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Role of Nanocarriers for Enhancement of Drug Bioavailability

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ABSTRACT

There is constantly increasing demand of nanocarriers systems in the field of nanotechnology from the last two decades. The nanocarriers systems are widely used in the delivery of biotech drugs for the improvement of bioavailability and target delivery. Nanocarrier systems provide several advantages over the conventional formulations. This review describes an approach which encapsulates drug compounds within biodegradable and biocompatible nanocarriers such as Nanosuspensions, Polymeric, Lipid and Inorganic Nanocarriers along with their advantages and role in drug delivery. Development of new drug delivery systems always remains a challenging approach in the field of biotechnology that targets the drug to a specific site and provides the desired therapeutic effect at the required time. Due to low solubility, poor membrane permeability, or extensive pre-systemic metabolism, the drug compounds are not suitable for the conventional oral formulations. This article presents an overview of various types of nanocarriers including the method of Nanoparticles preparation. The problems arises in the drug delivery can be overcome by use of pharmaceutical nanocarrier systems.

Keywords: Nanotechnology; Nanocarrier; Bioavailability; Nanoparticle

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INTRODUCTION

Oral administration is the most commonly and widely used route for drug delivery due to its convenience and is mostly accepted by the patient. It offers many advantages among the various drug delivery routes such as painless and high patient compliance, the GI-tract act as a barrier for the several bioactive agents [1]. The factors that affect the oral delivery of bioactive agents are poor aqueous solubility and intrinsic dissolution rate. Around 40% of new drug substances shows poor aqueous solubility and such drugs belong to Biopharmaceutical Classification System in Class II (Low solubility/High permeability) or Class IV (Low solubility/Low permeability). Due to which oral delivery results in poor absorption and bioavailability [2]. The interest in nanocarrier system is increased since the last two decades. In order to overcome the problems associated with the oral administration, the nanocarrier systems are utilized [1]. Several bioactive substances like drugs, vaccines and nutrients can be prevented from degradation by using nanocarrier systems. In any case, to give focused on targeted controlled release is a key usefulness that can be achieved more effectively by utilizing nanocarrier technologies. The release profile of bioactive agents within the living system is directly influenced by particle size. Nanocarriers when compared with micrometer size carrier, they provide large surface area and can also have enhanced solubility and bioavailability, improve controlled release and specific targeting of the entrapped drug molecules to a great extent. The amount of drug required to provide specific effect at the target site when entrapped is always less than the amount required when unentrapped. The nanocarrier system can be selected on basis of

i. Characteristics of bioactive agents like size, solubility, charge etc.
ii. Safety and effectiveness of the drug-carrier complex
iii. Route of administration [3]

Recently, sub- micron systems i.e. nanosystems have got much attention due to their several advantages over existing systems. In order to target the drug to a specific site in the body, the design of drug delivery system is a

challenging approach [4]. To minimize or eliminate the side effects of bioactive agent, it is one of the significant approaches in nanotherapy. The importance of bioactive agents will be enhanced if it acts on its target site to produce the desired effect without producing any unwanted or side effects. Major challenges in nanotherapy are to minimize or completely eliminate side-effects. The importance of the bioactive agents will be enhanced if they act on their specific target site to produce the desired effect without causing any side effects on other systems [3]. Many of the bioactive agents require special formulation technologies to overcome certain problems such as poor solubility, drug instability in a biological system (i.e. Short half-life), poor bioavailability, and side effect. The high-protein binding property of certain drugs limits their passage into the brain and other organs.

Novel Techniques for Bioavailability Enhancement

The *in vivo* performance and bioavailability of any drug depends on the *in vitro* rate and extent of dissolution of the dosage form [5]. Therefore several advancements have been developed for the enhancement of solubility, dissolution rate and *in vivo* bioavailability of poorly soluble drugs, so that drug compounds made suitable for the development of optimal formulation. The novel techniques for the enhancement of solubility and bioavailability of poorly soluble drug candidates are nanoemulsions, solid lipid nanoparticles, solid dispersions, polymeric nanoparticles, nanosuspensions, niosomes and liposomes etc [6].

Nanocarrier in Nanotechnology

Nanocarriers are solid or liquid particles having diameters ranging from 10 to 1000 nm [7,8]. For the development of a number of systems for drug delivery, several advances have been made in the field of nanotechnology. There are a number of different nanoparticulate systems are currently available. Due to the small size of nanocarrier, they can efficiently pass through the epithelium of GI tract results in higher absorption and bioavailability [9]. Nanotechnology is the developing area in which nanoparticle materials are formed. Studies on nanomaterials are increasing day by day. Nanocarrier contains the biologically active material which is dissolved, entrapped or encapsulated in the carrier matrix. The active material is attached or adsorbed at the surface of carrier [10]. Nanocarriers are the materials of nanosize (<1µm) and made up of biodegradable substances like natural or synthetic polymers, lipids or phospholipids. Nanocarriers provide increased dissolution rate due to submicron size have a very high surface to volume ratio [4].

Advantages of Nanocarriers

I. Nanocarriers can improve pharmacokinetics, achieve target site and reduce the toxicity of bioactive agents.
II. Drugs which are hydrophobic in nature, their solubility can be enhanced.
III. Improved stability of the drugs.
IV. They can be used for sustained or controlled release.
V. They can better deliver the drugs through biological barriers such as blood-brain barrier and tight epithelial junctions [10].

Types of Nanocarriers

The resistance caused by the biological barriers in the body can be overcome by use of nanocarriers because particle size affects the delivery of the drug to various parts of the body. Nanocarrier improves aqueous solubility of poorly soluble drugs results in increase bioavailability, sustained release and drug targetin [11,12]. Nanocarriers include a submicron system such as nanoparticles, nanocapsules, lipid complexes, polymeric micelles, and Dendrimers [13]. Figures 1 and 2 represents the various types of nanocarriers

Nanosuspensions

Nanosuspension or nanocrystals are crystals in which hundreds or thousands of molecules combine to form aggregates. They are formulated using the drug with a thin coating composed of surfactant or combination of surfactants or stabilizers. The method by which nanosuspensions are produced is known as nanonisation [14]. For the formulation of nanosuspensions, the aqueous solution of surfactant firstly prepared and then drug powder is dispersed in this aqueous solution followed by high-speed stirring. After this the macrosuspension are obtained then they are homogenized to nanosize by using different techniques such as:

a) Wet milling [15]
b) High-pressure homogenization [16]
c) Nanocrystallization
d) Spray drying

The problems associated with the poorly soluble drugs like poor bioavailability, difficulty in the formulation of the parenteral dosage form, poor absorption pattern may be resolved by use of nanosuspension. In the nanosuspension, very less amount of surfactants or stabilizers needs to be added for the stabilization. Based on the physicochemical properties of the drug, dispersion medium for the nanosuspension can be aqueous (water, buffer) or non-aqueous (oils) [17,18]. In the top-down approach, large drug particles can be reduced to nanoscale particles using different techniques. In Bottom-up approach, nanoscale drug particles can be precipitated from the solution using precipitation techniques [19]. The crystalline nature of the drug can be influenced by the physicochemical properties of the drug which affects the dissolution rate and stability of nanosuspensions.

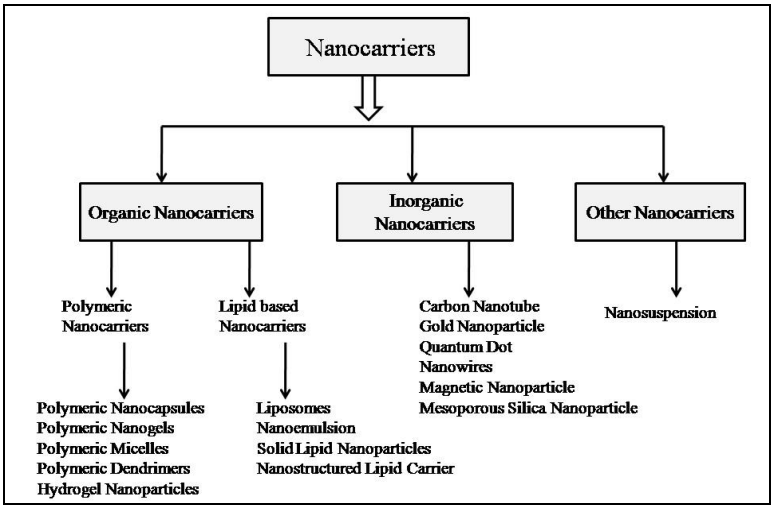

Figure 1: Various types of nanocarriers for drug delivery

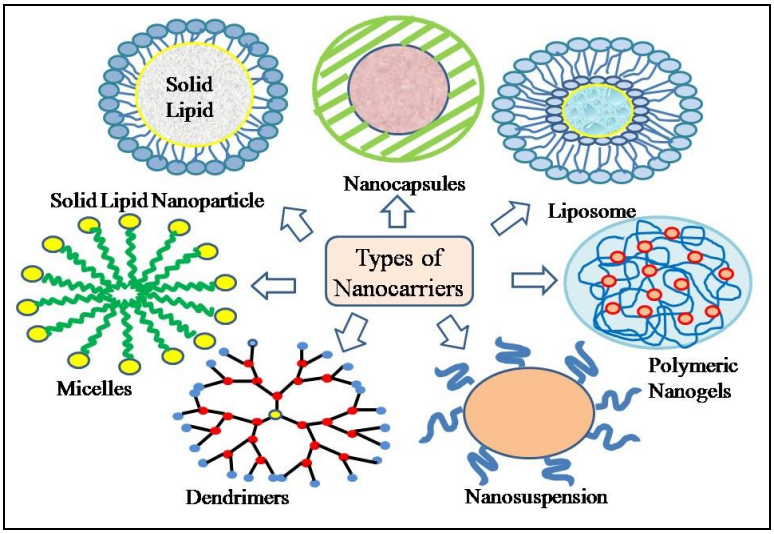

Figure 2: Various types of nanocarriers in nanotechnology

Nanosuspension preparation methods: Figure 3 represents the methods of Nanosuspension preparation.

Advantages of Nanosuspensions:

I. Nanosuspensions provide larger surface area which results in increased dissolution, absorption and faster onset of action.

II. Nanosuspension offers enhanced saturation solubility of the drug results in a greater concentration gradient.

III. They enhance the oral bioavailability due to increase adhesiveness of nanosuspensions to gastrointestinal mucosa.

IV. Nanosuspensions can be used for administration of the drug at less dose thus increases patient compliance.

V. Drugs which are prone to chemical/photochemical instability, enzymatic degradation, and pre-systemic metabolism should not be formulated as nanosuspensions. Nanosuspensions can reduce drug-related side effects [20] (Table 1).

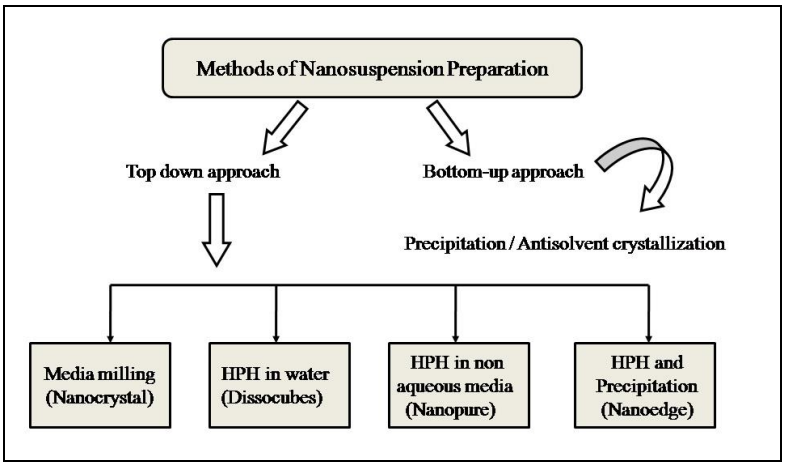

Figure 3: Nanosuspension preparation techniques

Table 1: Effect of type and concentration of stabilizer on the bioavailability enhancement of nanosuspensions prepared by various methods

Drug	Nanosuspension Method	Polymer/ Stabilizers	Advantages	Remarks	References
Esomeprazole	Precipitation Ultrasonication	Pluronic F-68 and Pluronic F-127	Simple and low-cost equipment	Effect of the drug, polymer conc. on particle size. Size ranges from 125-184 nm results in improved *In vitro* dissolution rate.	[21]
Curcumin	Milling and High Pressure Homogenization	Sodium dodecyl sulphate and Polyvinyl Alcohol	Ease of scale-up and Little batch-to-batch variation	AUC of the curcumin nanocrystals was 31502.8 µg min/L which was 4 fold greater than marketed curcumin capsule	[22]
Glyburide	High Pressure Homogenization	Sodium dodecyl sulfate	Narrow size distribution of the the drug in final product	Glyburide Nanosuspension shows 100% drug release in 30 minutes due to the improved solubility of the drug.	[23]
Aceclofenac	Microemulsion technique	Poloxamer-188	Require less energy, stable products, simple process	Aceclofenac solubility in Solid Lipid NS was 104.23 ± 3.05 mg/ml which was 6948 fold greater than the aqueous solubility.	[24]
Itraconazole	Acid base Neutralization/ Precipitation	HPMC, Poloxamer-407	Small size of particles and uniform particle distribution	The AUC of the dried ITZ nanosuspensions was 1.5-fold and 1.8-fold higher than the AUC of Sporanox pellets.	[25]
Simvastatin	Media milling	HPMC E3, HPMC E5, Poloxamer 188, Poloxamer 407, PVPK30	Enable formulation of very dilute nanosuspensions	Dissolution study of nanosuspension shows 85% of drug release which was fourfold greater than the marketed product.	[26]
Olanzapine	Solvent diffusion method and Sonication	Tween 80 and Pluronic F-68	Easy to produce by controlling the emulsion droplet	Freeze dried nanosuspension shows 92.67% drug release. AUC of Olanzapine NS was 2 fold greater than Olanzapine suspension.	[27]

Liposomes

Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer. Membranes are usually made up of natural or synthetic phospholipids that have a hydrophilic head group and a hydrophobic tail group. The head is attracted to water, and the tail, which is made of a long hydrocarbon chain, is repelled by water. When thin films of lipid are hydrated liposomes are formed [4]. Liposomes are spherical in shape which are vesicles produced by natural phospholipids and cholesterol. The properties of liposomes may be changed in terms of lipid composition, size, surface charge and preparation methods. They can be used for prevention of degradation of the encapsulated drugs and reduce systemic toxicity. The systemic availability of liposomes can be enhanced by attaching PEG units to the bilayer. The targeted delivery to specific sites can be achieved by conjugating with antibodies or ligands [13]. Liposomes can be targeted by use of surface polymers, carbohydrates. They were made up of biodegradable materials and can encapsulate solutes having different properties [28]. In the field of biology, biochemistry and medicine, liposomes have been used successfully [29]. The

pharmacokinetic profile of encapsulated drug can be changed to a greater extent in the case of proteins and peptides and can be easily modified by conjugation of PEG units [30]. The targeted specific delivery of potent drugs and genes will be achieved by use of liposomes. They are used in various fields such as in drug delivery, cosmetic delivery, diagnostic agents and in food industries [31]. Some drugs which are available in the market are based on liposome have been approved by Food and Drug Administration (FDA), used for the treatment of various diseases [32]. The biphasic behaviour of liposomes acts as carriers for both hydrophilic and lipophilic drug compounds [33]. Liposomes act as a promising vehicle for delivering ocular drugs because of the presence of natural phospholipids, cell-like membrane and biocompatibility. Liposomes can attach to corneal epithelium when they are applied topically, they release the bound drug thus improving pharmacokinetics and decreasing toxic side effects [34].

Nanoliposome

Nanoliposome refer to the nanometric size of liposomes has been introduced recently. Liposomes and nanoliposomes are similar in chemical, structural and thermodynamic properties. Larger interfacial area of encapsulated drug compounds with biological tissues can be achieved due to the smaller size of nanoliposomes and was used to increase the bioavailability of encapsulated compounds [35]. Due to enhanced permeation and retention effect, they can accumulate more in tumours for the solid tumour treatment [36]. For the production of nanoliposomes in aqueous solution, higher energy input is required [37]. The methods for nanoliposome production are sonication, freeze-thawing, extrusion, micro-fluidization and ether injection commonly used in laboratory scale. The production of the small size of nanoliposomes occurred due to the small pore size of extruder filtration. For the industrial-scale manufacturers, micro-fluidization method is commonly used which includes high-pressure device named as microfluidizer. In order to reduce the particle size of liposomes, flow stream passed through a fine orifice [38].

Advantages of Liposomes

- Liposomes provide selective passive targeting to tumour tissues.
- They provide increased efficacy and therapeutic index.
- Liposomes having increased stability via encapsulation.
- They reduce the toxicity of the encapsulated agents.
- They also provide Site avoidance effect.
- They provide improved pharmacokinetic effects.
- They provide active targeting after interaction with site-specific ligands [39].

Liposome preparation methods: Figure 4 represents the liposomes preparation methods.

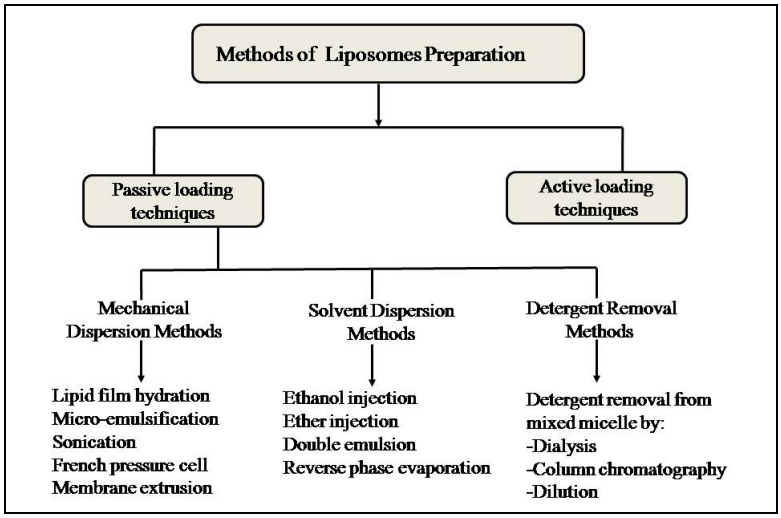

Figure 4: Various methods for liposomes preparation

Solid Lipid Nanoparticles

Solid lipid nanoparticles are the submicron colloidal carriers having diameters ranging from 50-1000 nm. They are made up of solid lipids dispersed in water or in an aqueous surfactant solution. The drug dispersed in the solid core containing high fat matrix. In the fat matrix, the hydrophobic chains of phospholipids are present. The emulsifier or

surfactant is added for the physical stabilization, depending on the type and concentration of the lipid. The commonly used surfactants are poloxamer 188, polysorbate 80, lecithin, polyglycerol methyl glucose distearate [4].
SLN are prepared by various techniques [40] such as High-pressure homogenization, microemulsion formation, precipitation, Lipid nano pellets and lipospheres. Various drug delivery routes have been employed such as oral, parenteral, pulmonary and topical. In comparison with Polymeric nanoparticles, SLN is non-toxic [41]. Cationic solid lipid nanoparticles can act as effective, potent and non-viral agent [42,43]. SLN acts as an effective carrier for vaccines to provide a maximum immune response by optimizing surface properties. Recently, chitosan coated lipid nanoparticles were prepared for oral administration of peptide drugs [44].
In the Recent years, much attention has been given to the use of lipid-based formulations for the improvement of oral bioavailability of poorly water-soluble drugs. The major goal of lipid-based formulations is to improve oral bioavailability and decreased leakage of water soluble drugs. SLN when compared with other nano or micro particulate carriers, they provide the following advantages:

1) Good tolerability
2) High biocompatibility
3) Controlled release
4) Protection of incorporated drugs
5) Improved oral bioavailability
6) Large scale production
7) Provide Chemical Stabilization [45,46]

SLNs can be produced by replacing the oil phase of an o/w emulsion with a solid lipid, which could be purified triglycerides, mixtures of glycerides or waxes. The bioavailability of poorly water soluble drugs can be enhanced by incorporated them in SLNs [47]. There are some drawbacks associated with SLNs e.g. limited drug loading capacity, the expulsion of the drug during storage. Nanostructured Lipid carriers are formed by nanostructuring the lipid matrix which overcomes the drawbacks with SLNs i.e. increases drug loading and prevents drug expulsion. The particle matrix of NLC remains solid at room temperature [48]. Advantages of NLC over SLN are as follows:

a) To improve the drug loading capacity for the hydrophilic drugs, Lipid drug conjugate (LDC) nanoparticles were invented.
b) LDC nanoparticles are the nanoparticles which consist of 100% LDC with suitable lipids.
c) By esterification or amidation hydrophilic drug is converted to lipophilic drug conjugate results in the formation of Lipid drug conjugate.
d) The melting point of LDC lie in the range of 50 to 100 due to which LDC can be nanosized by use of High-pressure homogenization [49].

Lipid nanoparticles act as a promising carrier system especially for hydrophilic drugs that show reduced stability in the gut and less bioavailability [50]. In comparison with liposomes, lipid nanoparticles offer a low-cost system and physically stable. NLC offers long-term colloidal stability and higher drug loading. NLC and SLN provide the ability for a drug to sustain the therapeutic level in the plasma [51]. Recent reports describe that SLN or NLC could be possible to convert into solid powder by using wet granulation method [52-57]. SLN or NLC can be possible to prepare in anhydrous liquids such as PEG 600 and this dispersion can be filled into soft or hard gelatin capsules (Table 2).

Polymeric Nanoparticles

The Polymeric nanoparticles contain polymer matrix in which drug can be dissolved, encapsulated, entrapped or chemically bound. Due to hydrophobic surface properties, they are very sensitive to opsonisation. Therefore the surface of nanocarrier requires being modified to prolong the circulation in the blood [58]. When the surface of nanoparticles modified with specific moieties, nanoparticles do not mark by opsonin proteins and recognised by phagocytes hence phagocytosis does not occur. The nanoparticles surface Coating with hydrophilic moieties such as PEG results in nanosystem escaping from RES. Nanospheres can be designed to provide mucoadhesive property and offers the ability to improve the peptide delivery when given by orally [59]. Targeted and controlled drug delivery may be largely influenced by the colloidal carriers which are based on biodegradable and biocompatible polymeric systems [60]. Nanoparticles are the submicron colloidal carriers made up of synthetic or semi-synthetic polymers having a size in the range from 10-1000 nm. Polymeric colloidal carriers provide the control for the pharmacokinetic behaviour of the encapsulated drug [61]. Biodegradable polymeric nanoparticles consist of several polymers like polylactic acid, polyglycolic acid, polylactic-glycolic acid and polymethyl methacrylate. These polymers are used in polymeric carriers for the effective delivery of proteins, genes and DNA [62]. Nanoparticles have been used in the delivery of oligonucleotides, and are prone to degradation by nucleases [63]. Polymeric nanoparticles along with peptides used for the sustained oral delivery and to enhance absorption and bioavailability [64].

Table 2: Bioavailability enhancement of lipid based carriers (e.g. liposomes, solid lipid nanoparticles) by various methods

Drug	Nanocarrier Type	Preparation Method	Lipid and Surfactants	Remarks	References
Vinpocetine	Solid Lipid Nanoparticles	Ultrasonic solventemulsification	Soya lecithin,Glyceryl monostearate Tween 80	AUC of the Vinpocetine SLN was 9.56 ±1.33 μg h mL^{-1} which were 4.16 fold greater than the Vinpocetine solution.	[53]
Clozapine	Solid Lipid Nanoparticles	Hot Homogenization andUltrasonication	Phosphatidylcholineand Poloxamer 188	Bioavailability of Clozapine SLN was 3.1 -4.5-fold greater on intraduodenal administration and high uptake in RES and brain after intravenous administration.	[54]
Quercetin	Solid Lipid Nanoparticles	Emulsification andlow-temperature solidification	Soya lecithin,Tween-80 and PEG 400	AUC of the Quercetin SLNs was 324.18 ± 41.3 μg h mL−1 which were more than 5 fold greater than the Quercetin suspension.	[47]
Pentoxifylline	Solid Lipid Nanoparticles	Ultrasonic-solvent evaporation-emulsification	Soya lecithin, Tween-20Poloxamer 188,	The particle size of the SLNs was 288nm.SLNs shows controlled drug release i.e more than 6 hours with enhanced bioavailability.	[45]
Silymarin	Liposome	Solution-enhanced dispersion by supercritical fluids	Phosphatidylcholineand Sodium glycocholate	AUC of SM-Lip-SEDS was18.406 ± 1.481 μg h mL^{-1} which were 4.8-fold greater than the Silymarin powder formulation.	[55]
Itraconazole	Liposome	Thin-film dispersion method	Lecithin, SodiumDeoxycholate and Cholesterol	AUC of ITZ-Lip-NaDC was 5547 ± 1951 ng/mL·h which was 1.67-fold higher than commercial capsules.	[56]
Fenofibrate	Liposome	Dry Film Dispersing,Sonication and homogenization	Cholesterol phosphatidylcholine,Sodium Deoxycholate	The bioavailability of SPC/SDC and SPC/CL liposomes was 5.13- and 3.28-fold greater than that of the micronized fenofibrate.	[57]

The problems occur with the use of synthetic polymers can be overcome by the use of natural polymers like chitosan, gelatin, albumin and sodium alginate [65]. Nanospheres and nanocapsules are the types of polymeric nanoparticles given specifically as a collective term i.e., Polymeric Nanoparticles. Nanospheres are the matrix systems in which the entire mass of particles is solid and the molecules adsorbed on the surface of the solid matrix or may encapsulate within the particle. Nanocapsules act as a type of reservoir, are the vesicular systems in which the substances may be entrapped or restricted to a cavity which consists of a liquid core which is surrounded by a solid material shell [66].

Figure 5 depicts the various drug delivey system of polymeric nanoparticles.

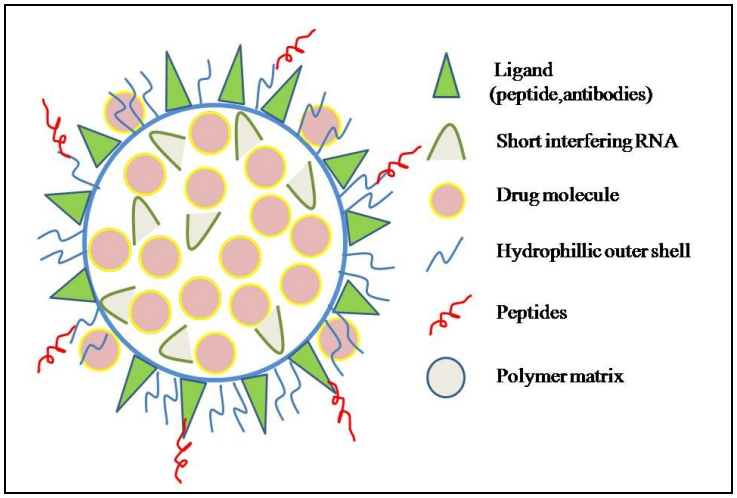

Figure 5: Polymeric nanoparticles based targeted drug delivery system

Preparation techniques for polymer nanoparticles:

Polymeric Nanoparticles can be prepared either from the dispersion of preformed polymers or by polymerization of monomers using various techniques. As shown in Figure 6.

Dendrimers

Dendrimers are the monodisperse three-dimensional macromolecules that have specific molecular weights and having entrapment properties [67]. They are highly branched artificial molecules that have similar structure like a tree. They are synthesized in a stepwise manner from branched monomer units. The structural components of

dendrimers are organic molecules and polymers, therefore, they have special physical and chemical properties. Dendrimers have empty internal cavities due to which they encapsulate hydrophobic drug substances [68]. When compared with conventional macromolecules, they have higher surface functional group density [69]. These functional groups present in the dendrimers allow them to enhance the solubility of many drugs [70]. A large number of surface functional groups present on the outer shell of dendrimers are responsible for high reactivity; hence they can be conjugated with guest molecules [71].

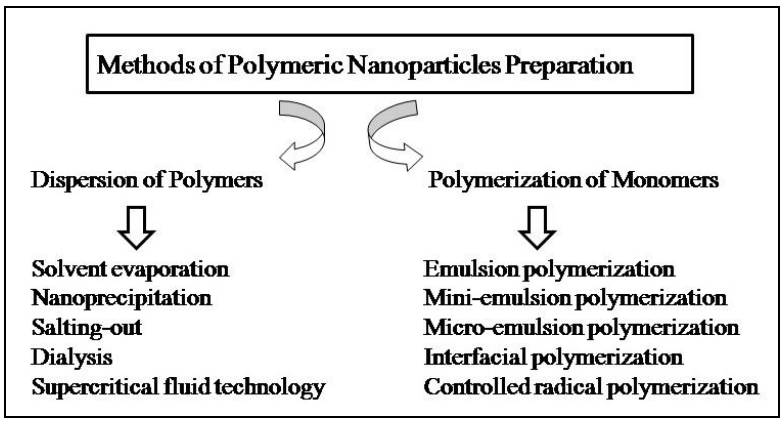

Figure 6: Polymeric nanoparticles preparation methods

Therefore the drugs can be either conjugated with the surface functional groups or encapsulated in the hydrophobic cavities of dendrimers. Thus dendrimers act as suitable drug delivery systems due to these specific properties. Dendrimers offer a new class of polymeric materials that have a spherical three-dimensional structure and provides a high degree of surface functionality. They have three structural components:

(i) Central core unit.
(ii) Interior layers or branches made up of repeating units attached to the central core.
(iii) Functional groups attached to the outermost interior layers [72].

Figure 7 depicts the strucutural components of dendrimers.

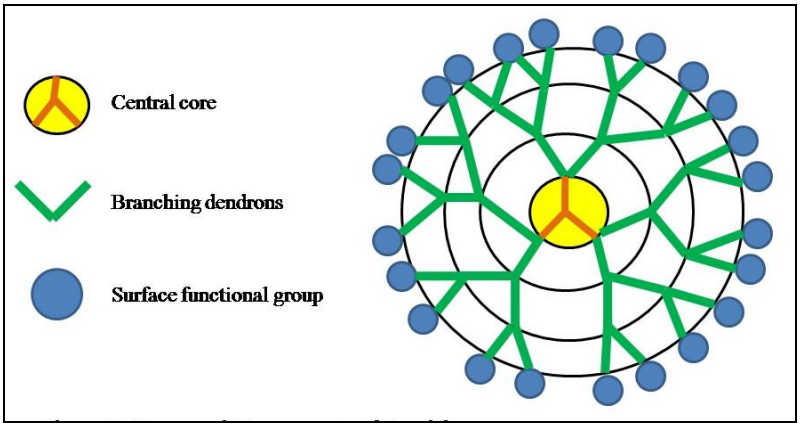

Figure 7: Structural components of Dendrimer

Dendrimers in Drug Delivery

Drug molecules can be encapsulated in the dendrimers as well as adsorbed to the surface functional groups due to presence many surface groups or well-defined 3D structure of dendrimer. Dendrimers can be used as drug carriers by conjugating the drugs with functional groups through electrostatic or covalent bonds.

Two mechanisms for drug delivery by dendrimers are:

1) *In vivo* degradation of covalent bond in between drug and dendrimer depends on the presence of enzymes for cleaving the bonds.
2) Due to changes in the physical environment such as pH, temperature, therefore, results in the release of the drug. The mechanism takes place in cavities of a central core or outer shell of the receptor [73,74].

Figure 8 depicts various types of dendrimers.

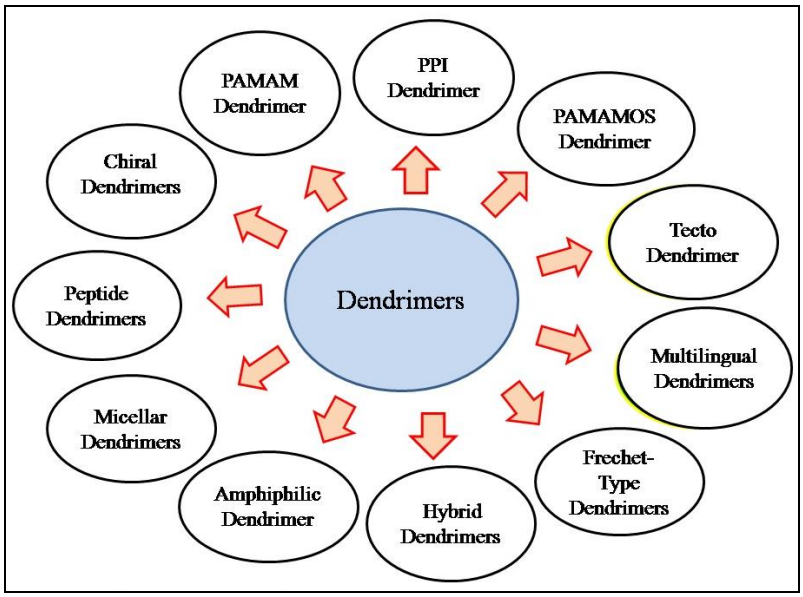

Figure 8: Various types of dendrimers

1. **Radially layered poly (amidoamineorganosilicon) dendrimers (PAMAMOS):**
   The interior layer or branches consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) and exteriors consist of hydrophobic organosilicon. They have the ability to conjugate and encapsulate various drug molecules in the central core.
2. **Poly (amidoamine) dendrimers (PAMAM):**
   Synthesized from the initiator core reagents like ammonia or ethylenediamine by the divergent method, they are available as methanol solutions commercially.
3. **Poly (Propylene Imine) dendrimers (PPI):**
   The end group of PPI dendrimers is generally poly-alkyl amines and the interior layer consists of tertiary trispropylene amines. They are available as AstramolTM and widely used in material science and in biology.
4. **Chiral dendrimers:**
   In these dendrimers, the chirality depends on the construction of a constitutionally different but chemically similar branch to the chiral core.
5. **Tecto dendrimer:**
   They are composed of a core dendrimer and are surrounded by several dendrimers to perform the function required for a therapeutic nanodevice. Different compounds perform various functions like recognition of diseased cell, disease cell diagnosis, drug delivery.
6. **Hybrid dendrimers:**
   These dendrimers are formed by complete mono functionalization of the peripheral amines of polyethylenemine dendrimer and are hybrids of a dendritic and linear polymer having both the properties.
7. **Amphiphilic dendrimers:**
   They are made up by combining two segregated sites of the chain in which one-half is electron donating and other is electron withdrawing.
8. **Micellar dendrimers;**
   They are the unimolecular micelles which are water soluble hyper branched polyphenylenes.
9. **Multilingual dendrimers:**
   The multiple copies of a particular functional group are present on the surface of the dendrimer hence known as multilingual Dendrimers.
10. **Multiple antigen peptide dendrimers:**
    J.P.Tam in 1988 firstly introduced this type of dendrimer and found its use in biological applications i.e. vaccine and diagnostic research.
11. **Frechet-type dendrimers:**
    Hawker and Frechet recently developed this type of dendrimer based on poly- benzyl ether hyper branched skeleton. The surface groups in this dendrimers are carboxylic acid groups.

Applications of Dendrimers

I. Pulmonary drug delivery
II. Transdermal drug delivery
III. Ocular drug delivery
IV. Controlled Release drug delivery
V. Targeted drug delivery

Chitosan Nanoparticles

Chitosan is a characteristic polysaccharide surely understood for its important natural and chemical properties, for example, biodegradability, biocompatibility, bioactivity, and polycationicity. Chitin and chitosan (CS) polymers are natural amino polysaccharides having special structures, multidimensional properties. Chitosan is a natural polymer got by deacetylation of chitin. After cellulose chitin is the second most bottomless polysaccharide in nature. Different methods of synthesis of chitosan nanoparticles and their applications in nanomedicine, biomedical engineering, industrial and pharmaceutical fields were found [75].

General properties of chitosan and chitin: Chitin is insoluble in most natural solvents; Chitosan is promptly dissolvable in dilute acidic acid beneath pH 6.0. This is because that Chitosan can be viewed as a strong base as it has essential amino groups with a pKa estimation of 6.3. The presence of the amino groups demonstrates that pH considerably modifies the charged state and properties of Chitosan [76].

Methods of Preparation of Chitosan Nanoparticles

1. Ionic Gelation method
2. Coacervation/Precipitation method
3. Sieving method
4. Emulsion crosslinking method
5. Reverse micellar method

Pharmaceutical Applications of Chitosan Particulate System

Chitosan-based particulate system are drawing in pharmaceutical and biomedical applications as potential Drug delivery device. Some critical applications are discussed below.

a) Colon targeted drug delivery: Chitosan is a promising polymer for colon drug Delivery since it can be biodegraded by the colonic bacterial flora and it has mucoadhesive character. The pH-sensitive multicore microparticulate framework containing Chitosan microcores entrapped into enteric acrylic microspheres was reported [77].

b) Mucosal delivery: Mucosal surfaces, for example, nasal, peroral and pulmonary are getting a lot of consideration as alternative route of systemic administration. Chitosan has mucoadhesive properties and it appears to be especially valuable to formulate the bioadhesive dose foams for the mucosal organization (visual, nasal, buccal, gastro-enteric and vaginal-uterine treatment) [78]. Chitosan has been found to improve the drug absorption through mucosa without harming the biological system. Here, the mechanism of activity of Chitosan was recommended to be a combination of bioadhesion and a transient broadening of the tight intersections between epithelial cells [79].

c) Topical delivery: Because of good bioadhesive property and capacity to sustain the release of the dynamic constituents, Chitosan has been utilized in topical delivery systems. Bioadhesive Chitosan microspheres for the topical sustained release of cetyl pyridinium chloride have been assessed [80].

d) Ocular delivery: De Campos et al. [81] found the capability of Chitosan nanoparticles as another vehicle to enhance the delivery of drug to the ocular mucosa. Cyclosporin A (CyA) was picked as a model medication. An adjusted ionic gelation system was utilized to developed Cyclosporin A-loaded Chitosan nanoparticles. These nanoparticles with a mean size of 293 nm, a zeta capability of +37 mV, high Cyclosporin an associated efficiency and loading of 73% and 9%, separately were obtained.

e) Chitosan as a coating material: Chitosan has great film forming properties and therefore, it is utilized as a coating material in drug delivery applications. Chitosan-coated microparticles offer many advantages e.g bioadhesive property and delayed drug release properties over the uncoated particles. Chitosan- loaded microsphere prepared from poly(lactic acid)– poly(caprolactone) mixes have been prepared [82]. Shu and Zhu [83] have arranged the alginate beads covered with Chitosan by three distinctive techniques.

Hydrogel Nanoparticles

Hydrogels are the three-dimensional hydrophilic structure and are formed by chemically or physically. It is also a type of polymeric system which consists of natural polymer amphiphiles like cholesteroyl pullulan, cholesteroyl dextran involving self-aggregation and self-assembled. In these hydrophobized polysaccharides, cholesterol group is responsible for cross-linking. The size and density of hydrogel nanoparticles can change by changing the degree of substitution of cholesterol groups [84]. Stimuli-responsive hydrogels have been found to be tissue compatible and they respond to changes in pH and temperature [85]. They have been used in the effective delivery of antigens, oligonucleotides and DNA [86]. The properties of the hydrogels must be evaluated such as safety, biodegradability, drug loading capacity and drug-release kinetics [87]. Cross linked hydrogel Nanoparticles ranges in 35-50 nm in diameter and composed of natural polymers. Hydrogel Nanoparticles utilizes hydrophobic polysaccharides for the delivery and encapsulation of the drug, protein or antigen. A novel delivery system shows great potential which utilizes cholesterol pullulan. For this, the four molecules of cholesterol combined to form a self-aggregating hydrophobic core with pullulan outside. The formed cholesterol nanoparticles resulting in the formation of this hybrid complex and helps in stabilization of entrapped proteins or drug molecule. Cholesterol Nanoparticles are readily taken up by the dendritic cells and stimulate the immune system. Larger hydrogels can entrap and release monoclonal antibodies. Curcumin has been known for its anti-cancer properties, a substance which is found in cooking spice turmeric. Due to poor solubility and less bioavailability, the use of the curcumin has been limited. The problem of poor solubility can be solved by encapsulating the curcumin in polymeric nanoparticle forming nano-curcumin. In the porous structure of hydrogels, the drug molecules can be loaded. The release rate of the drug can be determined by diffusion coefficient [88]. The hydrogels structure can be altered by environmental changes such as pH and temperature. Hence hydrogels can be used for developing stimuli responsive drug delivery system. Hydrogel Nanoparticles are one of the most effective nanoparticulate drug delivery systems due to certain features of a hydrogel system with nanoparticles like hydrophilicity and high water content. On the basis of natural and synthetic polymers, various polymeric hydrogel Nanoparticulate systems have been prepared and evaluated. Dandekar et al. found increase in the rate of absorption and delay curcumin release by formulating hydrogel NPs using hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone [89].

Advantages of Hydrogel Nanoparticles

i. The rapid clearance by phagocytic cells can be avoided by changes in particle size and surface properties allow both active and passive drug targeting.
ii. Provide therapeutic efficacy and reduction in side effects by providing the controlled and sustained drug release at the specific target site.
iii. Due to their small size, they provide the ability to target smallest capillary vessels.
iv. High drug loading can be achieved without any chemical reactions.
v. Hydrogel NPs also have the ability to penetrate the tissues by paracellular or transcellular pathways.
vi. They have the potential for delivery of the drug by various routes like oral, nasal, parenteral, pulmonary and intra ocular.

Polymers for Hydrogel Preparation

Tables 3 depicts the various polymers used for the preparation of hydrogel preparations.

Table 3: Polymers for hydrogel

Sr No.	Natural Polymers	Synthetic Polymers
1	Chitosan	Hydroxyethyl methacrylate
2	Alginate	Hydroxypropyl methacrylate
3	Fibrin	Isopropylacrylamide
4	Collagen	Vinyl acetate
5	Gelatin	Acryolic acid
6	Dextran	Polyethylene glycol acrylate

Polymeric Micelles

Micelles are nano assemblies having spherical shape and size ranges from 20-100 nm which act as potential drug delivery nanocarriers due to their specific properties like high solubility, high drug loading capacity and less toxicity [90]. The renal elimination and uptake by RES can be avoided due to the small size of the micelles [91]. Therefore this helps in targeting of the micelle to tumour tissue and prolongation in blood circulation. For the development of pH-sensitive micelles, many approaches have been described [92]. By attaching the titratable groups e.g. amines or carboxylic acids into block copolymers in which these groups donate protons and can control micelle formation.

When the block copolymer concentration increases above the critical micelle concentration or critical aggregation concentration the formation of micelles occurs. The hydrophobic portion of the block copolymers begins to associate and reduce the contact with water molecules at CMC results in the formation of core-shell micellar structure. If the hydrophobic fragments removed from the aqueous environment and hydrogen bond network results in a decrease in free energy of the system, formation of micelles occurs. Micelles formation occurs as the free energy decreases. The Polymeric micelles consist of Pluronics which are amphiphilic block copolymers that self-associate in aqueous solution to form micelles. Particle size and surface properties are the characterization parameters for the micelles (Table 4).

Structure of Polymeric Micelles

Polymeric micelles offer suitable drug delivery system for the drug compounds which are hydrophobic in nature and having poor bioavailability originates from the core-shell structure. The poorly soluble drugs are present in the hydrophobic inner core hence increasing their stability and bioavailability. The inner core of Polymeric Micelles is made up of hydrophobic segments of the block copolymers by hydrophobic interaction. Rather than hydrophobic interaction, Micelles can also be generated by electrostatic interaction with the help of charged block copolymers leads to the generation of Polyion complex micelles [93]. For oral drug delivery system, the block copolymers used for micelles formation should be:

i) Self-assemble in water
ii) Should remain stable upon dilution in GI tract
iii) Should be biocompatible and non-toxic
iv) Increase drug solubility

Table 4: Bioavailability enhancement of polymeric nanoparticles by various methods

Drug	Nanocarrier Type	Preparation Method	Lipid and Surfactants Used	Remarks	References
Paclitaxel	Polymeric Micelles	Dialysis method	Pluronic F-68, Pluronic F-127	The plasma conc. and AUC of the Paclitaxel was 1.8 and 2.5 fold greater than the Taxol and LHR PPMs.	[94]
Silibinin	Polymeric Micelles	Sonication method	Pluronic F-68	*In vitro* dissolution profile of Silibinin NPs shows six times more release than pure silibinin.	[95]
Octyl methoxycinnamate	Polymeric Nanocapsules	Emulsification–diffusion method	Cellulose acetate phthalate, Polyvinyl Alcohol	Incorporation of OMC in NE increased the penetration rate compared with EM and NCs.	[96]
Ketoconazole	Chitosan-based mucoadhesive nanoparticles	Ionic gelation method	Sodium Tripolyphosphate and Chitosan	NP formulation will remain adhered to the stomach and oesophagus for a prolonged period and improve the absorption and bioavailability of KZ.	[97]
Indomethacin	Nanoparticles, Nanocapsules	Interfacial deposition, Nanoprecipitation, Emulsification	Poloxamer 188, Polyvinyl alcohol, Polycaprolactone	The submicron carriers enhance the Indomethacin concentration in the cornea, aqueous humour a by more than 3 fold.	[98]
Celecoxib	Polymeric Nanoparticles	Emulsification and Spray drying method	Ethyl cellulose, Sodium taurocholate	The AUC values for the Nanoparticle and Spray dried dispersion were 36% and 26% higher than that of the commercial capsule.	[99]
Tamoxifen and Quercetin	Polymeric Nanoparticles	Solvent evaporation method and Centrifugation	Pluronic F-68, Polyvinyl Alcohol, Polylactic Glycolic acid	The AUC values of the Nanoparticles were 5.31-and 2.69- Fold higher as compared to free Tamoxifen Citrate alone and in combination with Quercetin.	[100]

Advantages of Polymeric Micelles

a) The polymeric micelles provide thermodynamic stability in physiological solution results in slow dissolution *in vivo* [101,102].
b) They also act as a suitable carrier for poorly aqueous soluble drugs due to the core-shell structure of micelles.
c) These poorly soluble drugs present in the hydrophobic core of micelles and outer hydrophilic layer helps in dispersion in aqueous media leading to a suitable carrier for intravenous administration [103].
d) Due to the nanometric size range of micelles, they allow easy passage through endothelial cells and avoids the RES [104].
e) They have been studied as drug carriers for suitable drug delivery. By conjugating the micelles with specific ligands such as antibodies helps in targeting drug delivery.

Methods of Preparation of Polymeric Micelles

Methods which are used for preparation or encapsulating poorly soluble drugs are:

- Dialysis method
- Oil in water emulsion method
- Solvent evaporation method
- Direct dissolution
- Complexation
- Chemical conjugation

Polymeric Micelles for Bioavailability Enhancement

The major mechanism for the enhancement of absorption of the drug by Polymeric micelles is:

i) Protection of the entrapped drug from the GI environment.
ii) Controlled manner release of the drug at specific sites.
iii) Prolonging the residence time in the gut by mucoadhesion.
iv) Efflux pumps inhibition for improvement of drug accumulation [105].

Several parameters that influence the transport of micelles across epithelium include surface hydrophobicity, particle size and polymer nature. Polymeric micelles offer a number of characteristics which allow them to pass through the epithelium e.g. suitable particle size of the polymeric micelles can be taken up and pass through the intestinal barrier [106]. For the better bioavailability achievement, the drug may be target at a particular region in the GI tract known as absorption window. Polymeric micelles can be attached with different types of polymers or by coupling functional groups at the hydrophilic end of the copolymer to target the absorption window. These functional groups are pH-sensitive and receptor sensitive groups [107]. For the delivery of the drugs to the absorption site, Polymeric micelles should maintain the stable core-shell structure and upon dilution should not undergo rapid dissociation. The concentration of copolymer should be above it CMC for a micelle to be thermodynamically stable. The hydrophilic-lipophilic balance (HLB) of the block copolymer influenced the Critical micelle concentration [108].

Targeting of the polymeric micelles can be achieved by one of the following mechanisms:

- Enhanced Permeability and Retention Effect
- Complexing specific ligands with micelle surface
- Active targeting by immuno- micelles
- Acid-Sensitive Polymeric Micelles
- Stimuli-Sensitivity
- Thermosensitive Polymeric Micelles [109]

Critical Micelle Concentration

When the concentration of amphiphilic polymers is higher than CMC, they can exist in the form of micelles in aqueous media and micelles may collapse when diluted below CMC. Hence formation and the stability of polymeric micelles largely depend on CMC. For the determination of CMC in aqueous media various methods are used which are Chromatography, Surface tension, X-ray scattering, light scattering, viscometry, differential scanning calorimetry. CMC is determined from the plot of surface tension versus the logarithm of the concentration [110].

The solubilization process of micelles results in increasing water solubility of hydrophobic molecules and bioavailability [111]. The GIT uptake of drug particles largely depends on the particle size. The size range of particles about 100nm results in higher uptake efficiency by the GIT as a comparison to that of micrometer-sized particles [112]. Hence Polymeric micelles result in enhance uptake and bioavailability of poorly soluble drugs.

CONCLUSION

For overcoming difficulties in the administration of drugs having poor solubility's, poor bioavailability, Nanoparticulate drug carriers provide great potential. With the advancement of Nanoparticulate carriers in the drug delivery, they have found to play dominant role in the field of molecular medicine. The important characteristics of the drugs such as solubility, bioavailability and Pharmacokinetic, Pharmacodynamic properties and can be improved by nano particulate carrier systems. It can be concluded that nanocarriers offer a promising vehicle for the improvement of bioavailability of poorly soluble drug candidates.

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