CHAPTER 1 INTRODUCTION

Transdermal drug delivery

Transdermal delivery gains benefit of bypassing gastrointestinal aggravations and hepatic metabolizing effects which are unit related to the oral route. Sustained and controlled delivery is also showed, it fulfills the patient requirement and easy in application and removal. Despite fact that percutaneous route of drug administration has several benefits, as it is limited to the low penetrability from the skin, due to stratum corneum which plays role of barrier. Hence, to enhance drug permeability through the skin, various penetration enhancers, prodrugs, superfluous vehicles, iontophoresis, phonophoresis and electroporation have been utilized to maximize the degree of skin permeation.One of the chief helpful ways for rising the volume of permeation through skin is that the utilization by permeation enhancers, which showed worthy outcomes. Iontophoresis, includes applying a direct current, utilized widely as a skin invasion technique utilizing external means. Still, due to the change in pH there's a chance of skin burning. So, the aqueous solution medication will exclusively be applied.[6-8]

At present, synthetic drugs have a considerable line of treatment into controlling inflammatory disease. Analgesics, NSAIDs and cortico-steroids are found usefull in treating RA. These drugs act at various sites within the schema of pathogenic mechanisms. Less compliance with older RA patients is the significant drawback in the drug therapy. Good patient compliance is observed in transdermal delivery of drug, so it is a better route of drug delivery.[9-13]

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[14]

Routes of skin permeation

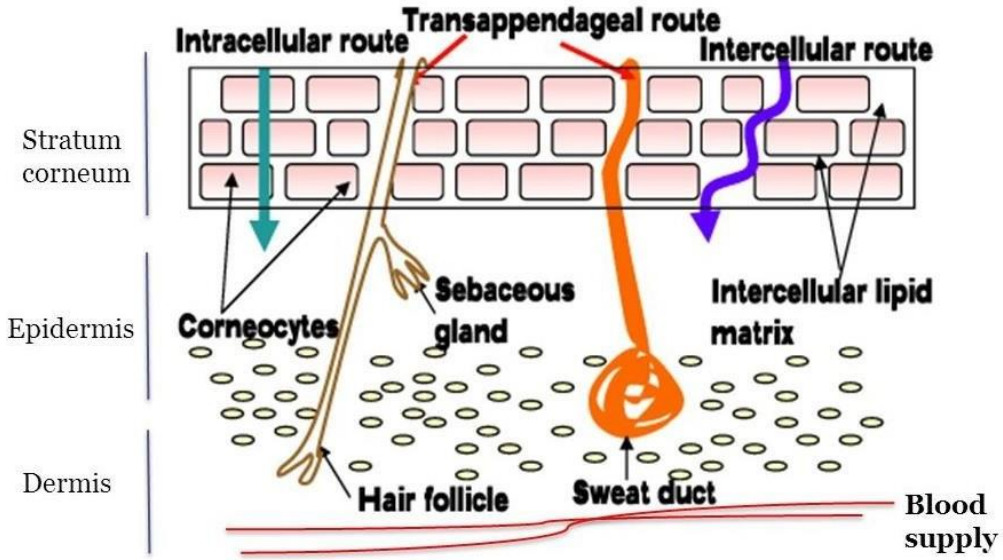


Figure No 1.1. Illustration of macroroutes of drug permeation across intact skin

The Macro route, transports substances through perspiration organs and the follicles of hair with their subordinate sebaceous organs. In transepidermal route the corneum transport is through intracellular and intercellular areas. Diffusement of polar and non-polar substances via transcellular and intercellular is seen by totally unique mechanisms. Hydrous corneum which has Polar pathway consisting of free water 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 permeation of drug. The transappendageal route is taken into account to be of minor importance due to their comparatively little space. Yet, this route is significant for large polar compounds. Several mathematical models to explain the porousness across stratum are reported. These models can be comprehensively grouped into homogeneous and heterogeneous models[15-16].

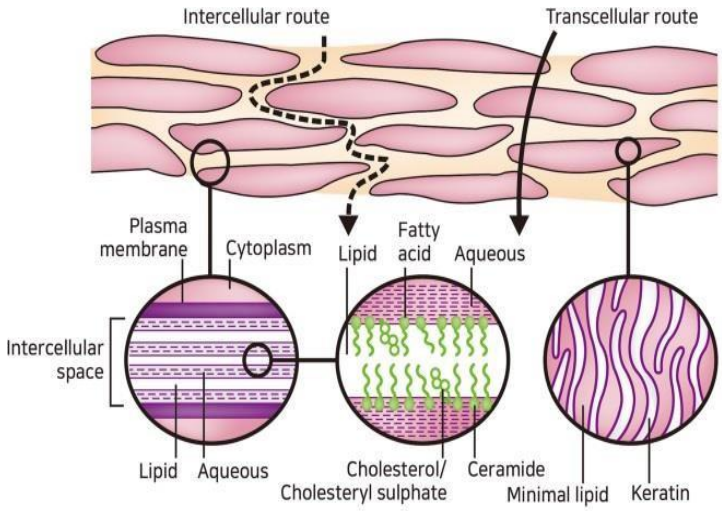


Figure 2.Possible micro routes for drug penetration across human skin intracellularor Trans cellular

Transmembrane diffusion process

Drugs are considered to move from skin by passive diffusion, it is described by a ficks Law and thedrug release rate. Diffusion of drugs in corneum layer having low molecular weight is consistent. Hair follicles in association with sebaceous glands, by sweet ducts or over the stratum corneum these are three possibilities by which drug can reach from skin. The availability of surface for the intention of diffusion from the skin tissues is almost very small, up to 1%. This route might is significant to particles and enormous charged molecules. Drug reaches systemic circulation by the plexus of capillary after diffusing from corneum layer. The molecules travels a convoluted attach and need to intersect, successively and over and over, various aqueous and lipid layers. Around ten times elongated duration required to attain Cmax when the proportional given by most common route of administration. Drug which ishaving extrem affinity or extremreplling property towards water is absorbed poorly Along with pH of the vehicle molecular size of the drugs has an importance in infiltration of the skin. Solubility, melting point, ionization state of drug molecule is also considered.[17-18].

Moleculare weight and flux perameation has ainverse relationship between them. So faster rate of diffusion is observed with smaller molecules and diffusion slows down with molecule 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 which are used are mostly weak acids or weak bases depending upon the pH of used formulation and pH of the layer through which drug has to diffuse[19].

Factors like age, presence of disease, occurance of skin structure, physiochemical property of corneum are responsible to influence skin permeability. Corneum hydration also plays an important role. Permeability of hydrophilic drugs through corneum is boosted by quantity of water available in corneum layer[19].

Transdermal therapeutic systems (TTS) are the self-contained discrete drug delivery systems that regulate the drug delivery into blood stream via skin onto application on the skin[19]. Transdermal systems are flexible pharmaceutical preparations of varying sizes, containing an active component. Development of TDDS

to deliver the drug molecules beyond different layers of skin into systemic circulation to bypass the first pass metabolism It shows benefit as drug administration by IV route and to achieve rate controlled systemic delivery of drugs[20].

In the permeation of most of the drugs, Stratum corneum acts as rate limiting barrier. Thus, a few dynamic improvement innovations have emerged as strategies to upgrade extent of transdermal medication. One of such technique is Iontophoresis,which upon application of direct current (DC) as a physical mean and that follows the principle of "like repels like", and which helps drug molecules to drive through the skin layers[21].

Enhancment Techniques for Skin PenetrationPhysical 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 thetherapeutic agent, and a uninterested cathode is located anywhere on body. Active molecules replled 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 electrodterminal, 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[22-23].

Electroporation

It is one more electrical improvement strategy that can incorporates utilization of less time, large voltage (50-1000 volts) towards skin. Tranport 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 is 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[24].

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 μm and having width min 10 to 50 μ 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[25].

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 presene 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 porousness. Application of heat changes patch physiochemical properties and causes hydration of skin, which facilitates the drug permeation[26].

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 N2 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[27].

Medicated tattoos

These are transformation of brief tattoos which are containing active drug for delivering it transdermaly. 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 corenum. 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[28].

Pressure wave

Extreme radiation laser creates pressure waves that can make the corneum more permable 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 contatining 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[29].

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 KHz < f <100 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[30].

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[31].

Radiofrequency

In this 100 KHz high frequency currend 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.[32]

Chemical Concept

Utilization of permeation enhancers

Including permeation enhancers will help to promote permeation of drugs withmodifying corneum hindrance property. Penetration enhancer should not show any phamocological 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[33].

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[34].

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[35]. 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 hydrophilicproperties and lipophillic 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[36].

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 phopholipid 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[37].

It contains phospholipids, cholesterol also some surface acting agents like

sodium cholate.The surface acting agents are "edge activators", presenting mostvasularity 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[38].

Ethosomes are liposomes made essentially of phospholipids, sometime glycols and water in generally high concentrations[39]. 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[40].

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[41].

1. Satisfactory skin porosity:

1) Lesser low molecular weight drugs
2) Lesser melting point drugs
3) Moderate oil and water solubility having drugs
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 prolong administration
2) Required to increase patient compliance
3) Required to reduce adverse effects 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 inlimit of hearable sound. >20 KHz sound frequency meant as Ultrasonic. The force (I, denoted as

W/cm2), 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:

$$I= p2/2\rho c$$

Therefore, ρ 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 lossacross 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 usefullness 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[42-44].

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 representedlike 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[46-47].

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[48-49].

- 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[50]

- Reservoir systems
- Matrix systems
- Microreservoir 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[51].

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[52]. 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.[53]

Electrically sensitive polymers would set up through polyelectrolyte[54-57].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[58]. Electrically sensitive polymers contact

close to anode, so water oozes near cathode 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[59].

Graft copolymerization

Grafting strengthen the features of natural polymers also yield another property. The normal polymers are frequently favored for graft polymers than the manufactured polymers because of its non-harmful, minimal effort, free accessibility and biodegradability. Extra advantage of this graft copolymer incorporates transformation to ionic structure by method of hydrolysis of amide groups to get pH-responsive copolymer. Certain copolymers can be utilized for the focusing to the lower some portion of the GIT like Colon.[60]

Grafting of engineered polymer onto natural polymer is the promising technique for the polymer alteration, as the framed copolymer will have the extra properties than the substrate. Due to some useful properties of natural polysaccharides like biodegradability, water solubility, it is by all accounts the reasonable possibility to be utilized as the beginning material for combination of graft copolymers. The greater part of grafted copolymers is integrated from vinyl or acryl monomers which are grafted upon network foundation of different characteristic polysaccharides. Uniting of vinyl/acryl monomers synthetically varies with non-vinyl/acryl monomers. Polycondensation is the strategy by which the non-vinyl/acryl monomers can be grafted, yet the cruel states of normal Polycondensation responses like high temperature are not appropriate for the polysaccharide spine. Henceforth the polycondensation technique isn't utilized for the union of graft copolymers of polysaccharides. Synthesis of grafted polymers can be done by two ways; a) microwave technique and b) conventional technique. The conventional technique may lead to degradation of polysaccharide and are not amenable for the formation of block copolymer. While microwave assisted technique is cleaner, simpler, straight forward, highly reproducible and eco-friendly.

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 ould be utilized to control the delivery of drug in transdermal administration, buccal administration and in network tablets[61-63].

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 chemicaly modify:

- Grafting copolymerization
- Carboxymethylation
- Oxidation reaction
- Esterification

Graft copolymerization

Graft copolymerization is the strategy that improves the characteristic features holding by natural polymers. The regular polymers are frequently favoured for the joining than the engineered polymers due to their non-harmful, minimal effort, free accessibility and biodegradability. Another benefit position of this join copolymer is this could be effortlessly changed within ionic structure by removing amide groups bringing about electrically responsive copolymers.[64]

Synthesis of cellulose graft copolymers

Grafting of synthetic polymer onto natural polymer is the promising method for the polymer modification, as the formed copolymer will have the additional properties than the substrate. Due to some useful properties of natural polysaccharides like biodegradability, water solubility, it seems to be the suitable candidate to be employed asthe initiating material for synthesis of grafted polymers. A large portion grafted polymersare synthesized by vinyl or acryl monomers grafting upon network of different characteristic polysaccharides. Grafting of vinyl/acryl monomers artificially varies according to the nature of monomers.Polycondensation is the method by which the non- vinyl/acryl monomers can be grafted, but the harsh conditions of typical Polycondensation reactions like high temperature are not suitable for the polysaccharide backbone. Hence the polycondensation procedure is not utilized for synthesis of grafted copolymers of polysaccharides.[65]

Grafting forms branched structure copolymer, where the backbone of main polymer

or substrate is get covalently bonded by the side chains of synthetic monomer. Graft copolymers have a wide range of and valuable properties 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 initaiator 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 uing 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. Raditation/ microwave light is utilized to perform grafting[66].

Vinylic/acrylic graft copolymerization

Grafting of materials made with vinylic 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.

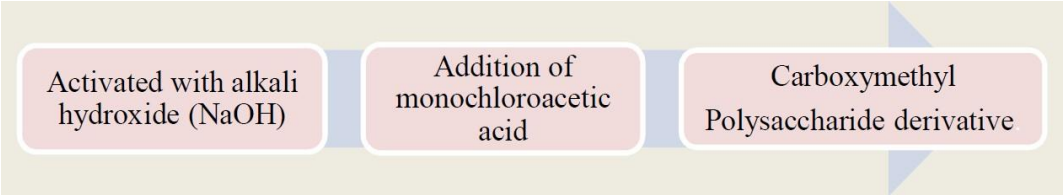


Figure No 1.3.Williamson ether synthesis process

In process the natural polysaccharide was made to dissolve in aqueous solution of NaOH, under constant stirring. The temperature of the reaction was maintained at 70^0C with constant stirring for 30 min, after the addition of monochloroacetic acid solution. After cooling the reaction mixture was added with 80% (v/v) methanol to get the precipitate which was then filtered and washed. 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.

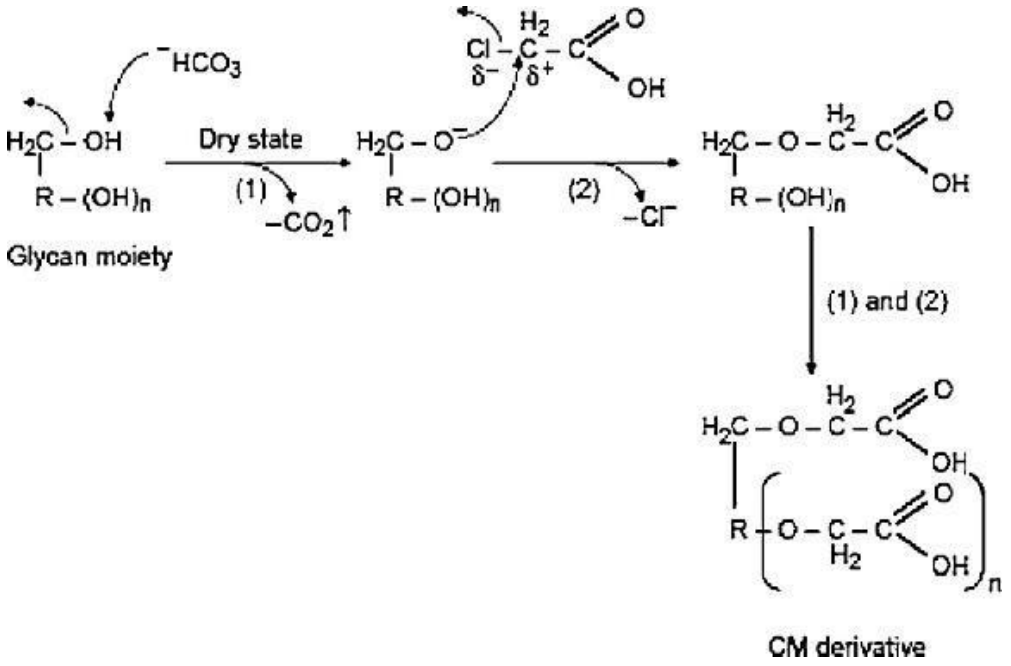


Figure No 1.4.Carboxymethylation of natural gums

Etherification method containing carboxymethylatedgroups is also known as carboxymethylation. Many natural polysaccharide including cellulose and starch can be chemically modified by this method.In transdermal delivery system Carboxymethyl locustbean, guar& Xanthan gum is used[65].

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 upto 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 Phosphation.
- Sulfurization by sulfuric acid.
- Reaction with derivatives of carboxylic.
- Nucleophilic reactions of displacement.[67]

The practice in herbal medicine is come into existence since ancient times as the primary form of medicine. In this era where the technology is very much advanced, herbal medicines are still flourishing and are finding exceptional acceptance in both developing as well as in developed countries due to its natural origin and decreased side effects. Besides it's the use of botanicals as medicinal products in developing countries, such products are becoming a part of the integrative healthcare systems of the industrialized nations, known as complementary and alternative systems of medicine, fastly. A number of herbal traditional medicines have been arised which are now dominating the practice of alternative medicine. This includes the western herbal tradition based on Greek and Roman sources, the essentially Ayurveda tradition of India, Thai and the Chinese herbal medicine. Botanicals or phytomedicines have always been a major component of traditional systems in developing countries, which have also been an integral part of their history and culture. In the ancient Indian system of medicine, Ayurveda and Siddha are such examples.

In early days it was well known that plants are a rich source of a variety of chemicals constituents with therapeutics properties. Seeds, herbs belong to general botanicals of various types which are also often the aromatic plants used especially in medicine or as seasoning. Seeds can be used directly as whole or their extracts may be used in the production of drugs, sometimes. A drug or preparation made from a plant or plants and used for any of such

purpose is better known as herbal drug. Opium, aspirin, digitalis and quinine etc currently available are having long history as use as herbal remedies. Techniques like purification and quantification of these plant or part of plant extracts makes them more predictable and chemical processing can sometimes modifies their effects in desirable ways, herbal remedies tend to have a more complex of chemicals, and can sometimes offer access to drugs or combinations of drugs, that the pharmaceutical industry has not yet exploited.

The widespread use of plants or their parts in traditional medicine has also increased demands as Herbal remedies be regulated as a drug to ensure quality standards and to prove its scientific basis. Herbal drugs promise not only prevention but also the treatment of various types of diseases. There are over 760,000 plants on earth, but only a very few have been studied for their therapeutic purpose. Most of the research done on herbals is focused on identifying and isolating active ingredients. Traditional medical practitioners and scientists are also going towards medicinal plants now a days for curing ailments such as inflammation, rheumatoid arthritis, cancer, diabetes, wound healing and many more because of the fact that they possess less or no side effects being natural origin. These extracts are formulated into different formulations for their ease of administration. The novel formulations are reported to have number of advantages as conventional forms of plant actives and extracts which preferably include enhancement of solubility, bioavailability, free from toxic effect, enhancement of pharmacological activity, enhancement of stability, sustained delivery, and protection from physical and chemical degradation.

Gout and use of herbal extracts in its treatment

Gout is a common type of arthritis which causes intense pain, swelling, and stiffness in joints. It usually affects the joint in the big toe. Gout attacks can come quickly and keep returning over time period. It slowly harms tissues in the region of its inflammation. It is the most common form of inflammatory arthritis in men, and although it is more likely to affect men, women become more susceptible to it after the menopause. The Centers for Disease Control and Prevention (CDC) report that 8.3 million Americans were affected by gout.

Following are some key points about gout

Gout is a form of arthritis caused by excess uric acid in the bloodstream.

The symptoms of gout are due to the formation of uric acid crystals in the joints and the body's response to them.

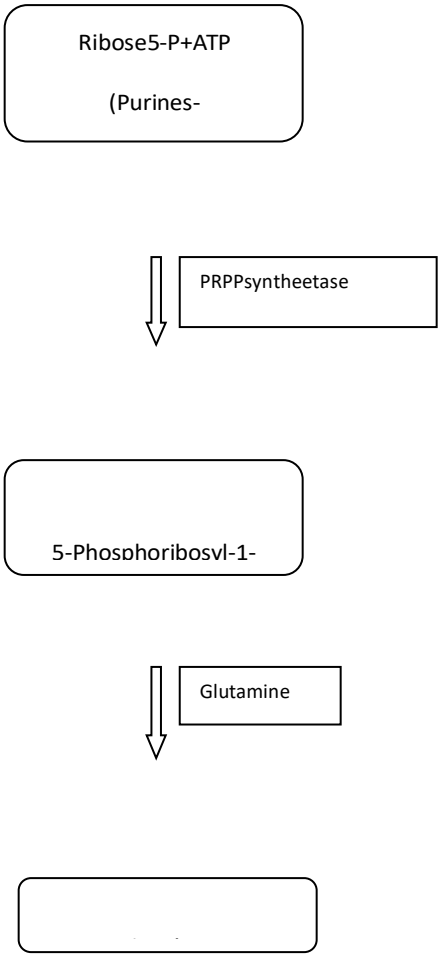
Gout most classically affects the joint in the base of the big toe.

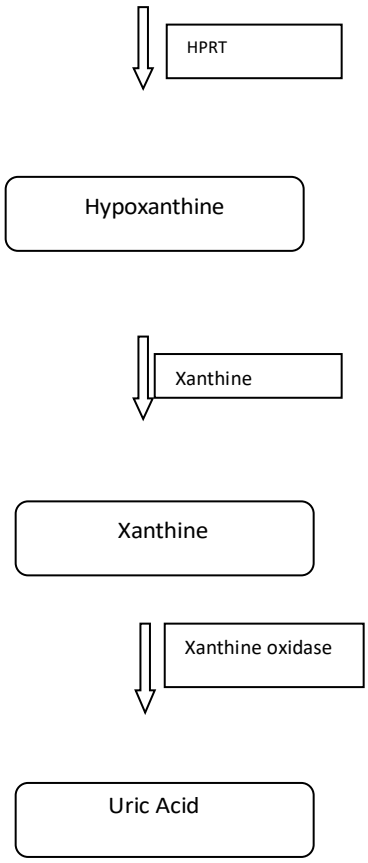
Gout attacks often occur without warning in the middle of the night.

Most gout cases are treated with specific medications.

Uric AcidMetabolism

Biosynthesis of Urate:





(Hypoxanthine-guanosinephosphoribosyltransferase)

Figure No 1.8: Urate Biosynthesis

In humans, uric acid is the end product of purine metabolism in the liver (Figure1.8).

Uric Acid Excretion

Human uricase, helps to degrade uric acid to highly soluble allantoin. About Two third of the urate is expected to excrete by kidneys. In this post-secretary reabsorption in the S3 segment of proximal renal tubule is the major part that contributes for the reabsorption urate which is filtered. The major genes that encode ion transporters involved in urate renal transport have been identified. The most important among these is the anion exchanger URAT1 encoded by SLC 22 A 12 (solute carrier family 22 [organic anion/ urate transporter] member 12) gene on

chromosome 11q13 which drives urate anions reabsorption. The hexose transporter SLC2A9 (also called the glucose transporter 9, GLUT9, or fructose transporter encoded by gene on chromosome is involved in voltage-dependent urate absorption the proximal tubule. Genetic polymorphisms of SLC2A9 may point towards the mechanisms by which high fructose intake and hyperglycemia are linked with hyperuricemia and gout. Single nucleotide polymorphism (SNP) of ABCG2 (ATP-binding cassette subfamily G member 2), acts aschief transporter for tubular secretion of urate; is strongly associated with hyperuricemia in men, post-menopausal women and hormone therapy users.

Types of Gout:

Asymptomatic hyperuricemia

It is possible for a person to have elevated uric acid levels without any outward symptoms. At this stage, treatment is not necessary as much, though urate crystals are being deposited in tissue and causing slight damage. Patients who are suffering from asymptomatic hyperuricemia advised to take certain steps in order to address any possible factors contributing to uric acid build-up.

Acute gout

This stage occurs when the urate crystals deposited suddenly which may cause acute inflammation and intense pain. This sudden attack is referred to as a "flare" and will normally subside within 3 to 10 days. stressful events, alcohol and drugs, as well as cold weather can be the causes of Flares.

Interval or intercritical gout

This stage is considered as the period in between attacks of acute gout. Subsequent flares may not occur for months or years, though if not treated, over time, they can last longer and occur more frequently. During this interval, further urate crystals are being deposited in tissue.

Chronic tophaceous gout:

Chronic tophaceous gout is the most enfeeble type of gout. Permanent damage may have occurred in the joints and the kidneys. suffer from chronic arthritis may developwhich may lead to development of tophi, big lumps of urate crystals, in cooler areas of the body such as the joints of the fingers. Usually It takes a longer duration of time without treatment to reach the stage of chronic tophaceous gout (May be last for around 10 years). As this most debilitating type of gout chances are rare to overcome from this disorder.

Pseudogout:

One condition that is easily confused with gout is pseudogout. The symptoms of pseudogout are very similar to those of gout. The major difference between gout and pseudo gout is that the joints are irritated by calcium phosphate crystals rather than urate crystals. Pseudogout requires different treatment to gout.

Stages of Gout

1) Asymptomatic hyperuricemia- This is the period prior to the first gout attack. There are no symptoms in this stage, but uric acid levels in blood are high and crystals are forms in the joint.

2) Acute gout, or a gout attack- It happens when uric acid levels high and to spike the crystals that have formed in a joint, which lead to trigger the attack. The resulting inflammation and pain usually strike at night and intensify over the next 8 to 10 hours. The symptom fades after a few days and likely goes away in a week to 10 days. Some people never experience a second attack, but at about 60% of people who have a gout attack will have a second one within a year (Approximately).

3) Interval gout–It is the time between attacks. Although there's no pain, the gout isn't treated completely. Low-level of uric acid inflammation may damage joints. This is the time to begin management of gout to prevent attacks of gout in future.

4) Chronic gout- It develops in people whose uric acid levels remain high over a number of years. Attacks become more frequent and the pain not goes away as it used to. Damage to joint may occur, which can lead to a loss of mobility. With proper management and treatment, this stage is preventable.

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

Transdermal Drug Delivery:

For the treatment of diseases, drugs can be delivered either to the systemic blood circulation or to the local target area. For systemic delivery, various routes are available of which the oral route is the most common one. However, the oral route has the disadvantage of the hepatic first-pass effect. Therefore, alternative routes of administration are of great interest. Out of these Transdermal is most preferable. Transdermal delivery has the potential to deliver drugs continuously into the systemic circulation thereby preventing the first-pass metabolism. However, when focusing on drug delivery to regions in the skin such as the hair follicle, sweat and sebaceous glands, application of the drug on the skin surface also has the potential to increase the drug concentration at the site of action. Additionally, the delivery into the systemic circulation might be decreased thereby reducing possible side-effects. The rational of topical delivery may be of particular interest for skin diseases such as acne, cancer and alopecia, which originate in the pilosebaceous unit.

Furthermore, it also of interest for cosmetic products to improve e.g., the hair condition. Local delivery can be improved by two approaches. The first approach is the selection of an appropriate formulation, which might contain particulate carriers and additives such as ethanol, surfactants and propylene glycol. A second approach is the selection of a possible drug candidate. The physicochemical parameters of the drug, e.g., size, charge and lipophilicity, may affect the degree of delivery and targeting. In such cases where adaptation of the formulation is not feasible, delivery and targeting can only be improved by changing the physicochemical parameters of the permeation enhancers itself.

Topical drug delivery has been accepted as one of the potential non-invasive routes of drug administration having advantage of prolonged therapeutic action, less side effects, easy to use and better patient compliance. However, development of topical products primarily impeded by the low permeability of the skin. So, to overcome this problem now a days various chemical penetration enhancers has been synthesized for topical drug delivery which provides easy passage for drug molecule to pass through the skin. These chemical enhancers aid absorption of

co administered drugs are currently believed to improve solubility within the stratum corneum or increase lipid fluidity of the intracellular bilayer.

Skin: Skin is the largest interface between the human body the eternal environment. Therefore, it helps to regulate what enters the body via the skin as well as exits. In general, the skin allows entry for very low size matter, since other tissue such as the permeable epithelia of the GI tract and lung provide the primary means of regulated entry into the body. This remarkable barrier of the skin is due in large part to the stratum corneum, which represents the thin outer layer of the epidermis. In contrast to other tissues in the body, the stratum corneum consists of corneocytes which composed primarily of aggregated keratin filaments encased in a cornified envelope that are surrounded by an extracellular milieu of lipids organized as multiple lamellar bilayers. These well-structured lipids prevent excessive loss of water from the body and likewise block entry of most topically applied drugs, other than those that are lipid soluble and of low molecular weight. This poses a significant challenge to administering medications via skin either for local cutaneous effects or as systemic therapy following entry into superficial dermal capillaries.

Structure of skin: Different layers of skin

Skin does the dual work as a barrier between the outside environment and our body. The layers of the skin are epidermis and dermis;

Epidermis: -

Horne layer

stratum lucidum

Stratum granulosum

Dermis:

1) Malphagian layer

2) Papillary Layer

3) Reticular layer

Epidermis: -

The epidermis is the outermost layer, having a thickness of 0.1 to 0.6 mm as per its location on our body.[7] 90-95% of cells in the epidermis are keratinocytes. The bottom most layer of epidermis has a layer of undifferentiated keratinocytes which are in contact to the dermis. These rows of cells divide constantly and thereby producing new cells outermost layer of skin is stratum corneum which is similar to brick and more far.

Dermis: -

Inner layer of skin between epidermis and other layer of tissue fat muscle, etc. Thickness is 0.3 to 0.4 mm. Blood vessels supplying nutrients to all skin layers are in dermis. Extracellular proteins immune cells, reside in dermis.

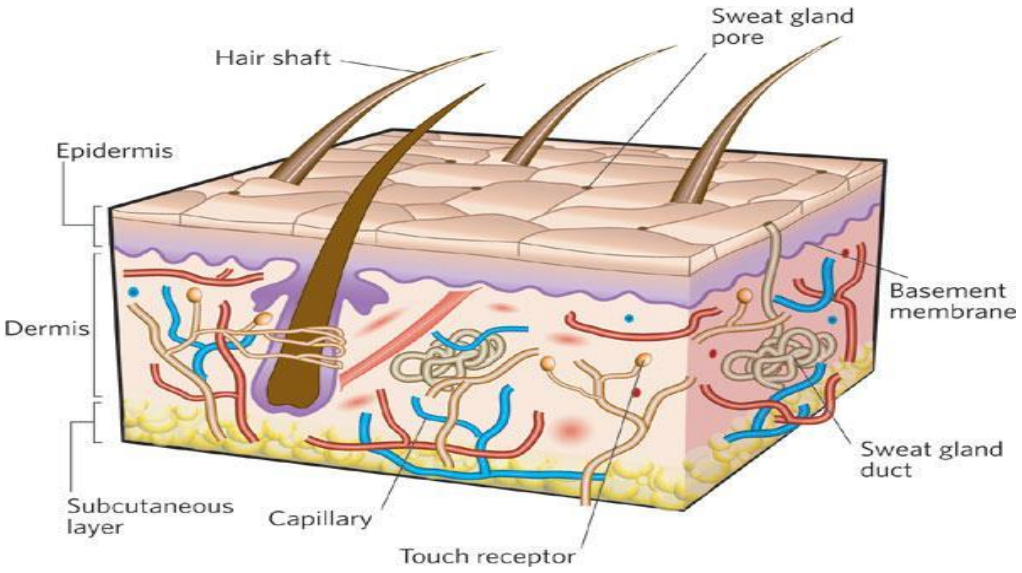


Figure. No. 1.9: Different parts of the Skin

Percutaneous Drug Absorption

The skin is made up of several layers including stratum corneum, viable epidermis and dermis. It contains appendages that include sweat glands, sebaceous glands, and hair follicles. The stratum corneum is the outermost 'horny' layer of skin, comprising about15-20 rows of flat, partially desiccated, dead, keratinized epidermal cells. Depending upon the region of the body, the thickness of this layer ranges from10-20□m. The thickest layer is on the palms of the hands and soles of the feet. The stratum corneum is a remarkably more formidable barrier to drug transport than the epithelial barriers of gastrointestinal, nasal, buccal, vaginal, or rectal delivery routes. Transport of hydrophilic molecules are especially difficult attribute able to the lipid-rich nature of the stratum corneum and its low water content; this layer is composed of about 40% lipids, 40% protein and only 20% water. The transport of these lipophilic drug molecules is generally facilitated by their dissolution into intercellular lipids around the cells of the stratum corneum. Absorption of hydrophilic molecules into skin can occur through 'pores' or openings of the hair follicles and sebaceous glands. So, Relative surface area of these openings is barely 1% of the total skin surface. This small surface area limits the amount of drug absorption. Percutaneous absorption of drug molecules is important in the case of transdermal drug delivery system because the drug has to get absorb to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of treatment. In other words, once drug molecule crosses the stratum corneum barrier, passage into deeper

Drug absorption into the skin occurs by passive diffusion. The rate of drug transport across the stratum corneum follows Fick's Law of Diffusion. The rate of drug transport depends not only on its aqueous solubility, but is also directly proportional to its oil/water partition coefficient, its concentration in the formulation vehicle, and the surface area of the skin to which it is exposed; it is inversely proportional to the thickness of the stratum corneum. The stratum corneum is thickest in the plantar (soles) and palmar regions and thinnest in the post auricular, axillary, and scalp regions of the body. Understanding of the transport behavior of drugs is more important for designing an effective topical or transdermal product, as well as reasonably predicting and comparing drug behavior in various formulations. The latter is of practical importance to the pharmacist who is required to suggest one or more effective drug products out

of the many commercial formulations available or to counsel patients on proper use and handling of topical and transdermal products.

During penetration through the stratum corneum, two possible routes can be distinguished, i) penetration alternating through the corneocytes and the lipid lamellae (transcellular route) and ii) penetration along the tortuous pathway along the lipid lamellae (intercellular route). Generally, it is accepted that the predominant route of penetration through the stratum corneum is the intercellular route. This is mainly caused by the densely cross-linked cornified envelope coating the keratinocytes. However transcellular transport for small hydrophilic molecules such as water cannot completely be excluded.

The content of the eccrine sweat glands is mainly hydrophilic, while the content of the follicular duct is lipophilic. This is mainly due to the sebum excreted into the opening of the follicular duct. passive transdermal penetration.

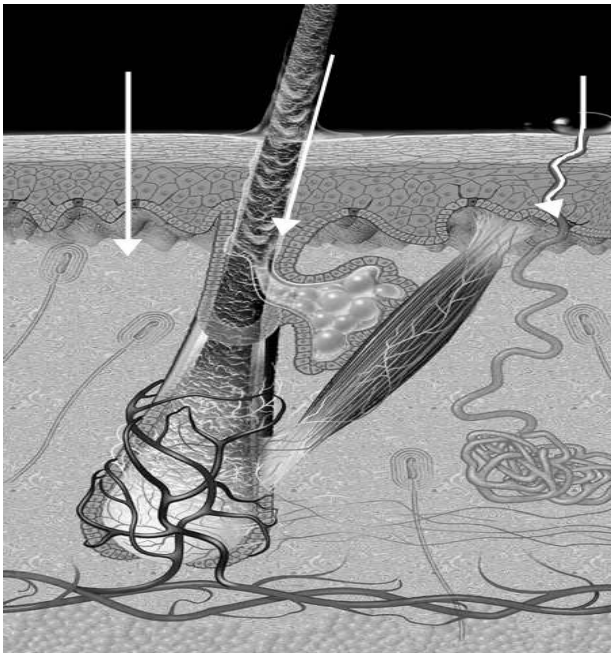


Figure No. 1.10: **Transepidermal (A) and transappendageal route of transport into the skin. The transappendageal route (B) includes diffusion via the hair follicle and the sweat gland**

Topical Formulations:

Most favorable therapeutic outcomes require not only right drug selection but also successful drug delivery. As skin is best and biggest available space for drug delivery, developing a suitable drug delivery becomes much more important in the pharmaceutical industry over last several decades. The required pharmacological response and undesired effect of a drug is dependent mainly on the concentration of the drug at the site of action which depends upon the dosage form and the amount of absorption of the drug at the site of action. The possible area of the whole skin as the harbor of drug administration to the human body has been recognized for some decades, but skin is an extremely difficult barrier to the access of materials allowing only small quantities of a drug to go through over a period of time. It is one of the most gladly reachable organs of the human body.

Drug substance for Topical Drug Delivery System:

Drug Substance plays a very important role in the successful development of a topical product

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

Table No.1.1: Ideal properties of drug & some factors to be consider during preparation of topical drug delivery

Natural penetration enhancers:

Essential oils, terpenes and terpenoids:

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

Chemical structure of terpenes and terpenoids consist of number of repeated isoprene units which is used to classify terpenes.

Monotrepenes: Have two isoprene units.

Sesquiterpenes: have three isoprene units.

Diterpenes:Have four isoprene units.

Terpenes and terpenoids: are constituted of volatile oil. Terpenes are compounds which contains carbon,hydrogen and oxygen alone. Eucalyptus and chenopodium are effective penetration enhancers.

The chemical structure of terpenes and the physicochemical properties of the drugs play an important role in the permeation enhancing activity of terpenes. Permeability coefffient of various terpenes have been determined experimentally using human skin and the results suggest that terpenes with larger Log*p*. It has also been observed that the liquid terpenes could form a greater number of hydrogen bonds with intercellular lipids of stratum corneum and produce better enhancing effects than solid terpenes. Triterpenes and tetra terpenes generally had poor penetration effect than other terpenes when evaluated, while presence of aldehyde or ester functional group increases their efficiency.

Fatty acids:

Fatty acids consist of an aliphatic hydrocarbon chain and a terminal carboxylic acid group. They differ in their aliphatic chain length, which is either saturated or unsaturated in the number, position and configuration of double bonds and may have branching and other substituents.

Fatty acids as a skin permeation enhancer appear to be clinically acceptable penetration enhancers as indicated by some advantages, like it shows high skin flux, no skin irritation and compatibility with wide variety of drugs. A wide variety of long chain fatty acids have a potential utility as skin permeation enhancers.

Saponins:

Saponinsconstitute a highly diverse group of glycosides occurring in plants, which possess either a steroidal or a triterpenoid aglyconeto which one or more sugar chains are attached. They are characterized as natural surfactants and hence acquire great potential for use as percutaneous permeation enhancers.

Saponins molecules arranged in ring with their hydrophobic moieties combine with cholesterol around the outer parameter resulting in lesions in the plane of membrane due to micelle like aggregations.

Herbal extracts:

Herbal extracts have the ability to penetrate the skin surface fast. In vivo skin penetration investigations of the chamomile flavones apigenin, luteolin and apigenin 7-o-beta-glucoside concluded that the flavonoids are not only absorbed at the skin surface but also penetrate into deeper skin layers. This is a important feature for their topical use.

EXAMPLES OF NOVEL NATURAL PENETRATION ENHANCERS

BASIL OIL

is the natural penetration enhancer. It is used to enhance the permeability of drug across the skin. It is used as Antibacterial, Antioxidant, and Diuretic.Mechanism act by extraction of lipids from stratum corneum as well as by loosening the H-bonds between ceramide subsequently leading to fluidization of lipid layer.

CLOVE OIL

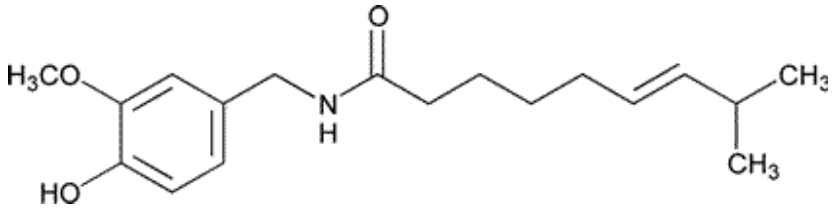
It is a natural penetration enhancer. It is used to enhance the permeability of drug across the skin. It is used safely in food, beverages, and toothpaste. It is also used as Antiseptic and Analgesic.

CAPSAICIN

It is used as penetration enhancer to increase the permeability of drug across the skin. Topical Capsaicin formulations are used for pain management.

Mechanism- several mechanisms are involved. These include receptor inactivation, block of voltage activated calcium channels, intracellular accumulation of ions leading to osmotic changes and activation of proteolytic enzymes processes.

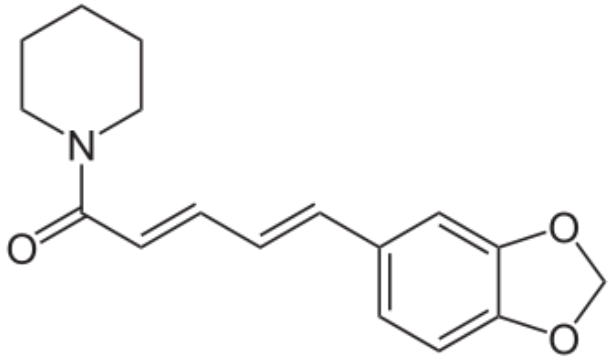
Dray A: Mechanism of action of Capsaicin like molecule on sensory neurons. Pub Med.



Capsaicin

PIPERINE:

Piperine, an amide alkaloid of black pepper, was investigated for transdermal enhancer activity using human cadaver skin in vitro with aceclofenac as the model drug. Furthermore, FT-IR studies were conducted to understand to possible enhancement mechanism. These results indicate that Piperine enhances transdermal permeation of aceclofenac by biphasic mechanism involving partial extraction of stratum corneum (SC) lipid and interaction with SC keratin.



Gels:

The term “gel” represents a physical state with properties intermediate between those of solids and liquids. However, it is often wrongly used to describe any fluid system The rigidity of a gel develops from the presence of a network formed by the interlinking of particles gelling agent. The nature of these particles and the type of force is responsible for the linkages, which responsible for determination of the structure of the network and the properties of gel. The individual particles of hydrophilic colloid may consist of either spherical or an isometric aggregate of small molecules, or single macromolecules. Possible arrangements of such particles in a gel network. Gels are swollen networks which possesses both the cohesive properties of solids and the diffusive transport properties of liquids. Due to Elasticity they tend to be soft and somatically they are highly reactive. They are semisolids being either suspension of small organic particles or large organic molecules interpenetrated with liquid. Gels are transparent to opaque semisolids containing a high ratio of solvent to gelling agent. Upon dispersion in an appropriate solvent, gelling agent merge to form three-dimensional colloidal network structures. This network limits fluid flow by entrapment and immobilization of the solvent molecules. The network structure is also responsible for a gel resistant to deformation and because of this it possesses viscoelastic properties. Gels are useful as liquid formulations in oral, topical, vaginal, and rectal administration. Gels can be clear formulations if all of the particles completely dissolve in the dispersing medium. But this doesn't occur in all gels and so some are turbid. Clear gels are preferred by patients. If the gel contains small discrete particles, the gel is called a two-phase system. If the gel does not appear to have discrete particles, it is called as a one-phase system. Two-phase systems are thixotropic, e.g., they are semisolid on standing but liquefy when shaken. If the particle size in a two-phase system is large, the gel is referred to as magma.

Examples of two-phase systems include Aluminum HydroxideGelandBentoniteMagma.Single-phasesystemscontainlinearorbranched polymer macromolecules that dissolve in water and have no apparent boundary with the dispensing medium. These macromolecules are classified as natural polymers like tragacanth), semi synthetic cellulose derivatives (i.e., methylcellulose), or synthetic polymers like Carbomers. Single-phase gels made from synthetic or natural macromolecules are called mucilage.

Classification:

Gels are classified on colloidal phases, nature of solvents used, physical nature and rheological properties:

1. Based on colloidal phase:

These are classified into inorganic type i.e., two phase system, a type of force that is resposnsible for the linkages which determines the structure of the network and the properties of the gel.

i) Single phase system:

These consist of large organic molecules which are existing on the twisted strands dissolved in acontinuous phase. This larger organic molecule either natural or syntheticpolymers are referred as gel formers, they tend to entangle with each other their random motion or bound together by Vander waals forces of attraction.

ii) **Two phase system**

If partcial size of the dispersed phase is large and form the three-dimensional structure throughout gel, such a system consists of floccules of small particles rather than larger molecules and gel structure, which lead to formation of unstable system. They must be thixotropic-forming semisolids on standing and become liquid on agitation.

2. Based on nature of solvent Hydro gels (water based)

Here they contain water as their continuous liquid phase E.g., bentonite magma, Gelatin, cellulose derivatives, carpooler, and poloxamer gel.

Organic Gels (with a non-aqueous solvent)

These contain a non-aqueous solvent as their continuous phase. E.g. (low molecular wt. polyethylene dissolvedin mineral oil and dispersion of metallic stearate in oils.

Xerogels

Solid gels with low solvent concentration are known as xerogels. These are produced by evaporation of solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid, they swell and can be reconstituted. E.g., Tragacanth ribbons, acacia tear β-cyclodextrin, dry cellulose and polystyrene.

3. Based on rheological properties Martyn's Physical pharmacy and pharmaceutical science, PetricJ.Sinko, 6th edition, Pg.No. 849-888.

Generally, gels exhibit non-Newtonian flow properties. Depending on these gels are classified into,

a) Plastic gels

b) Pseudo plastic gels

c) Thixotropic gels.

(a) Plastic gels E.g. - Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.

(b) Pseudo-plastic gels E.g. - Liquid dispersion of tragacanth, sodium alginate, Na CMC etc. exhibits pseudo-plastic flow. The viscosity of these gels decreases with increasing rate of shear, with no yield value. The rheogram results from a shearing action on the long chain molecules of the linear polymers. As the shearing stress is increased the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from gel matrix.

(c) Thixotropic gels: The bonds between particles in these gels are very weak and can be broken down by shaking. The resulting solution will revert back to gel due to the particles colliding and linking together again (the reversible isothermal gel-sol-gel transformation). This occurs in

colloidal system with nonspherical particles to build up a scaffold like structure. E.g.: Kaolin, bentonite and agar.

4. Based on physical nature

(a) Elastic gels Gels of agar, pectin, Guar gum and alginates exhibit an elastic behavior. The fibrous molecules being linked at the point of junction by relatively weak bonds such as hydrogen bonds and dipole attraction. If the molecule possesses free –COOH group then additional bonding takes place by salt bridge of type –COO-X-COO between two adjacent strand networks. E.g.: Alginate and Carbapol.

(b) Rigid gels This can be formed from macromolecule in which the framework linked by primary valance bond. E.g.: In silica gel, silic acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

Common Gelling Agents

There are many gelling agents. Some of the common ones are acacia, alginic acid, bentonite, carbopols (now known as carbomers), carboxymethylcellulose, ethylcellulose, gelatin, hydroxyethylcellulose, hydroxypropyl cellulose, magnesium aluminum silicate (Veegum), methylcellulose, poloxamers (Pluronics), polyvinyl alcohol, sodium alginate, tragacanth, and xanthan gum.

Emulgels

Emulgels are emulsions, either of the oil-in-water or water-in-oil type, can be converted into gel by adding some gelling agent. Both oil-in-water and water-in-oil emulsions are extensively used for their therapeutic properties and as vehicles to deliver various drugs to the skin. Emulsions possess aesthetic properties and are easily washed off whenever desired. They also have a high ability to penetrate the skin. In addition, the formulator can control the viscosity, appearance, and greasiness of cosmetic or dermatological emulsions. Oil-in-water emulsions are most useful as water-washable drug bases and for general cosmetic purposes, while water- in-oil emulsions are employed more widely for the treatment of dry skin and emollient applications. Gels for

dermatological use have several acceptable properties such as being thixotropic, free from greasiness, easily to spread, easily washable, emollient, non-staining, compatibility with several excipients, and water-soluble or miscible.

So emulgels have a high patient compliance since they possess, above mentioned advantages of both emulsions and gels. Therefore, they have been recently used as vehicles to deliver various drugs to the skin. In the market, 2 emulgels are available: Voveranemulgel (Novartis Pharma, Basle, Switzerland), containing diclofenac diethylamine, Nucoxia (Ziduscadila) containing etoricoxib, Miconaz-H emulgel (Medical Union Pharmaceuticals, Egypt), containing miconazole nitrate and hydrocortisone. A major limitation of gels is in the delivery of hydrophobic drugs.

Important constituents of gel preparation

Aqueous Material:

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols.

Gelling Agent:

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent. Carbopol, HPMC are commonly used gelling agents.

Permeation Enhancers:

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability. Alcohol, Oleic acid, some essential oils can be added as penetration enhancers.

Drug

Topical route of administration cannot be employed for all types of drugs. It depends upon optimal physicochemical properties of the drug, its biological properties. In addition, consideration of the pharmacokinetic and pharmacodynamic property of drug is necessary.

The physicochemical properties are as follows:

- The drug should have a molecular weight less than approximately 1000 Daltons.
- The drug should have affinity for both- lipophilic and hydrophilic phases.
- Extreme partitioning characteristic are not conducive to successful drug delivery via skin.
- The drug should have a low melting pointless than200°C.
- Since the skin has pH of 4.2 to 5.6. Solutions, which have this pH range, are used to avoid damage to the skin. However, for a number of drugs, there may also be significant transdermal absorption at pH values at which the unionized form of the drug is predominant.
- The biological properties are as follows:
- The drug should be potent with a daily dose of the order of a few mg/days.
- The half-life t½ of the drug should be short.
- The drug should be non-irritating and nonallergic
- Drugs which degrade in the GI tract or inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.
- Permeation enhancers
- One challenge in designing topical drug delivery systems is to overcome the natural transport barrier of the skin. Oils and surfactants can easily penetrate the superficial layer of the skin.

The word "herb" has been derived from the Latin word, "herba" and an old French word "herbe". Now days, herb refers to any part of the plant like fruit, seed, stem, bark, flower, leaf, stigma or a root, as well as a non-woody plant. Earlier, the term "herb" was only applied to non-woody plants, including those that come from trees and shrubs. These medicinal plants are also used as food, flavonoid, medicine or perfume and also in certain spiritual activities. Plants have been used for medicinal purposes long before prehistoric period. Recently, WHO (World Health Organization) estimated that 80 percent of people worldwide rely on herbal medicines for some aspect of their primary health care needs. According to WHO, around 21,000 plant species have the potential for being used as medicinal plants?

Buchanania lanzan Spreng.

It is a member of the family Anacardiaceae, originated in the Indian sub-continent, is an excellent multipurpose tree species. Traditional indigenous knowledge reveals the immense value of almost all parts of the plant i.e. roots, leaves, fruits, seeds and gum for various medicinal

uses. Buchanania lanzan is a deciduous tree which produces seeds that are edible to humans. It is known as Chironji (or Charoli). These almond-flavoured seeds are used as a cooking spice primarily in India.

Figure No 1.5 seeds and plant of *Buchanania lanzan*

As per data available over three-quarters of the world population relies mainly on plants and plant extracts for their health care needs. More than 30% of the entire plant species, at one time or other was used for medicinal purposes. It has been estimated, that in developed countries such as United States, plant drugs constitute as much as 25% of the total drugs, while in fast developing countries such as India and China, the contribution is as much as 80%. Thus, the economic importance of medicinal plants is much more to countries such as India than to rest of the world. These countries provide two third of the plants used in modern system of medicine and the health care system of rural population depend on indigenous systems of medicine. Treatment with medicinal plants is considered very safe as there is no or minimal side effects. These remedies are in sync with nature, which is the biggest advantage. The golden fact is that, use of herbal treatments is independent of any age groups and the sexes. Medicinal plants such as Aloe, Tulsi, Neem, Turmeric and Ginger cure several common ailments. These are considered as home remedies in many parts of the country. It is known fact that lots of consumers are using Basil (Tulsi) for making medicines, black tea, in pooja and other activities in their day-to-day

life. In several parts of the world many herbs are used to honour their kings showing it as a symbol of luck. Now, after finding the role of herbs in medicine, lots of consumers started the plantation of tulsi and other medicinal plants in their home gardens. In India, use of herbal medicine is perhaps more prevalent than western countries. Some of the examples of herbal medicines are Echinacea, Kava, Valerian, Gingko Biloba, Ginseng and St. John's Wort.

Scientific classification

Kingdom: Plantae

Phylum – Tracheophyta

Class - mangnoliopsida

Order: Sapindales

Family: Anacardiaceae

Subfamily Anacardioideae

Genus: Buchanania

Species: B. lanzan

Binomial name: Buchanania lanzan

Synonyms: Buchanania latifolia ROXB. almondette, cheronjee, cuddapah almond.

General description

English Name: almondette, cheronjee, cuddapah almond Hindi Name : achar, char, charoli, charoli-kernel, chiraunji, chironji, Kannada Name : chaara pappu, chaaruvaala, chalaali, char, charoli, Sanskrit Name : akhatta, bahulavalkala, cara, chara, charaka, dhanu, dhanushpatta, Tamil Name : modama, moraimaram, morala, mudaikkai, mudaima Parts Used : roots, leaves, fruits, seeds

MORPHOLOGY

Morphology of the plant Sub deciduous trees, to 18 m high, bark 10-12 mm thick, surface black or dark brown, rough, tessellate the cracks being deep and narrow, somewhat resembling crocodile hide; blaze red. Leaves simple, alternate, estipulate; petiole 12-22 mm, stout, glabrous; lamina 10-23.5 x 5-12 cm, broadly oblong, base round or acute, apex obtuse or emarginate, margin entire, glabrous above and densely tomentose beneath, coriaceous; lateral nerves 10-20 pairs, pinnate, prominent, pubescent, secondary laterals prominent, intercostae reticulate, prominent. Flowers bisexual, greenish-white

Traditional uses

Traditional indigenous knowledge reveals the immense value of almost all parts of the plant i.e. roots, leaves, fruits, seeds and gum for various medicinal uses. The gum from the tree is used against leprosy in traditional medicine. 1 Charoli seeds are used in the Ayurveda and Unani systems of medicine. The roots are acrid, astringent, cooling, depurative and constipating. They are useful in the treatment of diarrhoea. 2 The fruits are used in treating coughs and asthma. The seeds are used as expectorant and tonic. The oil extracted from kernels is applied on skin diseases3 and also used to remove spots and blemishes from the face. The juice of the leaves is digestive, expectorant, aphrodisiac, and purgative. 4 The gum after mixing with goat milk is used as an analgesic.

The permeation enhancement properties of Buchanania lanzan spreng seed oil was evaluated using Ethyl cellulose transdermal patches of Glipizide using some essential oils as penetration enhancers. Effect of drug loading and penetration enhancers was investigated on the in vitro permeation of drug through rat skin. Incorporation of essential oils increased the moisture content, moisture uptake ability and permeation of Glipizide across skin barriers. Buchanania lanzan spreng seed oil is found to be most effective when compared with others. it was also concluding that the seed oil can be used in permeation enhancement of various types of tropical preparation.

Simmondsia chinensis

Jojoba *Simmondsia chinensis* (Link) Schneider is a precious, drought resistant shrub. Jojoba is mostly a woody, evergreen, perennial shrub that produces small seeds, which contains liquid wax very similar to whale sperm in value. The oil is used mostly in the pharmaceutical industry, Native Jojoba is found in Sonoran desert climatic, this area receive annual precipitation of 80-450 mm and temperatures ranging from 9-54^{o}C. Jojoba grows naturally on soils of marginal soil fertility, fertilization of field plots with nitrogen and phosphorus improved plant growth and increase seed production. Jojoba plant is drought resistant, also jojoba cosmetics, weight reduction in livestock, also as bio degradable lubricants in the motor industry, moreover, jojoba oil is used for bio-fuel production, and it is a new solution of fuel in coming era. Plants are extremely tolerant of drought and their foliage is a source of nutritious forage for sheep, goats, and cattle, as well as for wild ungulates and smaller browsers such as rabbits. In arid and marginal lands there are only a few crops being grown mainly for survival purposes. These areas lack cash crops which are drought tolerant.

In recent decades, there has been considerable interest in using multipurpose crops which can tolerate stress conditions such as jojoba (*Simmondsia chinensis*).

Figure No 1.6: Jojoba *Simmondsia chinensis*

Uses

Jojoba considered multipurpose crops, and is a promising cash crop as well as provision of income to the poor communities, Jojoba used to combat and prevent desertification in the Thar Desert in India and 6 October desert in Egypt. The applications of jojoba oil are numerous in pharmaceuticals or cosmetics and it can be used in many different reactions such as hydrogenation, halogenation or sulfuration to obtain high-added value products. In cosmetics industry Jojoba oil is used in a number of skin care products, mainly as a moisturizer, also in hair conditioners and as lubricant.

In pharmaceuticals jojoba oil, wax and extracts obtainable promising activity for a number of skin and scalp disorders, skin emollient, anti-acne, anti-psoriasis, anti-inflammatory anti-hypercholesterolemia, antioxidant and wound healing properties and it could be used as a remedy for skin infections.

Jojoba is used as a bio diesel fuel as well as biodegradable lubricants. It is a new solution of fuel in coming days. However, the research of Jojoba oil has been mainly focused on the alcoholysis of this oil and NOx, CO and CO2 emissions related to the use of different blends

of Jojoba oil and conventional fuel in a diesel engine. The mixture of long monounsaturated alcohols (11- eicosenol, 13-docosenol and 15-tetracosenol) produced after crystallization has a high value in the market because of its pharmaceutical properties against enveloped viruses whereas the co-product might be used for energy purposes, which could be the starting point for a biorefinery implementation. Jojoba used in cosmetics, pharmaceuticals, waxes, animal feed supplement (20-30% protein content of oil less meal), and as ornamental plant. The seed meal (plant material after extracting the oil) is rich in protein 29–30%, in addition to simmondsin which toxic for livestock, these toxicants could be broken and the meal could be used as livestock feed ingredient from other side Simmondsin have insecticidal, antifeedant and antifungal activities.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely prescribed medication in the world. Their main benefit derives from their anti-inflammatory and analgesic effect, but the use of these agents is not innocuous since they mainly increase the risk of gastrointestinal (GI) and cardiovascular complications compared with non-NSAID users. NSAIDs injures the upper and lower gut by depleting COX-1 derived prostaglandins and causing topical injury to the mucosa. If NSAID therapy is required, patients at risk will need prevention strategies including co-therapy of NSAID with gastroprotection (PPI or misoprostol) or the prescription of COX-2 selective inhibitors. The probable introduction of NO-NSAIDs in the market in the near future may open a new therapeutic option for patients with hypertension who need NSAIDs.

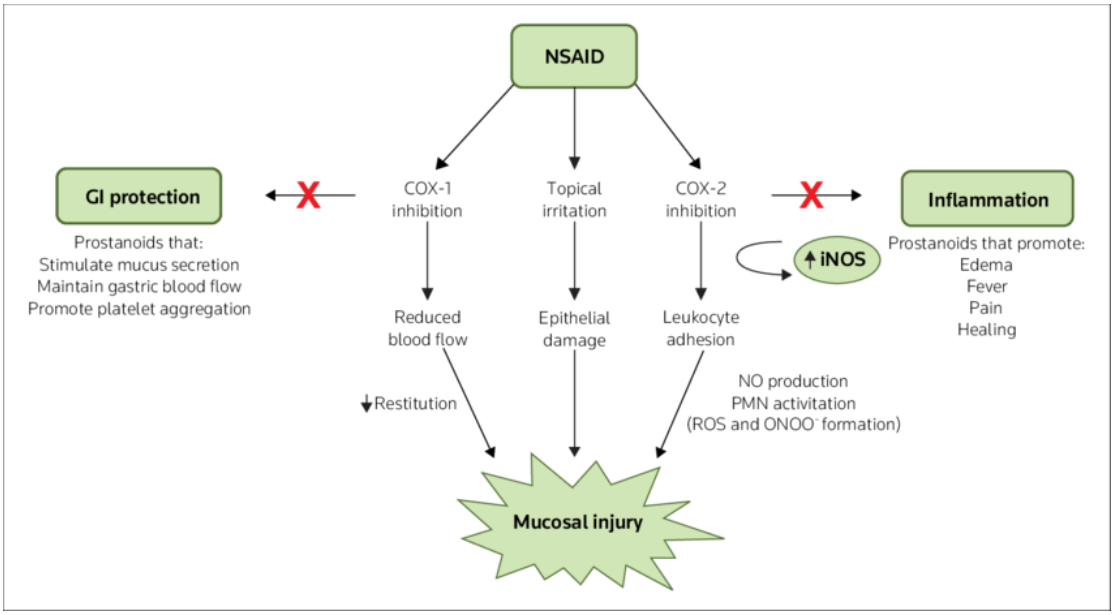


Figure No 1.7: Pathophysiology of NSAID's