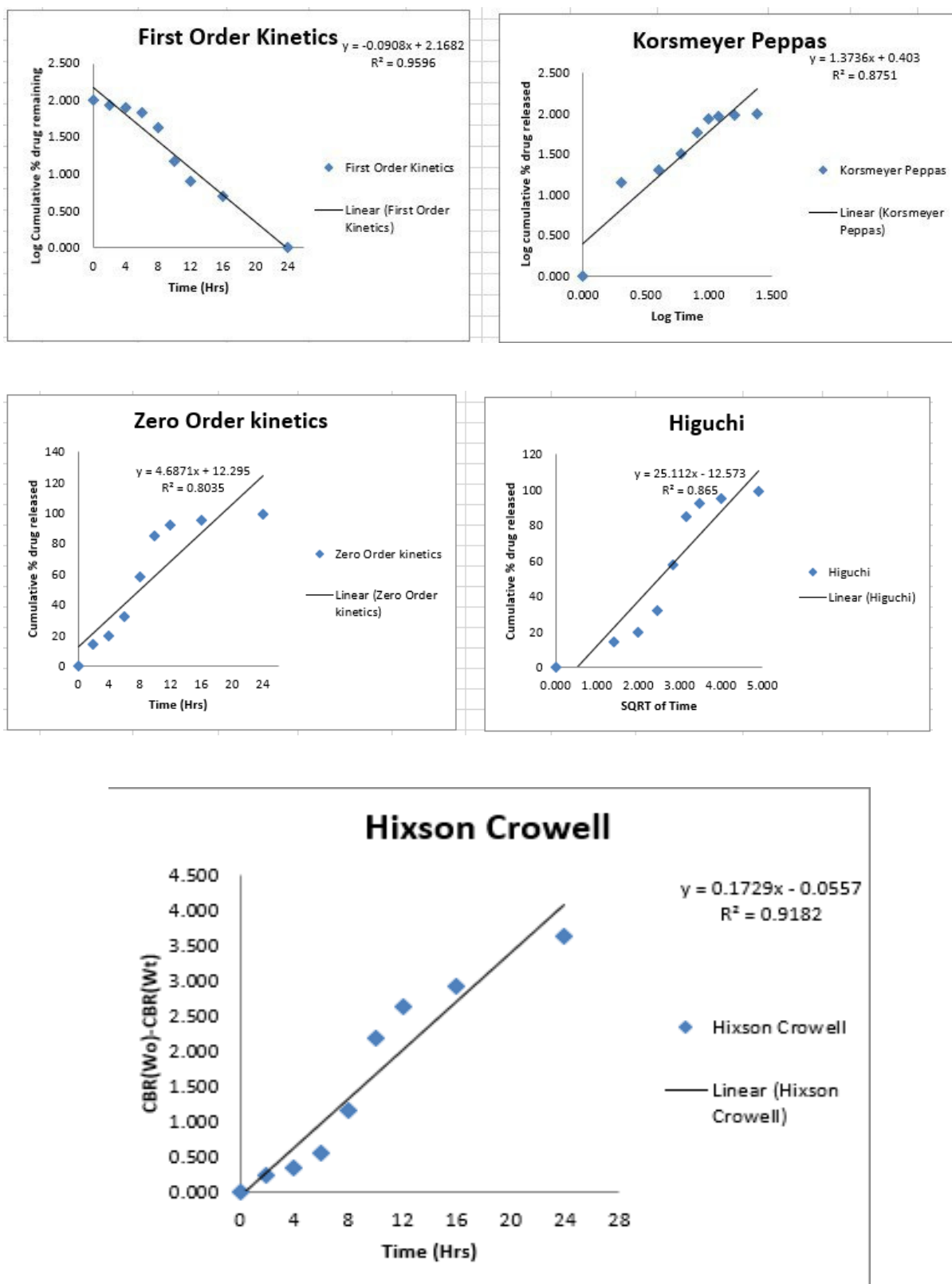


Figure No. 6.135: Time vs cube root of drug remain

## SNAKE SKIN DRUG RELEASE OF FORMULATION SCO5

Table 53: *In-vitro* drug release data for optimization of SCO5

Time (Hr.)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	4.101125	95.89888	1.000	1.982	0.000	0.613	4.101125	4.577	0.065
2	6.17185	93.82815	1.414	1.972	0.301	0.790	2.070725	4.544	0.098
3	8.389175	91.61083	1.732	1.962	0.477	0.924	2.217325	4.508	0.134
4	17.11188	82.88813	2.000	1.918	0.602	1.233	8.7227	4.360	0.282
5	33.9159	66.0841	2.236	1.820	0.699	1.530	16.80403	4.043	0.599
6	57.20698	42.79303	2.449	1.631	0.778	1.757	23.29108	3.498	1.144
7	89.49563	10.50438	2.646	1.021	0.845	1.952	32.28865	2.190	2.452

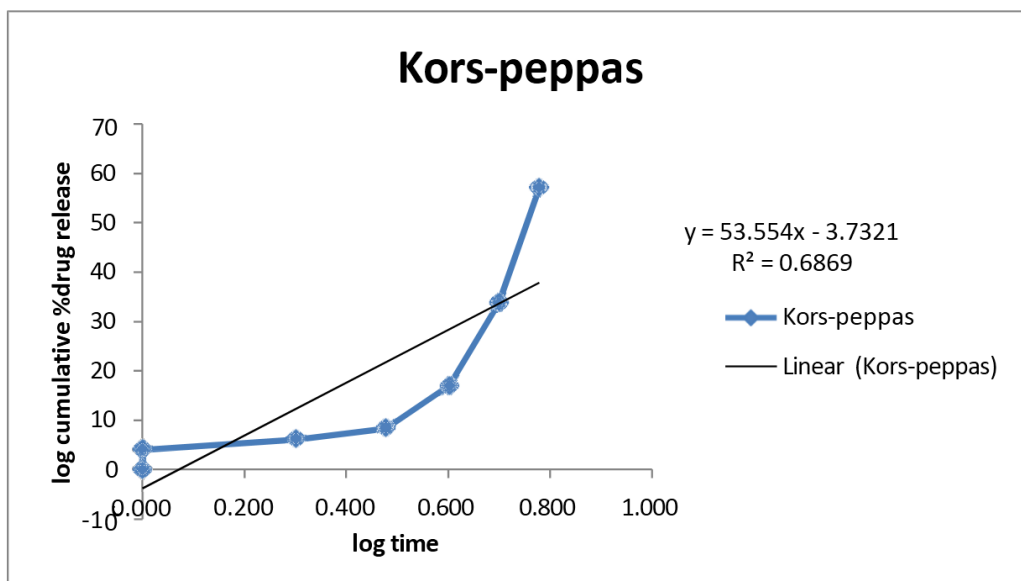


Figure No. 6.136: Log time vs log cumulative % drug release

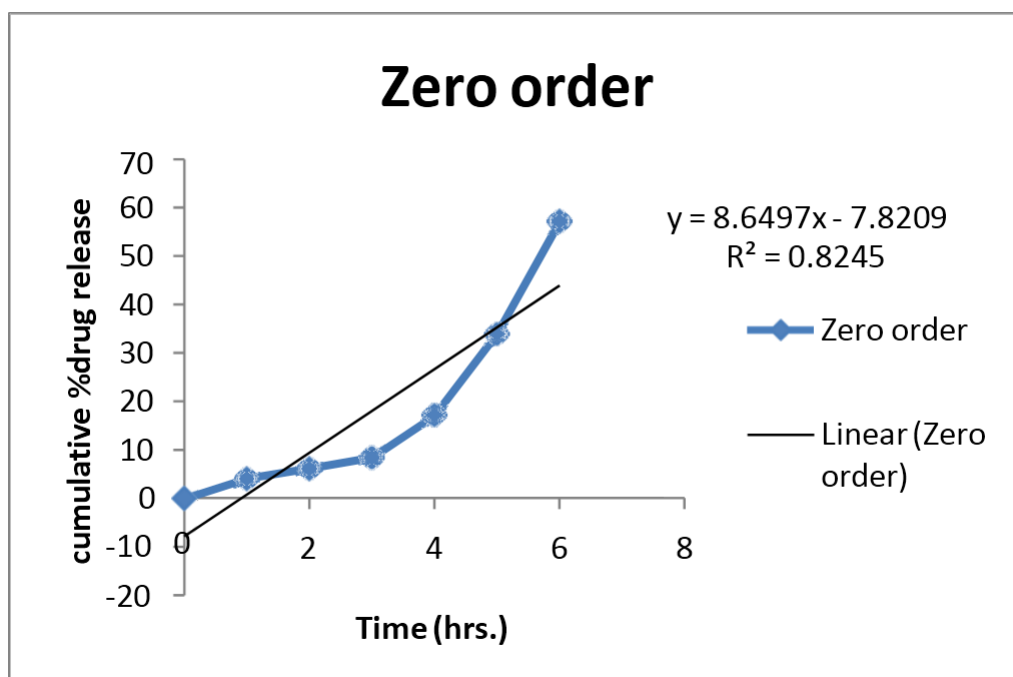


Figure No. 6.137: Time vs cumulative % drug release



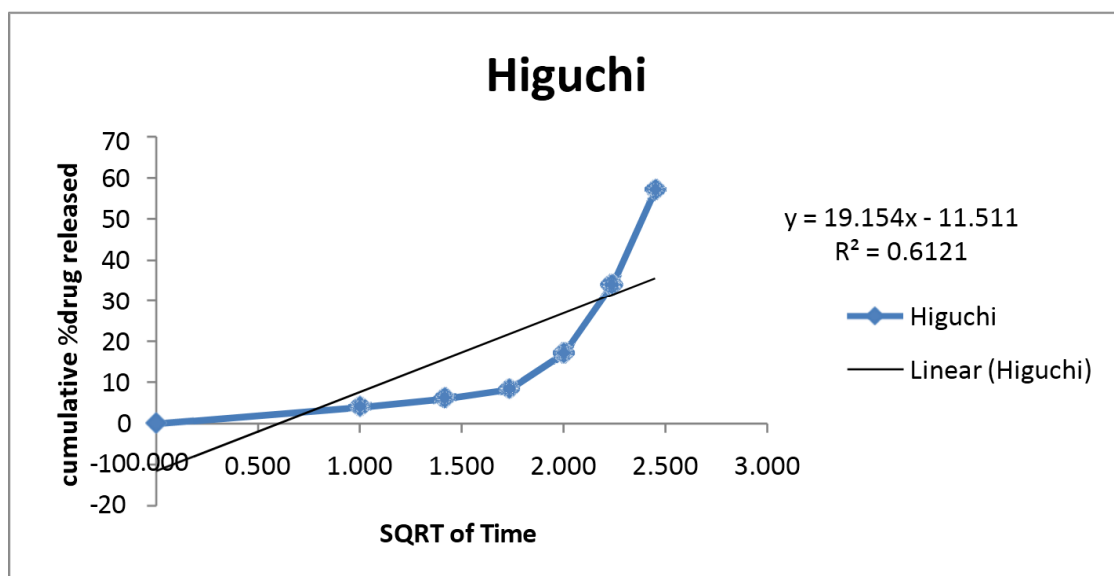


Figure No. 6.138: Sq root time vs Cumulative % drug released

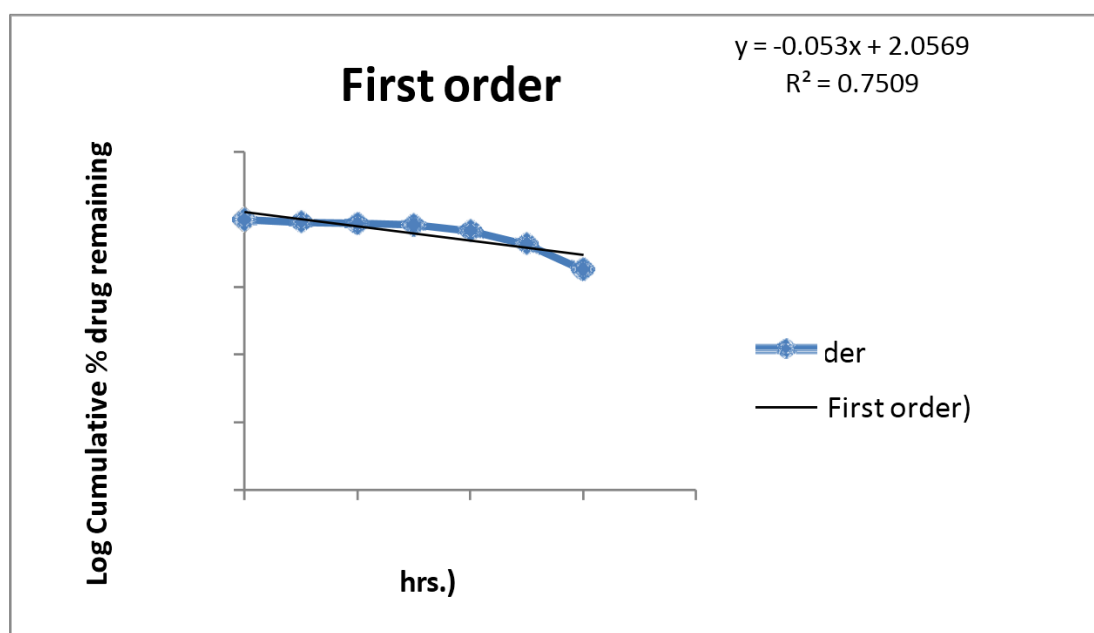
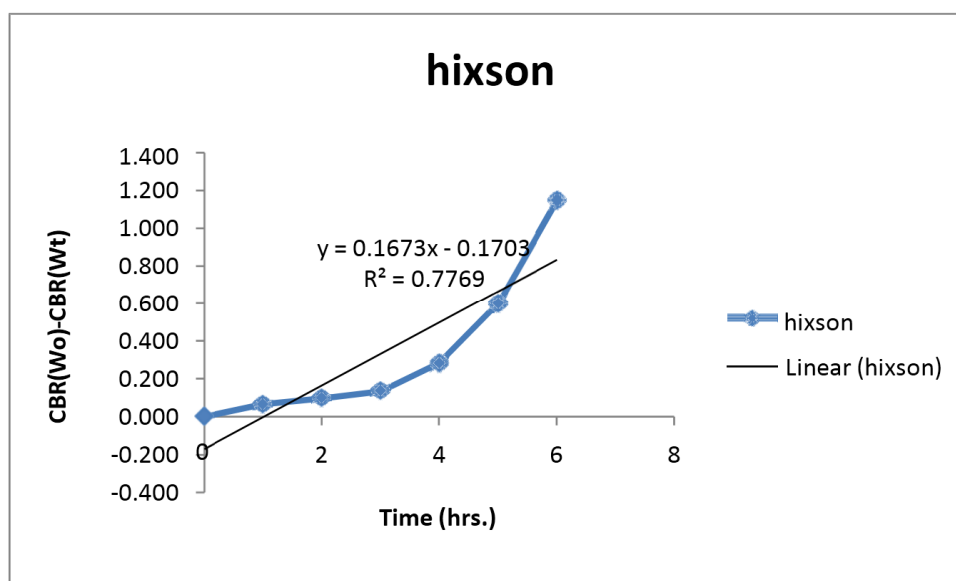


Figure No. 6.139: Time vs log cumulative % drug remaining



**Figure No. 6.140: Time vs cube root of drug remain**

Table 54: *In-vitro* drug remain data for SCO5

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

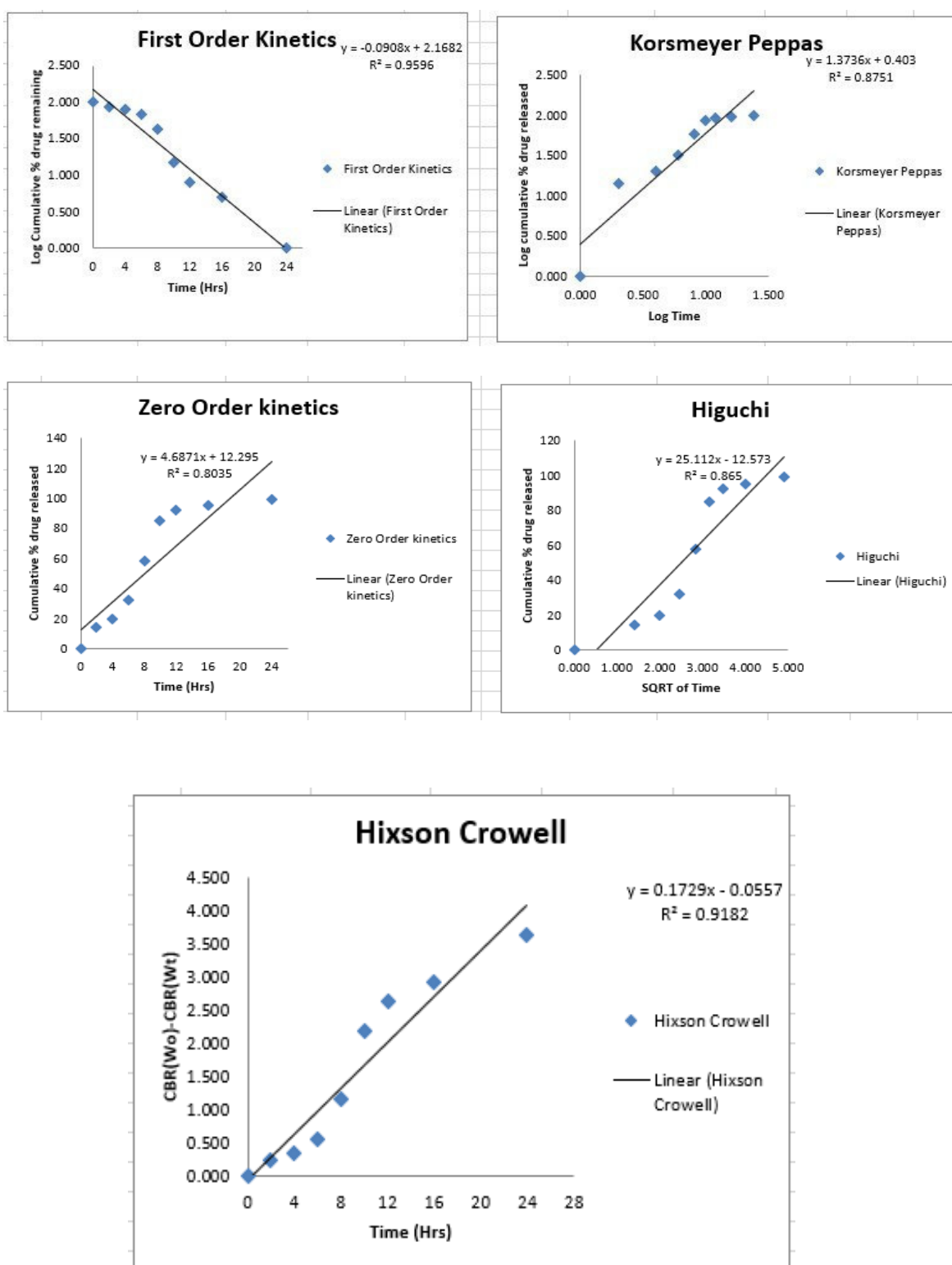


Figure No. 6.141: Time vs cube root of drug remain

## SNAKE SKIN DRUG RELEASE OF FORMULATION SCO6

Table 55: *In-vitro* drug release data for optimization of SCO6

Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	Log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
1	3.736525	96.26348	1.000	1.983	0.000	0.572	3.736525	4.583	0.059
2	5.66065	94.33935	1.414	1.975	0.301	0.753	1.924125	4.552	0.090
3	7.731375	92.26863	1.732	1.965	0.477	0.888	2.070725	4.519	0.123
4	14.7132	85.2868	2.000	1.931	0.602	1.168	6.981825	4.402	0.240
5	28.67685	71.32315	2.236	1.853	0.699	1.458	13.96365	4.147	0.495
6	48.88933	51.11068	2.449	1.709	0.778	1.689	20.21248	3.711	0.931
7	71.0809	28.9191	2.646	1.461	0.845	1.852	22.19158	3.069	1.573

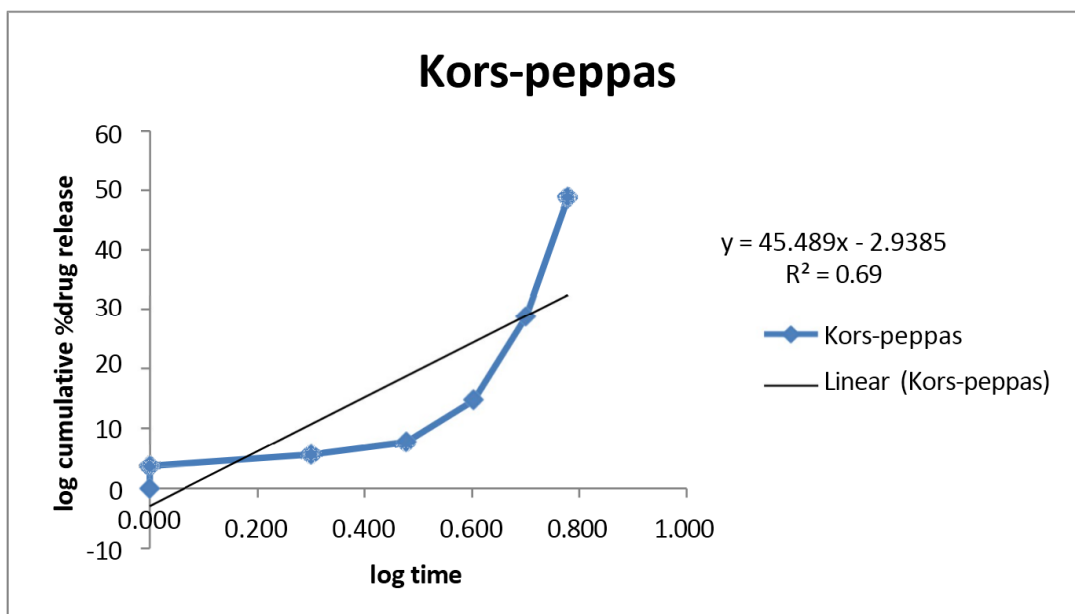


Figure No. 6.142: Log time vs Log cumulative % drug release

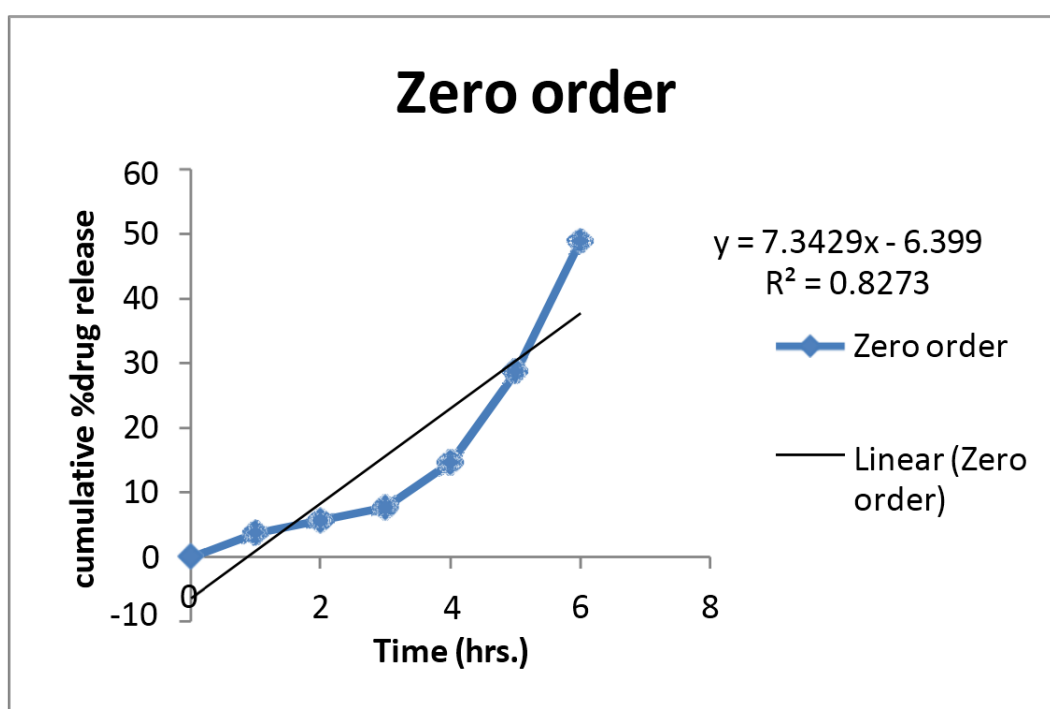


Figure No. 6.143: Time vs cumulative % drug release

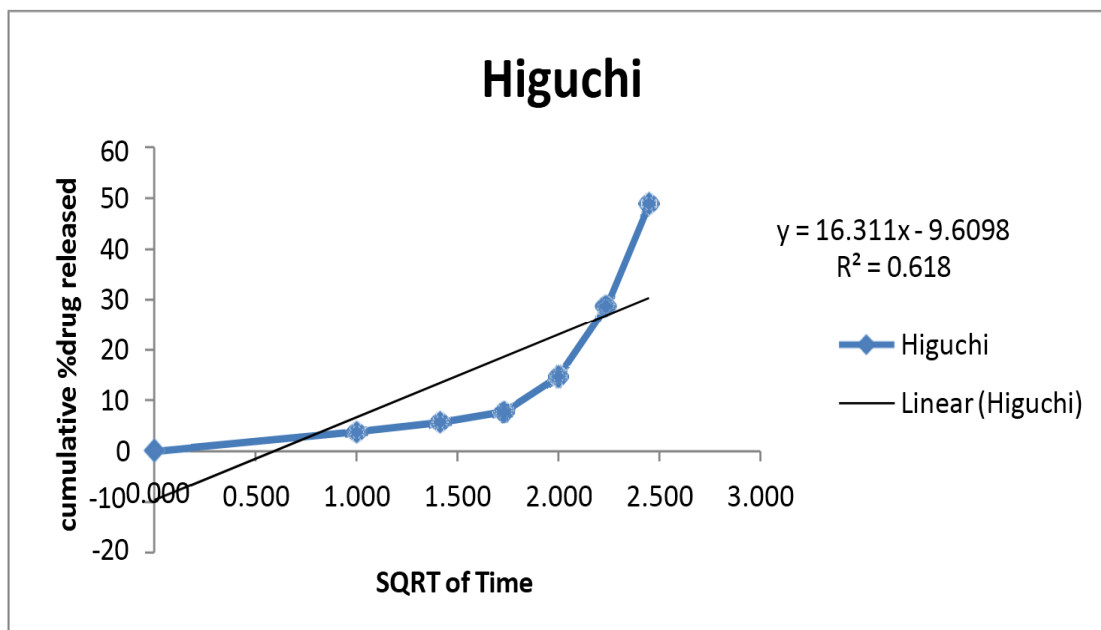


Figure No. 6.144: Sq root time vs cumulative % drug released

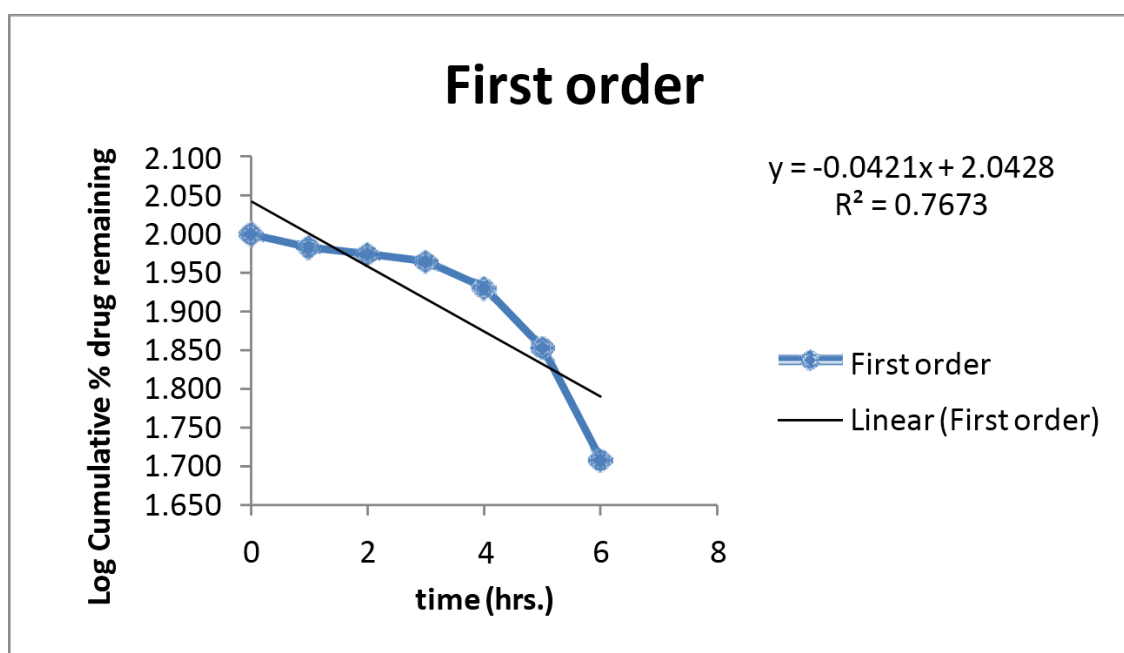
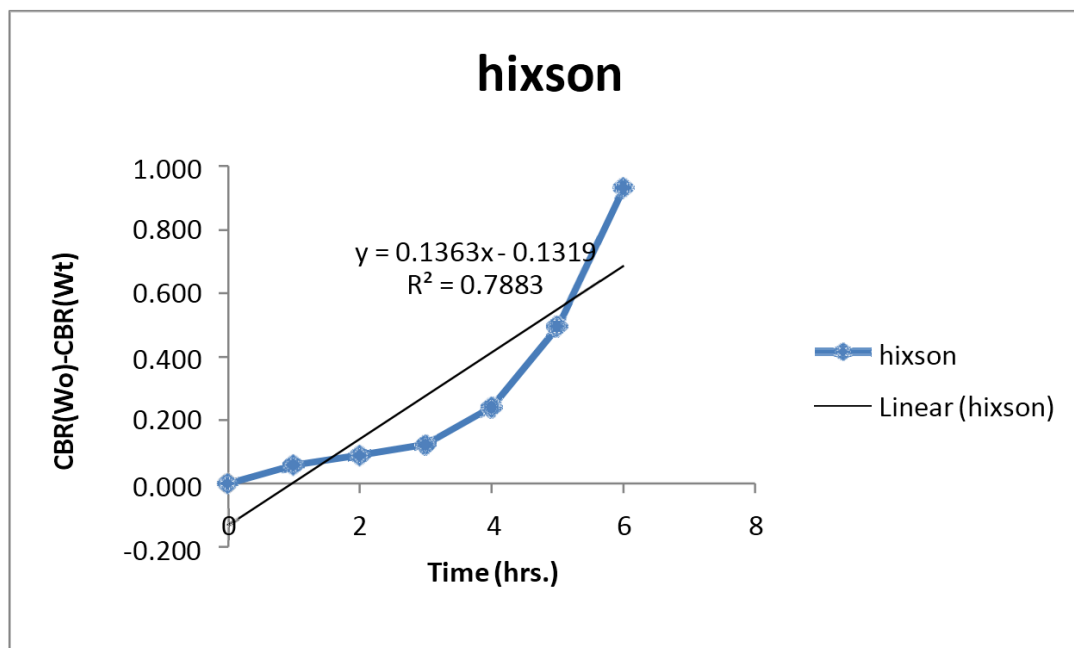


Figure No. 6.145: Time vs log cumulative % drug remaining



**Figure No. 6.146: Time vs cube root of drug remain**



Table 56: *In-vitro* drug remain data for SCO6

Time (Hr.)	Cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	Log time	Log Cumu % drug released	% Drug released	Cube Root of % drug Remaining (Wt)	Wo-Wt
0	0	100	0.000	2.000	0.000	0.000	100	4.642	0.000
2	14	86	1.414	1.934	0.301	1.146	14	4.414	0.228
4	20	80	2.000	1.903	0.602	1.301	6	4.309	0.333
6	32	68	2.449	1.833	0.778	1.505	12	4.082	0.560
8	58	42	2.828	1.623	0.903	1.763	26	3.476	1.166
10	85	15	3.162	1.176	1.000	1.929	27	2.466	2.176
12	92	8	3.464	0.903	1.079	1.964	7	2.000	2.642
16	95	5	4.000	0.699	1.204	1.978	3	1.710	2.932
24	99	1	4.899	0.000	1.380	1.996	4	1.000	3.642

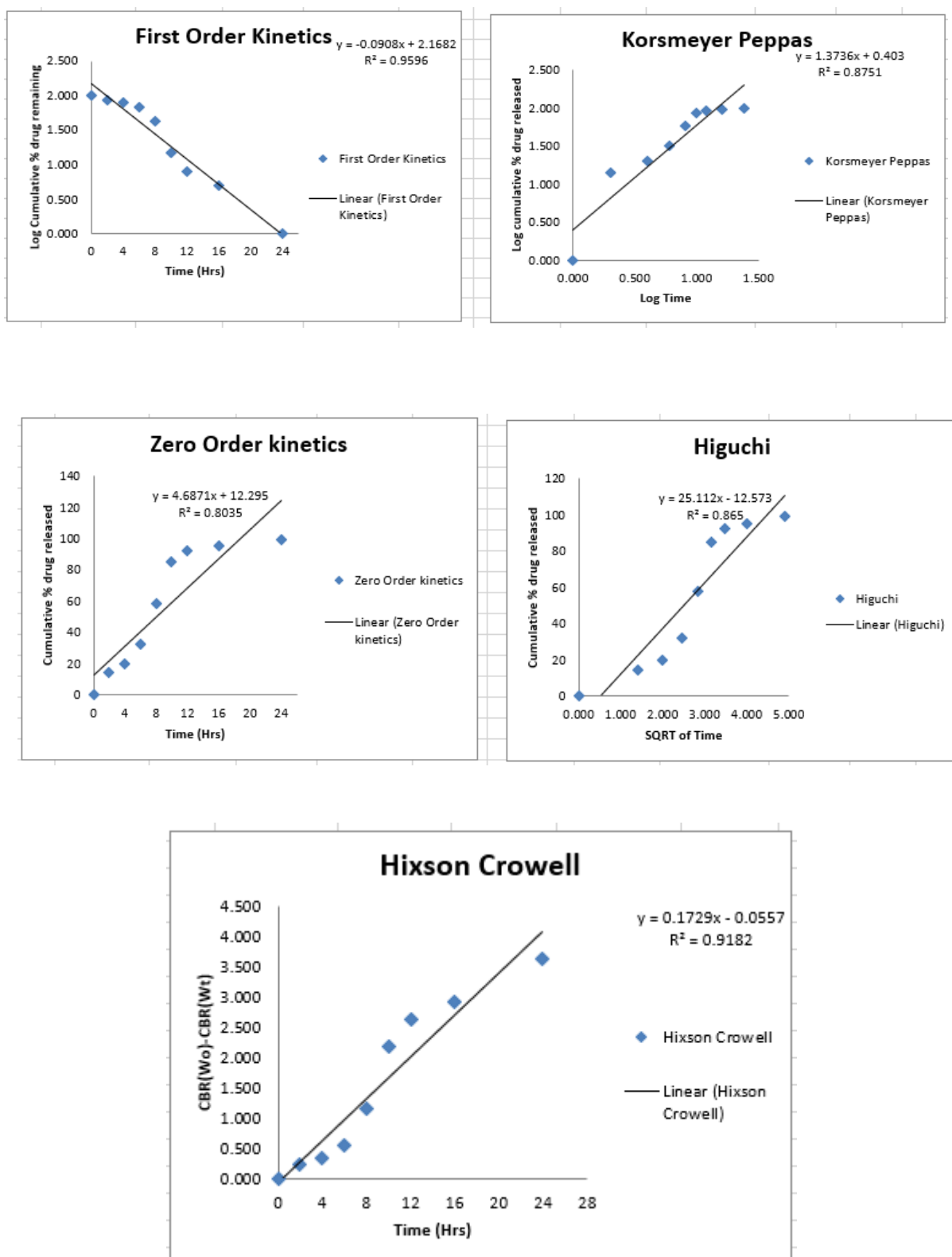


Figure No. 6.147: Time vs cube root of drug remain

The majority of the time, computational approaches are used for understanding the mechanism of drug release from a pill. Understanding the dose structure's drug absorption characteristics is an essential tool. The best match for releasing the medication was found to be the Higuchi had quadratic model, with  $r^2 = 0.865$  for BL4 and SCO4,  $r^2 = 0.865$  for BL5 and SCO5, and  $r^2 = 0.865$  for BL6 and SCO6. This implies that the ejection of a medication is a square-root-dependent, diffusion-controlled process. The disintegration info was additionally plotted using the Hixson–Crowell method, which, for BL4 and SCO4,  $r^2 = 0.9182$ ,  $r^2 = 0.9182$  for BL5 and SCO5, and  $r^2 = 0.9182$  for BL6 and SCO6, describes the change in the formulation's surface area and diameter with the progressive dissolution as a function of duration. A factor bigger than 0.8751 for  $n$  (Release exponent) in the model Korsmeyer-Peppas force law relationship reveals an instance of transmission, indicating that the drug release from the system is consistent with Super case II transport.

#### DRUG RELEASE GOAT SKIN

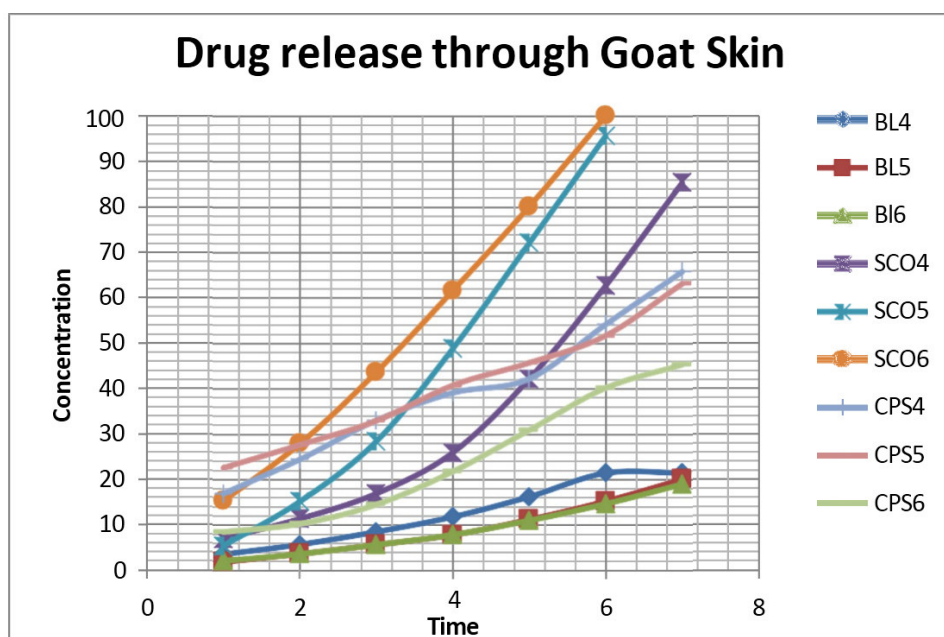
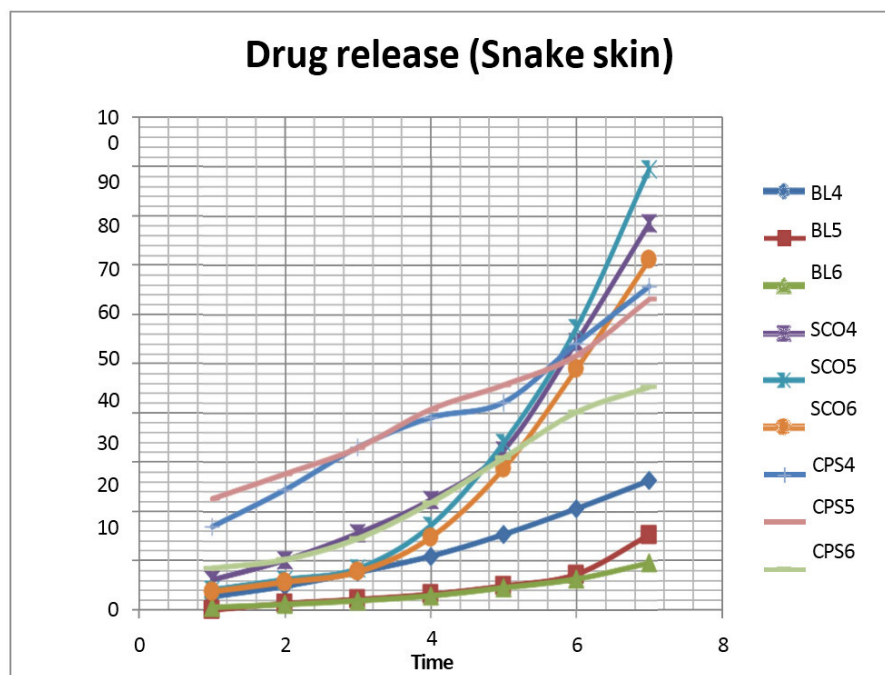


Figure No. 6.147: Time vs % Drug release through goat skin

## DRUG RELEASE SNAKE SKIN



**Figure No. 6.149: Time vs % drug released through snake skin**

**Application of gel****Standard Drug administration****Formulation B5****Formulation S5****Figure No 6.50: *In-vivo* animal study by application of conlchicine gel**

Reports on Estimation of Pharmacokinetics parameters of stand colchicine, topical formulation BL6 and SL06 after topical skin application in Wistar rats

#### Pharmacokinetic study parameters

**Table 57: Pharmacokinetic parameters of Optimized formulations**

Sr. No.	Parameters	Standard Colchicine	Test sample BL6	Test sample SL06
1.	Slope	-0.06	-0.011	-0.016
2.	Intercept	3.69	3.050	3.356
3.	Kel (per hour)	0.14	0.025	0.037
4.	t <sub>1/2</sub> (hours)	4.98	27.651	18.908
5.	C <sub>0</sub> (pg./ml)	4910.52	1121.877	2268.132
6.	V <sub>d</sub> (Liters)	101822.27	445681.550	220445.739
7.	clearance (liters/hours)	14183.45	11169.664	8079.497
8.	AUC <sub>0-t</sub> (pg.hr/ml)	3545.99	2792.541	2019.999
9.	AUC <sub>1-t</sub> (pg.hr/ml)	44583.17	31590.000	62347.325
10.	AUC <sub>1-∞</sub> (pg/ml)	71.79	11902.490	10460.911
11.	AUC(TOTAL)(pg.hr/ml)	48200.95	46285.031	74828.235
12.	C <sub>max</sub> (pg/ml)	12000.67	2993.300	7086.200
13.	T <sub>max</sub> (hour)	1.00	1.000	1.000

## Pharmacokinetic study Standard: Colchicine

Table 58: AUC of standard colchicine.

Sr. No.	Time(hours)	Concentration (pg/mL)	Logconc. (pg/ml)	AUC
1.	0.5	4000.59	3.602124045	4000.315
2.	1	12000.67	4.079205493	25502.12
3.	4	5000.74	3.699034275	6200.74
4.	6	1200	3.079181246	4800
5.	12	400	2.602059991	3000
6.	24	100	2	1320
7.	48	10	1	-240

## Test formulation: BL06

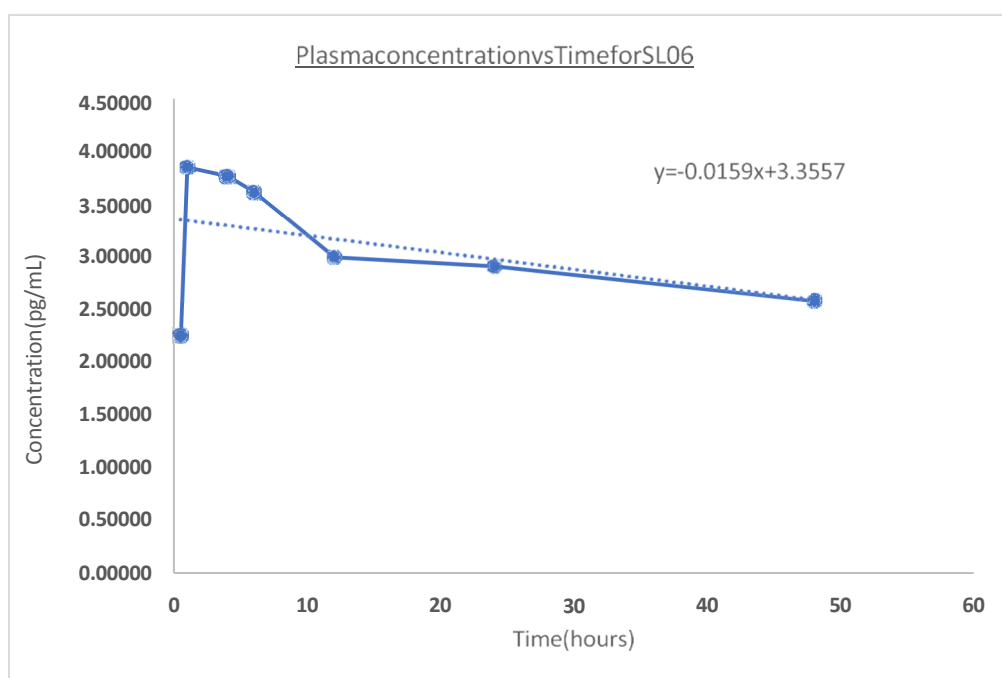
Table 59: AUC of BLO6

Sr. No.	Time(hours)	Concentration (pg/mL)	Log conc.	AUC
1.	0.5	143.3	2.16	784.15
2.	1	2993.3	3.48	7787.25
3.	4	2198.2	3.34	3652.4
4.	6	1454.2	3.16	6685.2
5.	12	774.2	2.89	8517
6.	24	645.3	2.81	11323.2
7.	48	298.3	2.47	-7159.2

SL06

Table 60: AUC of SCO6

Sr. No.	Time (hours)	Concentration (pg/mL)	Log Conc.	AUC
1.	0.5	178.9	2.25261	1816.275
2.	1	7086.2	3.85041	19388.55
3.	4	5839.5	3.76638	9941.6
4.	6	4102.1	3.61301	15267.9
5.	12	987.2	2.99441	10793.4
6.	24	811.7	2.90940	14341.2
7.	48	383.4	2.58365	-9201.6

Figure No. 6.151: *In- vivo* time vs concentration





# CONCLUSION



The intricate network that makes up our immune system is vital to our defense against external diseases and damaging stimuli. The two different immune units that the immune system uses to function are innate immunity and Adaptive defense. The primary line of protection for the host is the characteristic protected response. Defense, but the development of an adaptive immune response takes several days. Into operation. If our body is under attack from an invasive pathogen or damaging stimuli Inside our bodies, a complicated series of processes take place that entail the function of several types of incendiary cells, such as macrophages and neutrophils, and is referred to as the inflammatory reaction, and inflammation is the name given to the process. Generally speaking, there are two types of inflammation based on duration and severity.

Numerous medications have been created to date to lessen inflammation. Illness produced by the body, such as those treated with traditional NSAIDs, etc. However, these traditional medications have long been known to have negative effects. People have been anticipating the application of organic phytochemicals in medicine. Understanding Ayurveda and the traditional remedies utilized in the area have always been searched for when creating novel medications for a range of illnesses. The current investigations are intended to provide a revolutionary medicine delivery method, such as the transdermal patch.

- The research involves standardized seeds that have been extracted through a range of traits such as including ash value, extraction worth, transpiration on being dried, unreliable phytochemical examination, and fluorescent assessment, from the Simmondsiachinesis family of Simmondsiaceae and the B. Lanzas family of Anacardiaceae. The material contents and productivity percentage were separated for further screening following standards. Pre-formulation studies were carried out after the medicine was characterized to ascertain its organoleptic characteristics. When the medications' organic characteristics, such as appearance and odor, were studied, it was found that the liquid of B. lanzan was light yellow whereas the fluid of S. Chinesis was pale yellow.
- A graph of the calibration curve was made between transmittance and dose. For colchicine the correlated correlation (or "r<sup>2</sup>") values have been determined as 0.999

and 0.998; the parameters used are given in Table 6.3.

- The reference spectral and the FTIR spectra of the two medications were evaluated. Equivalent maxima for groups of functions have been seen in the typical spectrum which was reported in pharmacopeia and the spectrum was found to be compatible with each other. This shows that the drugs are pure.
- From the above analysis it was found that the saponification values obtained for both the oils were within the range of their standard values. It can be said that the saponification value of *Buchananialanzan* possesses a high saponification value. The lower acid value shows low rancidity of oil. But the higher value which was found in the case of *simmondsia chinensis* shows more rancid than the other one. The percent free fatty acid and glycerol varied from 2.26% to 8.83% and 1.02% to 14.2% respectively.
- It was found that the pH of preparations falls under a variety of 6.70 to 7.95 which shows its acceptability towards application to skin as all the values are close or near neutral pH. It means the optimized gel was compatible with the skin.
- No any sign of irritation was observed upon topical application of gel, evidence towards the safety profile of gel.
- The acute toxicity was performed on albino mice. Acute toxicity studies reveled that, no any abnormalities were shown by the mice throughout the study.
- Prepared gel formulations were subjected to a skin irritation test and allotted score depending on the reaction shown on the skin of volunteers the score below 2 shows the acceptability of gel formulations to be applied on the skin.
- The optimized gel showed acceptable physical properties, pH, viscosity, spreadability, and extrudability.
- The release of Phytoconstituents would be in controlled manner at the site of achievement thereby decreasing the possible side effects
- It was discovered that the zero-ordered graphs were largely flat. The exact process

of releasing drugs via liposomal gel was ascertained by fitting the experimental release information to the Korsmeyer Peppas equation and computing the 'n' values. The range of  $0.5 < n < 1.0$  for "n" values demonstrates that the drug discharge appliance from the gel adhered to an anomalous transport method, that is, non-Fickian diffused. Drugs release from liposomal gel in an authorized way in 12 hours, while in the case of the promoted invention, there is no meticulous release of drugs via the gels.

- Additionally, the formulation stored in a cool condition for stability purposes over a period of four weeks no change in the content of the formulation

### **GOAT SKIN MEDICATION RELEASE**

When it comes to understanding the processes of how drugs escape into the dose form, mathematical frameworks are essential. Comprehending the medication release rates of the form of dosage is a crucial instrument. Higuchi, the square root models ( $r^2 = 0.865$  for BL4) proved to have the greatest match to the drug release data. This suggests that the drug administration is influenced by time, diffusion-controlled process with a root that is square. The breakdown information was displayed as well in accordance with the Hixson-Crowell theory ( $r^2 = 0.9182$  for BL4), which illustrates how the formulation's the size or thickness varied as the process of disintegration went on. The model Korsmeyer-Peppas power law solution further defines the type of dissemination; this was found by calculating the value of n (dispersion exponent), which is more than 0.875, signifying suggesting the drug is released via the procedure subsequent to Megabyte instance II passage.

The Higuchi square root model proved to provide the greatest fit with the release of the medication ( $r^2 = 0.865$  for BL5 and  $r^2 = 0.8365$  for BL6), suggesting that the medication releasing is governed by mobility and is a time-varying mechanism. The dissolving data was demonstrated as well in accordance to the Hixson-Crowell model, which shows how the formulation's surface area and diameter changed as a consequence of time ( $r^2 = 0.9182$  for BL5 and  $r^2 = 0.9725$  for BL6). The kind of diffusion is also stated by the classical Korsmeyer-Peppas power regulation equation; this was determined by evaluating an amount of n (dispersion factor), which is above 0.875, indicating that the release of drugs from the network followed Extreme case 2 transportation.

When it comes to understanding the process of release of drugs from a dosage form, computational models are essential. Understanding the drug distribution rates of a form of administration is a crucial instrument. Higuchi squared root model  $r^2 = 0.7343$  for SCO4,  $r^2 = 0.865$  for SCO5, and  $r^2 = 0.7652$  for SCO6 was found to provide the most suitable fit with the release of the drug. This suggests that the release of the medication is a time-varying, diffusion-controlled mechanism with a root that is square.

The dissolving information was additionally displayed using the Hixson–Crowell method, which shows how the formulation's surface area and diameter changed as a result of the time for SCO4, SCO5, and SCO6 ( $r^2 = 0.8631$  and  $r^2 = 0.8282$  and  $r^2 = 0.9182$  respectively). The kind of dispersion is also stated by the typical Korsmeyer-Peppas power law equation; this was determined by evaluating the value of  $n$  (Release coefficient), which is greater than 0.79, indicating that the release of drug from the system followed Extreme case 2 conveyance.



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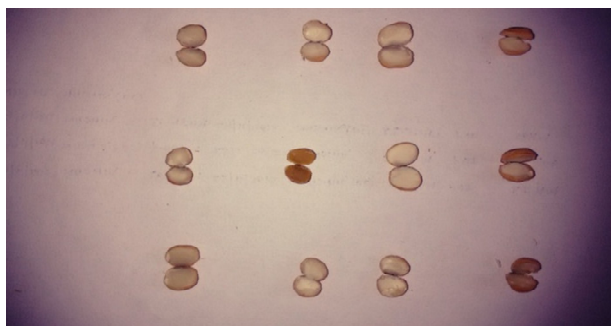
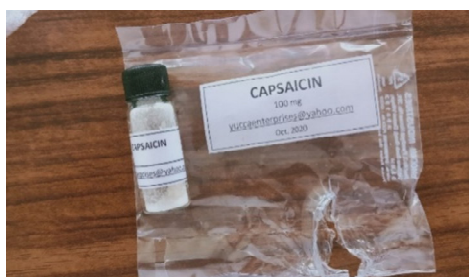
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ACUTE TOXICITY STUDIES OF EDIBLE OIL EXTRACTED FROM INDIGENOUS  
SEEDSKiran A. Suryavanshi<sup>1\*</sup>, Dr. Yogesh V. Ushir<sup>2</sup> and Dr. Venkat Chellam<sup>3</sup><sup>1,3</sup>Department of Pharmaceutics, Pacific Academy of Higher Education and Research, Udaipur, Rajasthan.<sup>2</sup>SMBT Institute of Diploma Pharmacy, Dhamangaon, Nashik.

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## ABSTRACT

Now a days ayurvedic dosage forms are preferred over allopathic. So for the safer use these plants and its preparations need to be evaluated for their toxicity. The main aim of this study was to test the acute toxicity of natural oils extracted from indigenously edible such as *Buchanania lanzan spreng.* belonging to family Anacardiaceae, commonly known as Chironji in Hindi, *Buchanania lanzan spreng.* is a tree of 12-15 mt high, with straight trunk, and *Simmondsia chinensis.*, belonging to family from Simmondsiaceae commonly known as Jojoba in Hindi is a large, evergreen, forest tree more than 30 mt in height a tree. These two plants are easily available and their various parts are used in treatment of various diseases traditionally. The acute toxicity study was studied on Swiss mice with a dose of 2 g/Kg body weight orally. The single administration exposure of the seed oil on Swiss mice was carried out and the exposure route was oral with water as a vehicle. The observations of changes in body weight, food and water intake as well as cage side observations were reported. The plants were found to be nontoxic as no mortality was recorded even at the highest dose level.

**KEYWORDS:** Ayurvedic, Toxicity, Natural oil.

## INTRODUCTION

*Buchanania lanzan spreng* belonging to family Anacardiaceae commonly used as edible oil in food. Chemically, The kernels contains moisture, 3.0; protein 19.0; fat, 59.0; fibers, 3.8; carbohydrates 12.1; and minerals 3.0g/100gm; calcium, 279.0; phosphorus, 528.0 (phytin phosphorus, 158.0); iron, 8.5; oxalic acid, 2.0; magnesium, 373.0; sodium, 10.2; potassium, 436.0; copper, 0.86; sulphur, 186.0; chlorine, 25.0; thiamine, 0.69; riboflavin, 0.53; niacin, 1.5; and vitamins C, 5.0mg/100.<sup>[1]</sup> The roots are acrid, astringent, cooling, depurative and constipating, and are useful in treatment of diarrhoea. Leaves are used in the treatment of skin diseases. Fruits are used in treating cough and asthma. The fruit is sour, sweet, fattening, laxative, binding cooling, aphrodisiac; cures biliousness, fevers, thirst, ulcers, blood diseases. The seed is sweet; aphrodisiac, cardioprotective, astringent to the bowels; cures biliousness sensation of the body. The juice of the leaves is digestive, expectorant, aphrodisiac, purgative; purifies the blood; allays thirst; lessens biliousness. The oil extracted from the kernels of the fruit is used as a substitute for almond oil in native medicinal preparation and confectionery. It is also applied to glandular swellings to the neck.<sup>[2]</sup>

*Simmondsia chinensis* belonging to family Simmondsiaceae is a complex mixture of naturally

occurring long-chained linear esters with many functional cosmetic properties that are far superior to triglycerides. Over 97% of jojoba is composed of an array of liquid wax esters, with a combination of mixed tocopherols, free sterols and other unsaponifiable material making up the balance.<sup>[3]</sup>

In addition to the obvious chemical difference, jojoba differs from triglyceride seed oils in important functional features. Nearly all triglyceride fats and oils are easily hydrolyzed and oxidized for internal food metabolism. Jojoba, like other wax esters in nature, resists hydrolysis and oxidation for more effective, non-occlusive, moisture control and for photoprotection on the external surfaces of skin, hair, eyes and plant leaves.<sup>[4]</sup>

## MATERIALS AND METHODS

## Plant collection and authentication

The fruits were collected from local market of Maharashtra and Jaipur. The plant material was identified and authenticated from Dr. Wankhede, HOD, Dravyaguna Dept, SMBT Ayurved Hospital, Maharashtra, Nashik, India.

## Extraction

Oil was extracted by cold press method. Seeds were took to the Lakadi Ghana and was pressed and extracted.

### Animal Maintenance

15 male and Female Swiss albino mice of body weight from 25-30 g were procured. The animals were housed in polypropylene cages in air conditioned room with controlled temperature and alternating 12 hour periods of light and dark were maintained. The animals were acclimatized to standard laboratory conditions prior to experimentation. Guidelines of Organization for Economic Cooperation and Development (OECD) 2001- guideline on acute oral toxicity (AOT) Environmental health and safety monograph series on testing and adjustment No.423 were strictly followed.

### Composition of diet

The animals were fed on the standard pellet diet and water was given *ad libitum*. The standard pellet diet comprised 20% proteins, 5% lipids, 4% Crude, fiber, 8% ash, 1%, calcium, 0.6% phosphorous, 3.4% glucose and 2% vitamins and 55% nitrogen free extract (carbohydrates).

### Acute Pharmacological Study

Acute toxicity of oil was determined according to the OECD (TG 423) test guide line for testing of chemical. Albino mice (either sex) fasted over night, but allowed access to water *ad libitum*. Animals were randomly divided in to three groups. The control received water. Group I-III were orally treated with test material (OBL and OSC) at dose of 5g/kg.

## RESULT AND DISCUSSION

### Clinical observation

Assessment of the behavior of animals was carried out by general observations of each animal on alternative basis from the stage of dosing to the end of the study. Any changes or abnormalities recorded could be an indication of toxicity. The test animals at all dose levels showed no significant changes in behavior before and after the administration of oral dose of oil. The clinical observation for two oil under investigation detailed in Table 1.

**Table 1: Evaluation of LD<sub>50</sub> of oil obtained from seeds of *Buchananialanzan* and *Simmondsiachinesis* (linn.)** Dose 2000mg/kg BW, Species: Albino mice: Male and Female Date 23/03/2018, duration:15 days, TRE- Tremor, CON- Convulsion, SALI-Salivation, Diah- Diarrhea, LET-Lethargy) (×= Negative, √= Positive), OBL= Oil of *Buchananialanzan* and OSC=oil of *Simmondsiachinesis*

Sr.no.	Oil	Toxicity study		Time of death	Skin	Resp.	Eyes	CNS	Observation					
		Onset	Stop						Tre	Sali	Diarh	Let	Com	Sleep
1	OBL	×	×	×	×	×	×	×	×	×	×	×	×	×
2	OSC	×	×	×	×	×	×	×	×	×	×	×	×	×

### Body Weight Changes

Body weight is an important factor to monitor the ofhealth of the animal. The loss of body is frequently the first indicator of the onset of an adverse effect. A dose, which causes 10 % or more reduction in body weight, is considered to be a toxic dose. It is considered to be the dose, which produces minimum toxic effect, irrespective of whether or not it is accompanied by any other changes. All the animals from treated groups did not show any significant decrease in body weight for all the 14 days as compared with the 0 day it thus indicating no signs of toxicity.

### Food and water consumption

There was not significant change in water and food consumption.

### Mortality

Mortality is the main criterion in assessing the acute toxicity (LD<sub>50</sub>) of a drug. There was no mortality found or recorded even at highest dose level of all groups.

## CONCLUSION

From the results of this study it is observed that there is no significant change in body weight, food and water consumption by the Albino Swiss mice from all the dose groups. There was no mortality recorded even a highest dose level i.e. 2 g/kg body weight, which proves that oil extracted from *Buchananialanzan* and

*Simmondsiachinesis* (linn.) have no toxic effect in Albino Swiss mice. The results have indicated that these plants are safe and can be used for efficacy studies.

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**Authors: Kiran Arun Suryavanshi &  
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*by Suryavanshi Kiran Arun*

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**SURYAVANSHI KIRAN ARUN**



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