1. INTRODUCTION

Today nanomedicine is proving their efficacy in many diseases. These technologies are new but quickly increasing day by day. In this science materials the nanoscale range are utilized for the drug delivery purpose[1]. In disease contrast the major challenge is large sized drugs, there delivery and concentration at targeted site that includes the poor bioavailability, in vivo unsteadiness, and insufficient solubility that affects the absorption of drug in the body. The issue through targeted delivery not only reflects efficiency but adverse effects too. In these consequences recent approaches of targeted delivery may be a good option [2, 3].

1.1 Nanomedicine

is a promising field employing the usage of scientific information's through methods of nanoscience in disease management. Applicability of nanoscience is increasing day by day that is in nanorobots, nanosensors in dignostical kits which are not only providing treatment but health awareness too amongst the global population. Applicability of nanoparticle-based method reported which is having combined approach i.e. disease management and imaging modes for diagnosis puposes[4], this increases the applicability of mineral nanoparticles focused on specific delivery of drug. Nanoparticles seemingly give support to drugs from the destruction of gastrointestinal acid secretions and show usefulness in drug delivery of frugally water-soluble drugs.

The available research data suggest that Nanodrugs have higher oral bioavailability due to uptake method of absorptive endocytosis.

The Nanoparticles reside in systemic circulation for longer duration which enables release of complex drugs as per specific doses. These findings reduce the adverse effects and fewer plasma fluctuations[5].

The nanosized particles enter the tissues and provide the drug uptake through cells which give an effective delivery of drug with targeted therapeutic achievement. The drug acceptance through cells from nanoparticles is greatly than large particles with various sizes between 1 and 10 μm[6.7]. More ever, the targeted action of nanoparticles assures therapeutic efficacy with lesser toxicities.

The applicability of nanoparticles in drug delivery is related to physicochemical features of drugs therefore the natural bioactive compounds with nanoscience are growing quickly. It gives advantages and specificities to deliver the drug at targeted sites.

It is applicable for those drugs which are having poor solubility, lesser absorption can be targeted with these nanoparticles[8].

1.2 targeted drug delivery system

The basic rule that is applicable in the optimization is the therapeutic goals of drug with minimization of toxicities due to target related to dosages, molecular bases and concentrations at different sites[9].

The receptor targeting by drugs all the way through optimized drug delivery techniques is not the only way to achieve or enhance the therapeutic goals, however it's also important to decerease the toxicities related to low therapeutic index and elevated doses[10].

The applications of targeted drug delivery in many treatments and diagnostic procedures such as cancer , ocular and brain delivery, vaccines, radio imaging, transdermal delivery and many more.

1.2.1 Carriers used commonly for Targeted Drug Delivery

- **Colloidal Carrier drug delivery system**

These are nano scaled targeting vesicular dosage form, which includes noisome, multiple emulsions, liposomes, and nanospheres. They are helpful in improving the of drug efficacy also decreasing its toxicity. They are very important and promising entities basically essential for effective passage of drugs. It is the drug vectors, which appropriately deliver and hold the active drug to route of administration, although they deliver it within the area of targeted site[11].

- **Vesicular Carrier Systems**

Nanosomes are one of the recent advancements in these carrier systems. The different forms of nanosomes are ethosomes, liposomes, transferosomes, niosomes. These all are vesicular carriers nanosome according to modifications in their structure, however their individuality and concentration throughout preparation and storage proposed for therapeutic applications[12, 13].

- **Microparticulate Systems**

The microparticulate systems are based on minute sizes such as micro liter and millimeter on scale. The role of micro-particulate system is the enhancement in bioavailability of predictable medicines and to reduce the toxicities. The examples of micro-particulate systems are NPs, magnetic microspheres, and microparticles[14].

Polymeric Carriers

In formulation development polymer is one of important parameter as polymers have unique properties which have not accomplished by other ingredients. The advancement in polymer technology leads the progression of numerous NDDS, with specificity of surface and bulk properties that contribute the dosage form more effective with lesser toxicities. The Polymer technology is an important tool in advancement of drug delivery, as they give direction in delivery of excipients that allows controlled and targeted delivery of medicament[15].

Polymeric micelles

Polymeric micelles are nanosized structures which are having hydrophobic center and a hydrophilic covering, in which encapsulation of drugs are in the central part. The polymeric nanovesicles structure suggests bilayer in aqueous center which facilitates dividing the center from the exterior middle. The encapsulation also prevents the interaction between hydrophilic drugs and hydrophobic molecules inside the membrane; as a result these vesicles have the potential for delivering the incompatible drugs like proteins, anticancer drugs, and genes [16].

- **Dendrimers**

Other types of polymeric carriers are dendrimers which is used for drug targeting purposes. The dendrimers are mono-dispersed macromolecules which are having fit expressed and multi-branched structures with bulbous units. They contain three parts on functional basis that is central point, functional groups on external surface, and interior branching units.

The polar and non polar drugs targeted in dendrimers through electrostatic interface in addition to hydrophobic division. In dendrimers active medicaments are bounded with inner shell by covalent linking to outer groups. Nucleic acids and Gene plasmids are illustration which can link during electrostatic interactions. The release of drug is firmed by the character linkage[17]. The essential parameters for dendrimers are particle size, rigidity, surface, shape, flexibility, structural design and rudimentary composition should be considered[18].

- **Monoclonal Antibodies**

They are showing good results as beneficial agents in targeting delivery for various diseases, like cancer and viral/bacterial infections. The monoclonal antibodies are helpful in the disease management through conjugation among anti cancer drugs, bacterial toxins, enzymes radioisotopes, cytokines, and for targeting of tumors. Today human monoclonal antibodies are being formulated as anticancer drugs. The first human monoclonal antibodies adalimumab is convincingly approved for clinical use[19].

1.2.2 Drug targeting types

- **Active Targeting**

The challenge with active targeting is to determine the suitable targeting agent, selectivity and transport nanoparticle systems to cancerous tissue site. The strategies are based on the targeting agents' or ligands' ability to attach to the cancer cell. The interactions lead to beneficial delivery the therapeutic on the tumor-specific regions[20].

- **Passive Targeting**

In passive targeting the drug targets are available in systemic circulation and they work through the systemic physiology based on physic-chemical distinctiveness of drug which will depend on the concentration of drugs at targeted location, like in tumor tissue for anticancer drugs[21]. Nanoparticles are mostly used in passive targeting as a carrier for the targeted delivery which strengthen noteworthy concentration of the drug in targeted level the process is through slow lymphatic drainage the EPR effect[22].

- **Inverse Targeting**

This drug targeting is based on passive uptake of the colloidal carrier through reticulo-endothelial systems.

Dual Targeting

This targeting is based on carrier mediated delivery of molecule by means of its own beneficial activity and therefore escalating the curative effect of the drug[23].

- **Double Targeting**

The targeting is based on combination of sequential and spatial methods i.e. structural position to precise location and sequential delivery at a restricted rate.

- **Combination targeting**

This method is facilitated by delivery on targeted sites by means of carriers and other devices of molecular specific which provide direction to reach at target[19, 24].

- **Physical, Biological and Chemical Targeting**

In Physical targeting is based on various parameters like size, composition, or other characters not especially intended for the direction of a natural receptor.

Chemical targeting includes delivery of drugs on targeted sites at all the method through the utilization of prodrugs at specific site. Mediator agent can be bound for the region through enzymes or chemical reactions with the aim to guide them for the targeted delivery of drug and vehicle.

Biological targeting permits the delivery of antibodies, peptides and proteins, other bio-molecule in a precise way. Gene appearance is able to mark to zones for the cellular level explicit supporters in body systems[25].

- **Specific and systemic Targeting**

In systemic targeting the drug delivery is through curative systems based on a persistent route like i.e. administration of nano-technological structures. Local targeted approaches are aim to deliver the drug at the local site. These systems transport the drug through blood circulation after

the completion of distribution but main restrictions of this system take place in toxicities of drug in specific tissue [26].

- **Targeting based on Location and Disease**

Targeting the drug in intracellular is the best method i.e. gastrointestinal, brain, and respiratory tract targeting are a number of model of site specific targeting. The Intracellular drug distribution of proteins, nanocarriers, and Abs, permits the efficacy through nucleus or specific organelles. Various drug release systems have been employed with target specificity to the gastro-intestinal system. For treating tumors and other infectious diseases, disease-based targeted delivery is preferable to polymer based drug delivery like dopamine-liposome conjugates. It is possible to treat infections with nano-DDSs as an alternative to antibiotics. Designing of nano vaccines for accomplish superior targeting and enhanced cellular reaction is a new vision. Some important pathogens are targeted with specific and specialized approaches to prevent their persistence inside cells; that can be seen in the structures of antimicrobial agent's nanoparticles [26, 9, 27, and 28].

- **Carrier Systems, Vehicle for Targeted Drug Delivery**

In addition to specific carrier systems, TDDSs require specific targeting mechanisms by encapsulating or bonding with a spacer moiety. These drug-delivery vehicles are utilized as carriers for example lipoprotein-based carriers micelles, liposomes, and NP-based carriers[29,30].

The unique characteristics requires for carriers in delivery of drugs i.e. should be steady, biodegradable, biocompatible, and released out of the body and should not affect homeostatic parameters. The release of drug and biodegradation of polymer are vital steps in formulating the

nano-sized system. Other parameters such as diffusion, and solubility are necessary for drug release procedure [31].

1.3 Cancer

Cancer is the growing concern as it causes fatality across the globe, in the times past, many researches showed their interest in finding novel therapeutics to decrease the adverse effects related to available treatments. During the disease progression, tumor proliferates that creates a varied inhabitant cells distinguished by dissimilar structures and the various responsivity to treatments[32]. The Identification of important genes involves in tumor genesis and spread of cancer is key parameters for understanding pathophysiology of disease and finding therapeutic goals. Various researchers worked for identification of cancer biomarkers[33].

The most common cancers in males are in respiratory, excretory and urinary system related; however in women, respiratory, endocrine and reproductive system related are reported [34].

1.3.1 Pathogenesis of cancer

The disease pathogenesis based on the different forms of cancer i.e. primary cancer and secondary cancer[35]. Tumor means growth of unusual cell that is neoplasms, can be malignant, according to the findings the benign tumors are specific to small area but the malignant tumor can move and metastasize to other parts of body.

The findings suggest that proteinase an enzyme secerated by metastatic cancer cell, degrade proteins and help in the movement of these cells to other locations [36].

The angiogenesis process leads the removal of cellular waste from the blood and oxygen. In disease hypoxic conditions cause the induction of some proteins such as HIF-1(hypoxia

inducible factor-1alpha) which results in the increase expression of vascular endothelial growth factor [37, 38].

1.3.2 Role of immune system in cancer

Our immune system is enriched with different compounds and molecules like amino acid, cytokines which forms a network for biochemical progression to identify and show defense against the foreign Antigens. Our homeostasis play an important role in the maintenance for immune system through adaptive and innate responses that helps in first line of defense [39].

In the case of microbes and allergic antigens our nonspecific responses are mediated by innate this is so quick as far as time is concern because of immediate responses its short and hence not able to store in immunological memory. Inborn immunity system is not very strong to produce an immunological retention, but it is capable to distinguish within "self" and "non self" or dissimilar collections of pathogens and the threat related to pathogen[40]. On the basis of another theory the inborn (inert) immunity system conveys rapid defense to the host cell by involving signaling bioactive protein like cytokines. The cytokines protein has numerous persistence liable on the situation they were released in the cells and the site of the receptor it binds to[41]. The significant cell which is used in phagocytosis are usual killer cells called phagocytes which provides rapid host defense by engulfing cells[42]. In the case of adaptive immunity growth of immunological retention is related to definite kind of immune responses which targets the foreign antigens. Acquired immunity includes specific antibody and immune cells which attacks and abolish foreign antigens and is capable to protect from diseases by remembering in the future

of that substances impression and rising a new immune response. Such kind of immunity develops through the lymphocytes, called the T and B cells[43].

Some T cells can identify as "non self" organic molecules which do not require mediated antigen presentation.[44, 45].

According to the immunological reactions the binding of specific genes contributes the inhibition of T cell activation. Some researchers reported that some cancer cells also having the induction property which leads suppression of immune system[46].

In the maturation process of white blood cells are important because they activate the other helper cells that are having antibodies specific for the individual immunologic responses and they are known as immunoglobulins[47].

The functions of all antibodies are different in terms of their functions though the antibodies functions remain same that is to deactivate the antigen[48, 49].

1.3.3 Some common types of cancer

Cancer can be classified according to their presence in specific body part. It can be classified as[50]:

Carcinoma- That starts from skin and tissues, the different types of carcinomas are adenocarcinoma, carcinoma of basal, squamous and transitional cell carcinoma. As epithelial tissues find in the outer coverings of organs so carcinoma starts from these tissues and further progress tacks place inside the part.

- **Sarcoma-** the connective tissues support in the attachment of various parts of the body i.e. cartilage, bone muscles the sarcoma affects them and disease aggravation can be seen at these site specifically.
- **Lymphoma –** It is the important systems of our body and useful in immunity of the body through the network of capillaries which help in filtration of body fluid. The lymphoma starts from the lymph glands and further progress in this our white blood cell are dividing in atypical manner.
- **Myeloma-** Such type of cancer develops in plasma cell. Plasma cells are nothing but a kind of white blood cell, situated in the bone marrow. They are able to prepare antibodies known as immunoglobulins, very helpful to fight infections. It can be out of control by multiplying itself.
- **Leukemia-** This cancer is related to white blood cell[50]. This cancer is one of the commonest blood cancers among kids and teenagers, every one out of three cancers is leukemia. Leukemia is of two types, ALL and CLL. ALL is very common in children. Chronic lymphocytic leukemias are infrequent in children.

a) Acute lymphocytic leukaemia (ALL)- This is a cancer of white blood cells. This cancer develops, once bone marrow cell grows mistakes in its DNA assembly. Common symptoms are enflamed lymph nodes, frequent fever without proper cause, pale skin, fatigue, bleeding gums due to frequent infections. Chemotherapy and targeted drug delivery is mostly used in the treatment.

b) Chronic lymphocytic leukemia (CLL)- This kind of cancer develops in blood as well as bone merrow. Its progress is slower as compared to other type of cancer. Generally, it effects older adults. CLL symptoms cannot be seen for a year. When it starts showing symptoms it may cause fatigue, swelling of (but painless) lymph nodes, fever, weight loss, bruising etc. Treatment includes chemotherapy, bone merrow transplantation is the final treatment in the case of aggressive stage. Survival rate of patients now exceeded to 7- 8 years[51].

1.3.4 Blood cancer scenario in India

Studies recommend that in India, blood cancer is most communal reasons of death and around one lakh people identified every year with a type of blood cancer for example lymphoma, leukaemia and multiple myeloma. Lymphomas and leukemia influence adults as well as children but Myeloma is comparatively common disorder in adults [52]. Blood cancer scenario is shown in the figure.1.1.

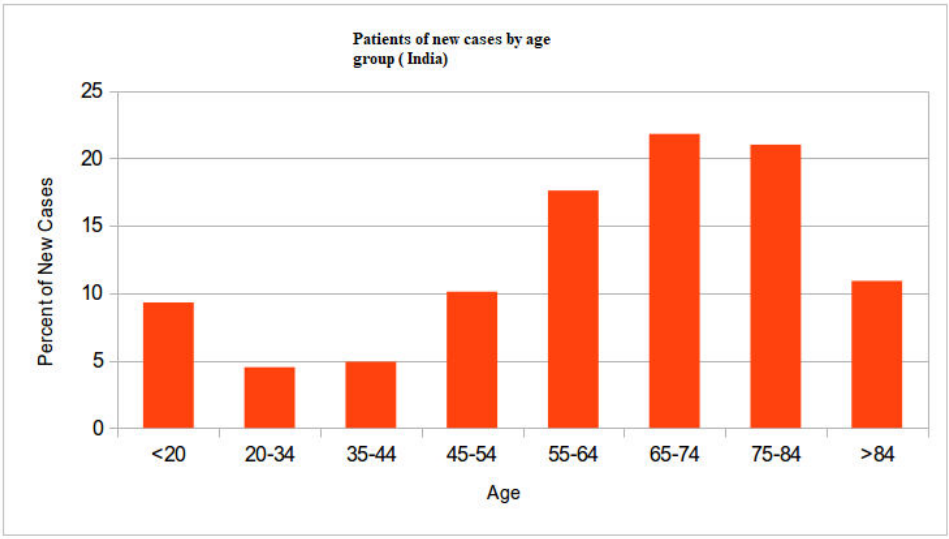

Figure 1.1. Blood cancer scenario in India

1.3.5 Disadvantages of anticancer drug

- Most of the drugs are poorly water soluble/hydrophobic in nature which promotes their precipitation in aqueous medium.
- Anticancer drugs are much weak in the selection of their targeted tissues.
- The anticancer drugs experience a huge distribution in a bulky body volume with chronic adverse effects in non-target tissues.
- Their unintentional eruption can cause harm of healthy tissues.

1.4 Types of nanoparticles:

A) Lipid based nanoparticles- This kind of nanoparticle is made up of minimum one lipid bilayer surrounding an internal water compartment.

a) Solid lipid nanoparticle: SLN mostly composed lipids and phospholipids that remain in solid segment and a surfactant is required for emulsification process. The size ranges from 50 to 1000 nm. SLNs includes inimitable character like minor size, big surface area, great drug loading efficiency, and having better ability to advance the performance of nanoparticles[53].

b) Liposomes: They are the most discovered nanoparticles used in site specific delivery systems. It is the sphere-shaped lipid vesicles (generally 50–500 nm in diameter made up of one or more then one lipid bilayers, because of emulsifying synthetic or natural lipids in an aqueous medium.

c) Nanostructured lipid carrier (NLC): They are having aqueous medium as core matrix already containing surfactants. Lipids are multipurpose particles that can produce inversely structured solid matrices. NLC may represent an inadequate loading efficiency because of drug removal next to polymorphic changes throughout the storage, mainly if the lipid matrix contains alike molecules.

B) Polymeric nanoparticles

a) Nano capsules – It is the systems of drug delivery in which active the drug is solubilized in a core material which is kept into a cavity enclosed by thin polymeric wall. Nanocapsules is used as nano sized drug carriers to achieve controlled release and effective drug targeting.

b) Nanospheres- Nanospheres are solid polymers in which have entrapped drug in the polymer medium. It is available in spherical shape and the particles size ranges between 10-200 nm[54].

c) Polymeric vesicles: It is also known as polymersomes made up of hollow spherical nanoparticles containing aqueous cavity surrounded by polymeric membrane. Polymeric vesicles having great abilities in drug delivery, gene therapy, theranostics, because of its exceptional cell membrane-like assembly.

d) Polymeric Micelles: Micelles characterize a significant drug delivery arrangement used for poorly water-soluble or hydrophobic anticancer drugs. Due to its nano size (10–100 nm), biocompatibility, high degree of stability and extended flow time period in the blood it is used as versatile carrier drug delivery[55].

e) Dendrimers- They are small-sized, outwardly symmetrical particles containing definite assembly with a characteristically balanced core, an internal shell, and an external shell.

A) Inorganic nanoparticles-

a) Nanoshells: They are sphere-shaped molecules containing a dielectric (poor conductor of electricity) core (silica) surrounded by a thin metallic cover (usually gold) most commonly gold. For its optical and chemical belongings, these nanoparticles are very useful in cancer treatment.

b) Quantum dots: They are nanocrystals of semiconductor material available in less than 10nm in size [56].

1.4.1 Method of preparation of polymeric nanoparticles- Polymeric nanoparticles can be prepared by following method:

- Solvent evaporation method
- Ionic gelation method
- Solvent diffusion method
- Salting out method
- Supercritical fluid technology

Solvent evaporation technique

This method comprises, dissolution of polymer in an organic (volatile) solvent (dichloromethane, acetone, chloroform) followed by dispersion of drug in polymer containing organic solvent to form dispersion. This dispersion solution should be added to large volume aqueous solution already containing some emulsifier. Finally, o/w emulsion is prepared by allowing the evaporation of volatile solvent at suitable temperature with continuous stirring followed by sonication and drying. It is very much useful in the formulation of hydrophobic drug.

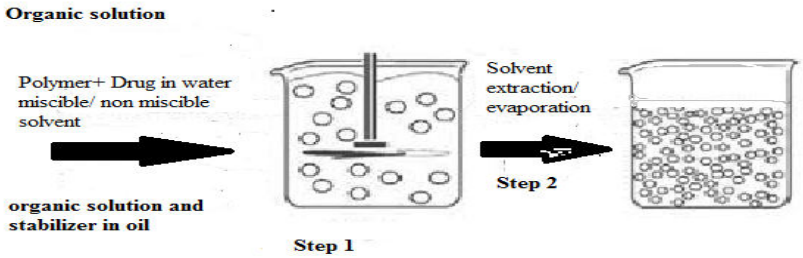

Figure 1.2. Solvent evaporation method

Ionic or inotropic gelation method

This technique includes a combination of two liquids (aqueous phases) here, first solution is the polymeric solution of chitosan polymer, and the second one is polyanionic tripolyphosphate. The method involves interaction of positively charged and negative charge of tripolyphosphate for the preparation of nanosized particle.

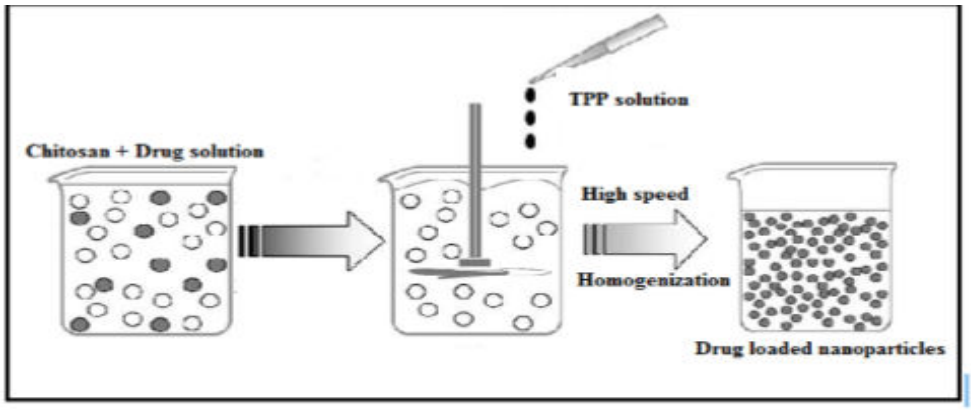

Figure 1.3. Ionic gelation technique

Solvent diffusion method

This method is the commonest method employed for miscible solvent depicted in figure no. 1.4.

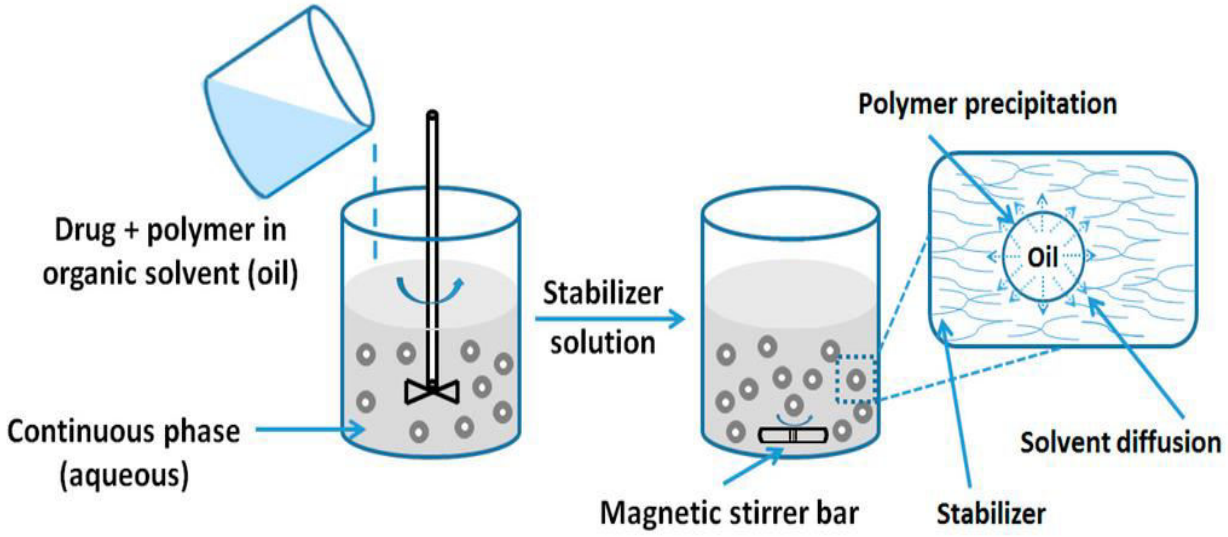

Figure.1.4. Solvent diffusion technique

Salting out method

This method is used for good solubility properties ease of separation from the aqueous medium, acetone is used as water miscible solvent. Generally drugs and polymer are mixed followed by emulsification by continuous stirring into the aqueous gel solution containing stabilizer and salting out agent. Finally, the diffusion of drugs and polymer will form nanoparticles. This method is appropriate for those drugs and polymers which are soluble in glacial solvents like acetone or ethanol.

1.5 Prospects of Nanoparticle drug delivery:

Nano-technology and concept of nanomedicine is growing day by day. In many diseases nanomedicine has played a vital role with target specific action. The uses of nanomedicine in targeted delivery not only reduce the dosage but toxicities too. In disease contrast the toxicities of anticancer drugs is already well known, many clinical trial is going on which will prove the efficacy and safety of anticancer nano formulations. The need of the hour is to develop the nano formulation with specific targeted delivery.