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COLLOIDAL TECHNOLOGY-AN APPROACH FOR ENHANCING BIOAVAILABILITY OF POORLY WATER-SOLUBLE DRUGS: A REVIEW

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ABSTRACT

The chemical environment and enzymes present in the gastrointestinal (GI) membrane limits the oral absorption of water-soluble drugs. The GI epithelium is also responsible for the poor permeability of numerous antioxidant agents. Thus, water-soluble drugs do not readily dissolve in the GI tract, and therefore they have low bioavailability. Colloidal technology has the potential to improve the target efficiency of oral drugs. The use of lipid nanocarriers for poorly water-soluble drugs administered orally can provide improved solubility, chemical stability, epithelium permeability, improved bioavailability, half-life, and fewer adverse effects. These lipid nanocarriers include liposomes, solid lipid nanoparticles (SLNs), dendrimers, polymeric nanomicelles (PMs), self-emulsifying drug delivery systems (SEDDS), β-cyclodextrin complexes. The use of nontoxic excipients and advanced material engineering of lipid nanocarriers allows for control of the physicochemical properties of the nanoparticles and improved GI permeation through mucosal or lymphatic transport. Furthermore, we highlight recent progress in developing lipid nanocarriers to improve oral bioavailability, increase solubility, and inhibit P-glycoprotein efflux. We also discuss the mechanisms of various colloidal technologies that are used to develop an orally administered drug.

KEYWORDS: Oral absorption, Water-soluble drugs, Improved solubility, Colloidal technology, Lipid nanocarriers, Oral bioavailability,

INTRODUCTION

Bioavailability is the availability of the drug or unchanged fraction of drug substances that reaches the systemic circulation when introduced into the body. So it can able to show its pharmacological response. According to the definition, when an intravenous dose of administration injects a drug, it will directly reach the systemic circulation causes 100% bioavailability. When a drug is administered orally or the extravascular route, its bioavailability decreases due to incomplete absorption or first-pass metabolism.[1]

Types of bioavailability

Absolute bioavailability: It will be denoted as (F). when systemic availability of a drug administered orally/ extravascularly is compared to its intravenous administration. So this will be determined by a pharmacokinetics study plotted against plasma drug concentration (µg/ml) Vs. Time (hrs). By using this, we will evaluate AUC for oral & intravenous administration. Usually, absolute bioavailability for intravenous administration is going to be F= 1, and absolute bioavailability for oral administration F<1.

$$F = \frac{(AUC)oral \times (Dose)IV}{(AUC)IV \times (Dose)Oral}$$

Relative bioavailability: It will be denoted as (Fr). It measures when the systemic availability of a drug after oral administration is compared with that of an oral standard of the same drug in the aqueous formulation, known as relative bioavailability.[2]

$$Fr = \frac{(AUC)test \times (Dose)Standard}{(AUC)Standard \times (Dose)Test}$$

Colloidal nanocarriers: The possibility of providing endless opportunities in the area of drug delivery

The use of large-sized materials in drug delivery poses significant challenges, including *in vivo* instability, poor bioavailability, poor solubility and poor absorption within the body, issues with target-specific delivery and therapeutic effectiveness, and probable adverse effects of the medicine. Therefore, using new drug delivery systems for targeting drugs to specific body parts might be an option that may solve these critical issues.[2,3] Colloidal technologies are utilized in the drug delivery system and act as novel drug carriers of poorly water-soluble drugs because they are unstable in an aqueous environment; protein and peptide compounds also are carried inside these novel nanocarriers because they are considerably susceptible to enzymes that are present within the gastric fluids and it will cause

proteolytic degradation or cleavage enzymatic degradation. Nanocarriers will carry a drug and reach a targeted tissue or selective area more precisely, with the help of controlled release system present within the nanocarriers, the drugs are going to be released at a continuing steady-state plasma level with further prolongation within the duration.

Colloidal technologies

Particle technology may be a bunch of techniques, use to enhance physicochemical, micrometrics and biopharmaceutical characteristics of the hydrophobic drugs, leading to their improved solubility and bioavailability.[4]

1. Freeze-dried liposomes.
2. Solid lipid nanoparticles.
3. Dendrimers.
4. Polymeric nanomicelle.
5. Self-emulsifying drug delivery system.
6. Complexation with β-CD.

1. Freeze-dried liposomes

Liposomes are close colloidal structures consisting of one or more concentric spheres of lipid bilayers enclosing compartments that are aqueous. Liposomes typically differ in size between 20 nm and a few hundred micrometers. Liposomes have been attracting attention that is increasing a drug carrier for drug delivery systems (DDS) because they can hold both hydrophilic compounds and lipophilic compounds.[5,6]

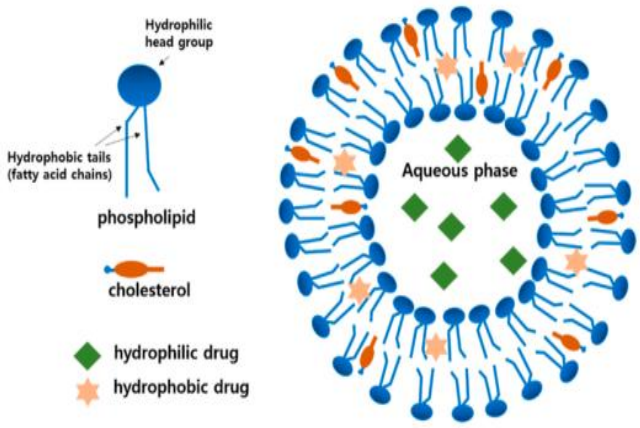

Figure 1: Formation of Liposomes and Its structural components.

Freeze-drying, also known as lyophilization, is the most commonly used method to liposomal that is dry. This method is widely utilized for pharmaceuticals to enhance the storage space

that is long-term of labile drugs such as for instance vaccines and proteins. A normal process is freeze-drying of three phases, namely, freezing, primary drying, and secondary drying. The period that is freezing is a cooling step where most of the solvent (e.g., water) is separated from the liposomes and additives, leading to the formation of ice. The drying is primarily initiated whenever the chamber pressure is reduced to some millibars, and the shelf temperature is risen up to provide an adequate amount of temperature to the liposomal suspension for water sublimation. Throughout the drying that is secondary water is desorbed from the frozen formulation at a heightened temperature and minimal stress.[7,8]

Mechanism of Transportation and Enhanced bioavailability

Liposomes can interact with cells by four adsorptions mechanisms that are different by specific interactions with cell-surface components, electrostatic forces, or non-specific weak hydrophobic, which is among the possible paths. The second mechanism is endocytosis by phagocytic cells of the reticuloendothelial system, such as macrophages and neutrophils. The third mechanism is with the plasma cell membrane by inserting this lipid bilayer for the liposome into the plasma membrane with the simultaneous release of liposomal content into the cytoplasm. Fourth is a swap of bilayer components, for instance, cholesterol, lipids, and membrane-bound molecules with aspects of cell membranes.[9,10,11]

Liposomes show a promising system to bypass the first-pass metabolism, enhance lymphatic absorption, and improve solubility and bioavailability.

Table 1: List of liposomal formulation in market.

Drug Liposome Formulation	Application of liposomes	Method
5- fluorouracil	Drug targeting	Thin-film hydration method[12,13]
Vinblastine sulphate	Cancer therapy	Sonication method[14]
Mafenide acetate	Antibiotic therapy	Solvent evaporation and microencapsulation[14]
Tetanus toxoid	Immunology vaccine	Reverse-phase evaporation method[15]

2. Solid lipid nanoparticle

SLNs introduced in 1991 represent an alternative and better carrier system to traditional carriers that are colloidal as emulsions, liposomes, polymeric micro, and nanoparticles.[16] SLNs are colloidal provider systems that consist of a melting that is high lipid as a good core coated by aqueous surfactant, and the drugs used are of BCS Class II and IV.[17]

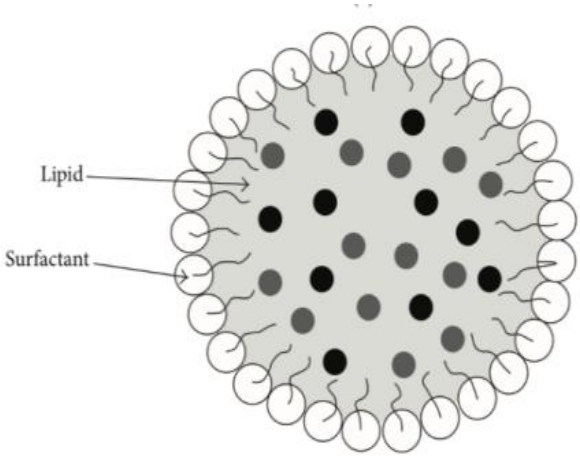

Figure 2: Structural formation of solid lipid nanoparticle.

Nitrendipine, an antihypertensive drug, has oral bioavailability between 10 and 20% as a result of a high metabolism that is first-pass. The solid lipid nanoparticles of nitrendipine were characterized for particle size, zeta potential, medication encapsulation efficiency, and crystalline behaviour of lipid and drug. The results of *in vitro* and *in vivo* medication launch study indicated solid lipid nanoparticles as being a carrier that is potentially enhancing the bioavailability of nitrendipine.[18] Nimodipine is highly lipophilic with just 13% bioavailability. SLNs of nimodipine had been made by 23 factorial designs, and factors like lipid, surfactant, and concentration that is cosurfactant studied. Ramipril is a medication that is water-insoluble; its oral bioavailability is just 28%. The SLNs were prepared by employing glyceryl and monostearate monooleate with Tween 80 and span 20 as stabilizers. The formulation glyceryl that is containing span 20 has shown an escalation in the bioavailability.[19]

Enhancement in oral absorption

Few mechanisms are described in increasing the oral bioavailability of drug particles by SLNs: Dissolution/solubilization: SLNs entering into the tract that is GI stimulates the gallbladder contractions and biliary and pancreatic secretions, including bile salts (BS), phospholipids (PL), and cholesterol, as a result of presence associated with lipid in the formulation.[20,21] These items, along with the shear that is gastric, form a crude emulsion that encourages the solubilization associated with the co-administered lipophilic drug.[22,23] Furthermore, the esters are rapidly hydrolyzed in the existence of pancreatic lipase, as well as the lipolytic services and products upon interaction with BS/PL from different micellar species that prevent the co-administered drug precipitation that is lipophilic. The surface-

active agents provide in the SLNs may further stimulate the solubilization of the ingredient that is lipophilic.

Stimulation of lymphatic transportation

The bioavailability of lipophilic drugs is also enhanced by the stimulation of the abdominal transportation path that is lymphatic.

Avoid first-pass metabolism

Solid lipid nanoparticles have been reported to boost oral bioavailability of certain highly lipophilic medications by accessing circulation that is systemic the lymphatic route, thus preventing their first-pass metabolic process.[24] Solid lipid nanoparticles can get by pulmonary and parenteral routes, which is additionally a factor that is crucial to counter the hepatic first-pass metabolism of certain drugs.

Table 2: Lipids and Emulsifiers used for preparation of SLNs.

Lipids	Hard fats	Emulsifiers
Non-Digestible lipids	Witepsol W 35	Soy lecithin
Mineral oils	Witepsol S 35	Egg lecithin
Sucrose polyesters	Witepsol H 42	Phosphatidylcholine

Lipids for solid lipid nanoparticles

The drug consumption capability from the SLNs that is prepared depends upon the kinds of lipids. Various types of lipids have actually been utilized by researchers for the preparation of solid lipid nanoparticles (Table 3). Non-digestible lipids consist of mineral oils, sucrose polyesters, which cannot be consumed through the gut lumen, tend to retain the lipophilic drugs within the oil, and therefore, may limit the consumption of the drug.[25,26] Digestible lipids, including triglycerides (TG), diglycerides (DG), phospholipids (PL), fatty acids (FA), cholesterol, and other synthetic derivatives, are suitable oils for drug delivery systems of lipophilic compounds. These lipids are usually defined in accordance with their carbon string length, i.e., long-chain triglyceride (LCT) or medium-chain triglyceride (MCT), lipid class, i.e., TG, DG, MG, or FA, level of saturation, and their conversation with water. The lipid-based delivery system has to maximize the rate and extent of drug dissolution and continue maintaining the drug in solution during its transit throughout the GI tract for successful oral consumption enhancement. Thus, methods for tracking the solubilization state of the drug following the dispersion of various delivery which is lipid-based in the GI tract are extremely needed. Based on them after oral administration, the lipidic component is subjected to

hydrolysis that is enzymatic. Salivary glands secrete lingual lipase together with gastric lipase, secreted from the gastric mucosa. These secretions are playing a role that is very important in the hydrolysis of triglycerides (TG) into the stomach and leads to the formation of diglycerides (DG) and fatty acids (FA). These diglycerides and fatty acids during passing through the sphincter that is pyloric the duodenum and also combined with the sheer movement of the stomach cause the formation of crude emulsion.[27] Lipids facilitate the secretion of bile salts (BS), biliary lipids (phospholipid (PL) and cholesterol ester), and pancreatic liquids to the duodenum. These agents absorb the oil/water interface and produce an even more emulsion that is stabilized with reduced droplet size. The hydrolysis is enzymatically completed by the action of pancreatic lipase, which upon complexation with co-lipase acts at the area of the emulsified TG droplets to produce the corresponding 2- MG and two FA.[21] Upon interaction with the endogenous BS and PL, these amphiphilic lipid digestion products form colloidal structures holding different levels of surface activity, which enables the solubilization of the co-administered poorly water-soluble compound, and prevents their precipitation in the aqueous GIT milieu. This procedure, which maintains poorly water-soluble drugs in solution and stops its precipitation, is thought to be the main mechanism by which lipid-based medication delivery systems augment the oral absorption of lipophilic medications in many cases.

3. Dendrimers

These will be the macromolecules, globular in framework, extremely branched (~ 20 nm in size) with many arms originating from a core. Moreover, they turned out to be an approach that is novel increase the bioavailability of poorly aqueous soluble drugs.[28] Dendrimers have usually been called the “Polymers of the century” that is 21st. Dendrimer chemistry was introduced in 1978 by Fritz Vogtle and colleagues.[29] He synthesized the“cascade particles” that are first. In 1985, Donald A. Tomalia synthesized your family that is first of[30] The word “dendrimer” descends from two words, the Greek word dendron, meaning tree, and meros, meaning part.[31]

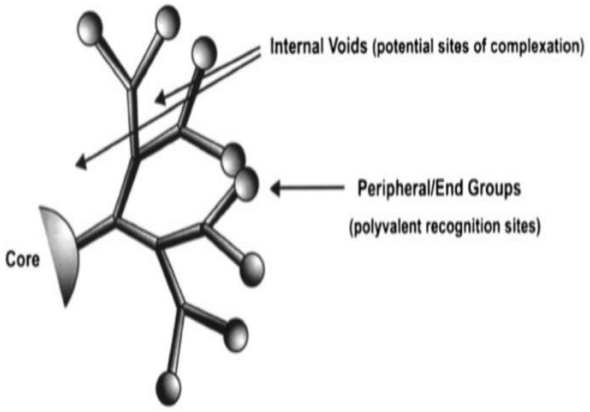

Figure 3: Structure of dendrimer.

System of Action and Interactions between Dendrimers and Drug molecules

The interaction between dendrimers and drug particles has drawn interest that is great these years. Different interaction mechanisms have actually been explored and they are broadly subdivided into three types: simple encapsulations, electrostatic interactions, and covalent conjugations (figure 4).

Simple encapsulation

The ellipsoidal or form that is spheroidal empty internal cavities and open nature of the architecture of dendrimers have the ability to directly encapsulate visitor molecules into the macromolecule interior (figure 4). These empty cavities that are internal have hydrophobic properties, which make them suitable to interact with poorly-soluble drugs through hydrophobic interactions.[32,33] In addition, you will find nitrogen or oxygen atom in these cavities, which can be internal that may connect to the medication molecules by hydrogen bond development. The relationship between the interior cavities of dendrimers and drug molecules may include real encapsulation, hydrophobic discussion, or hydrogen bonding because of these specific properties.

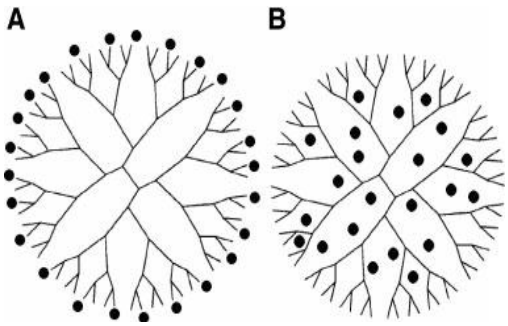

Figure 4: Potential Strategies for interactions between dendrimers and drug molecules (A) electrostatic interactions or covalent conjugate and (B) simple encapsulation.

Electrostatic interaction

The density that is a lot of groups (Such as amino groups and carboxyl groups) on the surface of dendrimers are expected to have potential applications in boosting the solubility of hydrophobic medications by electrostatic relationship. Take the G3 PAMAM dendrimer with ammonia core; for instance, it has a much higher amino group density in comparison to classical linear polymers (a G3 PAMAM dendrimer has 1.24 × 104 amine moieties per unit volume (Cubic Angstrom) in comparison to the 1.58 × 106 amine moieties per unit number of a regular star polymer). Earlier, nonsteroidal anti-inflammatory drugs with carboxyl teams, including ibuprofen, ketoprofen, diflunisal, naproxen, and indomethacin, have commonly been complexed with dendrimers by electrostatic interactions.[34,35-38] Studies on other drugs, such as some medications, which are anti-cancer anti-bacterial medications, have also been reported.[32,33,39,40] The property that is common in drug molecules is that they are weakly acidic drugs with carboxyl teams in the molecules.

Covalent conjugation

The clear presence of more and more practical groups on the top of dendrimers makes them suitable for the conjugation that is covalent of drugs with relevant functional groups.[41,42,43] The drug is covalently bound to dendrimers, and its launch occurs via chemical or enzymatic cleavage of hydrolytically labile bonds in this case. The encapsulation of drug molecules within hydrophobic cavities or absorption of medications towards the surface of dendrimers via electrostatic interactions preserves the chemical integrity and pharmacological properties of drug molecules, while covalent attachment of medications to the surface teams of dendrimers through chemical bonds offers the opportunity for better control over medication release than that can be achieved by easy complexation that is encapsulation/electrostatic of into/with the dendrimers.[43,44] In addition, covalent conjugation allows tissue targeting and controlled distribution as the drug–dendrimer conjugates diffuse slower compared to the free drug within the body and might be absorbed in specific interfaces. Naturally, a problem may arise as a result of coupling large numbers of medications to the dendrimer surface by covalent conjugation, that is, the insolubility of the item that is resultant. This problem often may be resolved through the attachment that is concomitant of PEG chains. Doxorubicin loaded-PAMAM dendrimers for oral management had been observed that dendrimer complex resulted in improved cellular uptake and 4–7 times more transportation capability of the loaded drug when compared towards the doxorubicin that is free. They figured doxorubicin-

loaded dendrimer might enhance the bioavailability of the loaded drug by more than 200-fold after oral administration when compared with the medication.[45] that is pure.

4. Polymeric nanomicelle

PMs are nanosized formulations that can carry water-insoluble drugs to their targeted areas. They are smaller in size (100 nm) and can swallow up cells contaminated by a system of macrophages.

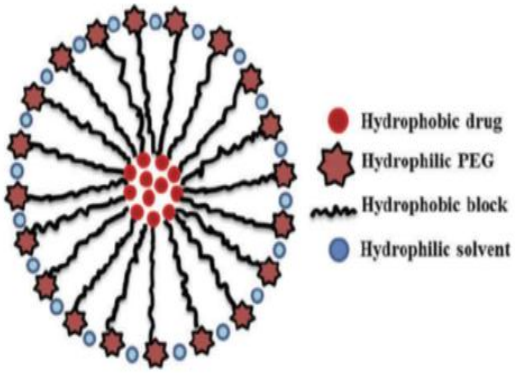

Figure 5: Polymeric nanomicelle.

PMs for enhancement of bioavailability

The critical mechanisms involved with the enhancement of drug consumption by PMs are (1) security for the drug that is packed the harsh environment for the GI tract, (2) release of the loaded drug in a controlled way at target sites, (3) prolongation of the residence time in the gut region by Mucoadhesion and (4) inhibition of efflux pumps to improve drug accumulation.[46] In addition, several physicochemical parameters will be influencing the translocation of micelles across the epithelium.[47] Thus, there exist many characteristics of PMs that enable them to traverse across the epithelium. For instance, PMs with appropriate particle size can be taken up then cross the abdominal barrier.[48,49] Also, to attain good bioavailability, it may deliver medications at a specific region in the GI tract, the so-called absorption screen. To reach the absorption window, PMs are manipulated by coupling different forms of polymers or by grafting different functional groups at the hydrophilic end of the copolymer, such as[50–52] that is a pH-sensitive receptor sensitive group.[53]

The remarkable stability of PMs for enhancement of bioavailability

As we discussed above, the GI tract is the barrier that is major oral medications. After oral administration, medications will encounter the harsh physicochemical environment of the tract that is GI, and it will be degraded due to the variation of pH levels and the existence of

enzymes or bile salts. To ensure the safe delivery of the carried drugs to the consumption sites, PMs must undoubtedly resist dissociation, that is, rapid dilution, and it will be retaining the stable core-shell structure before going to target sites. PMs possess two aspects of structural stability that are thermodynamic and kinetic, provided by the entanglement of polymer chains within the inner core.[54–56] For a micelle to be thermodynamically stable, the copolymer concentration should be above its CMC. The CMC is influenced by the balance that is hydrophilic-lipophilicHLB) of the block copolymer.[57] A reverse relationship between the CMC and hydrophobicity of the core-forming blocks has been shown in many respected reports: growth in the hydrophobic block length results in a reduced CMC if a hydrophilic section is kept[58] that is constant. Generally, CMC values in a range from 10^{-6} to 10^{-7} M. These CMC values are much smaller compared to those of micelles formed from low-molecular-weight surfactants (10^{-3}–10^{-4} M),[59] which permits a series of dilution and retain the micellar nevertheless structure. The second aspect, the kinetic security of PMs, comes into the picture once the copolymer concentration decreases below the CMC. Kinetic stability is more critical than thermodynamic stability for the non-equilibrium medication delivery conditions. The kinetic stability of PMs is increased for the rigid or bulky core framework, unlike micelles created from low molecular weight surfactant molecules. Consequently, the disassembly of PMs at a concentration below CMC occurs at a somewhat slow rate because of the relatively high stability that is kinetic. The slow dissociation allows PMs to regain their integrity and drug content before reaching the target sites, which is also helpful to enhance oral bioavailability.

Mechanisms of mucoadhesive PMs for enhancement of bioavailability

Mucoadhesion is a complex sensation, and many actions happen suggested in mucoadhesive bond formation. The first step is spreading, wetting, and dissolution associated with the mucoadhesive polymer during the interface. The second step is the mechanical or physical entanglement between the polymer and the tissue surface mucus layer, leading to an interpenetration layer. This action is next to the consequences of chemical interactions.[59] Mucoadhesion had formed by either interaction to the nonspecific mucosal area, such as covalent bonds, ionic bonds, hydrogen bonding, and van der Waals' interactions,[60] or specific interactions by functionalizing polymers with targeting ligands (e.g., lectins[61,62]) or reactive groups such as thiols.[63]

The fates of the mucoadhesive PMs into the GI tract include at least three different pathways:

- Mucoadhesion.
- Translocation through the mucosa or transportation.
- Direct elimination that is fecal.

The top charges of PMs seem to play an important role in particle uptake, one of the various factors. The negatively charged intestinal mucosa, because of the existence of glycocalyx, attracts more positively charged PMs on the one hand. Therefore, a considerable number have been conducted utilizing charged polymers such as chitosan to boost residence time in the GI tract.[64,65] Regarding the other side, particle mobility also is strongly influenced by surface charges, plus it indicates that transport rates were indirectly related to particle surface potentials. Adversely charged particles show significantly higher transport rates than near neutral or charged particles whose transport was probably limited by particle aggregation and electrostatic interactions that are adhesive mucosa. Crater and Carrier demonstrated a 20–30 times quicker diffusion for anionic particles when compared to cationic ones,[66] which proved the opinion discussed above. So, it is important to get a grip on the balance between Mucoadhesion and mucus penetration for efficient delivery that is oral.

5. Self -Emulsifying drug delivery system

Self-emulsifying drug distribution systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly water-soluble drugs. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drugs, lipids, and surfactants, usually with one or more co-solvents that are hydrophilic emulsifiers.[67] These systems can form fine (oil in water) emulsion instantaneously upon moderate agitation followed closely by dilution with aqueous media. 'SEDDS' is a term that is broad, typically producing emulsions with a droplet size ranging from a few nanometers to many microns. 'Self-micro emulsifying drug delivery systems (SMEDDS) indicate the formulations forming microemulsions which are transparent oil droplets ranging between 100 and 250 nm. 'Self-nano-emulsifying medication delivery systems is a term that is recent the globule size range less than 100 nm.[68]

Mechanism of drug transport from SEDDS

The pathway of lipidic transport from the GI lumen to the circulation is of paramount significance for interpreting the biopharmaceutical properties of oral lipid-based formulations and successful development. On oral administration, the SEDDS formulation undergoes digestive, absorptive, and circulatory phases. Figure 8 presents a comprehensive pictorial

view of such pathways through which the drug molecules form self-emulsifying systems and have a tendency to urge absorbed into the vascular system. Understanding the effect of lipid type and lipid digestion and drug load potential and, therefore the simple dispersion of the SEDDS formulation is critical to predict and explain *in vivo* bio performance. In addition, the intraluminal processing of lipids prior to absorption dictates the GI solubilization and bioavailability of the drug.

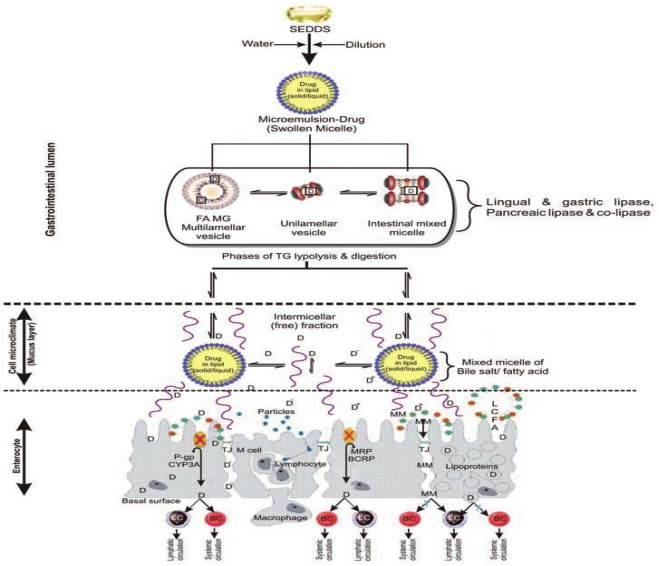

Figure 6: Diagrammatic representation depicting the probable mechanistic pathways for transportation of drugs across the GI lumen using SEDDS.

The combined effect of antral contraction, retropulsion, and gastric emptying during emulsion undergoes enzymatic hydrolysis in the oil/water interface, changing the digestion products into a form that is absorbable. This dispersed digestion that is a lipid, together with the undigested lipids, then empties into the duodenum,[69] causing the production of secretin through the duodenal mucosa, and also this, in turn, boosts the activity of pancreatic lipase and co-lipase through the secretion of bicarbonate.[70] Digestion is completed because of the action among these interfacial enzymes that act at first glance regarding the emulsified triglyceride droplets to quantitatively produce the corresponding 2-monoglyceride as well as two acids that are fatty. The digestion phase terminates using the interaction of essential fatty acids and monoglycerides with bile salts, leading to the synthesis of mixed micelles, while an element of the triglycerides and essential fatty acids may form vesicles after digestion in this phase that is preabsorptive. It really is as of this phase that the drug is released through the SEDDS as a result of either precipitation or dissolution into the media that are gastrically resolubilized as micelles or mixed micelles by emulsification.[71] These colloidal species

produced as a result of lipid digestion are taken up by passive diffusion, facilitated diffusion, or active transport through the enterocyte membrane during the absorptive phase. A fatty acid-binding protein transports these micelles through the apical membrane by a carrier-mediated transport process[72] in the cytosol. Alternatively, the absorbed drug that is free is merged using the chylomicrons (for example, intestinal lipoproteins) inside the enterocyte. These chylomicrons are relatively large colloidal systems with the capacity of selective intestinal transport that is lymphatic of lipophilic compounds.[73] The endothelial architecture regarding the lymphatic vessels facilitates the size-selective transport of chylomicrons which is why access that is simplistic to the blood capillary endothelium is restricted.[74]

Chylomicrons travel through the lacteals to participate in lymphatic vessels off their body parts and go into the systemic circulation through the thoracic duct into the subclavian vein, thus protecting the drug from hepatic metabolism that is first-pass. The blood-borne chylomicrons rapidly disassemble, releasing the encapsulated drug during the circulatory phase. The remainder constituent lipids of SEDDS can be used for the body.

Lymphatic pathway

The system that is lymphatic has a comprehensive drainage network spread through the entire body. It shadows the blood supply system and procedures mainly to go back fluid that has leaked into the space that is interstitial into the blood. The intestinal lymphatics also play a role that is essential in the absorption of products from lipid digestion, e.g., long-chain essential fatty acids and lipid-soluble vitamins. Features of drug delivery into the intestinal system that is lymphatic avoidance of hepatic first-pass metabolism in addition to the potential to a target-specific disease states proven to spread through the lymphatics (e.g., certain lymphomas, HIV, etc.). At the level that is cellular, three pathways have now been investigated to target the drugs into the intestinal lymphatics potentially. The selection of pathway is dependent upon the physicochemical properties regarding the drug candidate in addition to design regarding the drug-delivery system.[75] Possible mechanisms of drug transport through intestinal barriers making use of the SEDDS include a rise in membrane fluidity, facilitating absorption that is transcellular opening associated with tight junction to permit paracellular transport, mainly relevant for ionized drugs or hydrophilic macromolecules; inhibition of P-GP or cytochrome P450 to boost intracellular concentration and residence time; and stimulation of lipoprotein/chylomicron production. The latter two mechanisms are potentially the absolute most promising for the intestinal drug that is

lymphatic using lipid-based vehicles.[76] Lipid-based vehicles, in addition to the presence of food, often enhance absorption that is oral, particularly of poorly water-soluble drugs. The lymphatic system plays a significant role in this enhanced bioavailability in some instances. This indicates most probably, therefore, that the physiological processes of lipid absorption and digestion are strongly related to this enhanced drug delivery. The digestion that is the lipid absorption process, and its own direct association with lymphatic transport of lipophilic drugs, have now been extensively reviewed.[77] Briefly, lingual and gastric lipases[78] initiate hydrolysis of a finite quantity of triglycerides, forming the diglyceride that is corresponding essential fatty acids inside the stomach.[79,80,81,82] Lipid vehicles may enhance transport that is lymphatic of compounds by stimulating the creation of chylomicrons.[83] Lipophilic drugs enter the system that is lymphatic association using the triglyceride core regarding the chylomicrons. A strong correlation, therefore, happens to be established amongst the amount of lymphatic transport together with triglyceride content regarding the lymph through the transport of a lipophilic drug that is antimalarial.[84]

6. Complexation with β-cyclodextrin

Thus, the use of cyclodextrins (CDs) is one of several technologies available to improve the solubility of poorly water-soluble drugs. The most important property of CDs is their ability to change the physicochemical characteristics of molecules accommodated within their internal cavity to form the so-called inclusion.

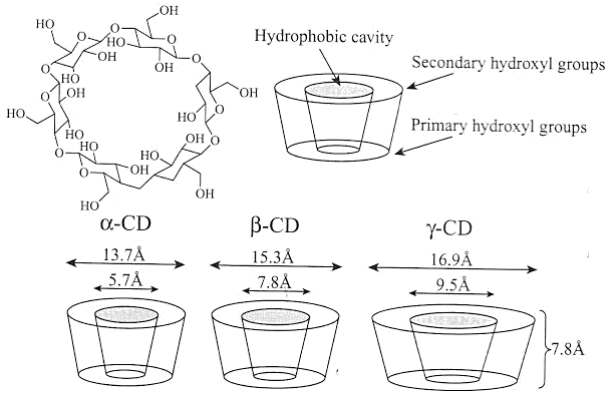

Figure 7: Schematic structures of the cyclodextrin.

CDs are used in many drugs that are local systems, including ophthalmic, nasal, pulmonary, buccal, vaginal, and rectal delivery.[85,86] The advantages of local drug delivery include reducing first-pass and side effects and increased effectiveness at relatively low doses.[87] Easy administration also increases convenience for patients.

Table 3: Some examples of marketed products containing β cyclodextrin.[88]

Drug	Formulation	Trade name	Company
Benexate HCl	Oral capsule	Ulgut®	Teikoku Kagaku Sangyou (Japan)
Dexamethasone	Dermal ointment	Glymesason®	Fujinaga (Japan)
Nicotine	Sublingual tablet	Nicorette®	Pharmacia (Sweden)
Piroxicam	Oral tablet	Brexin®	Chiesi (Italy)

Drug delivery through biological membranes

CDs improve the permeability of lipophilic drugs through the biomembrane. Thus, CDs increase the chemical stability of drugs outside the hydrophilic membrane.[89] The chemical structure of CDs (i.e., the large number of hydrogen donors and acceptors), their molecular weight is (>970 Da). Their very octanol/water that is a low coefficient (log Po/w approximately −3 to 0.00) are all characteristics of compounds that do not readily permeate through biological membranes.[90,91] Indeed, experiments have shown that only negligible amounts of hydrophilic CDs and drug/CD complexes can penetrate through lipophilic membranes such as the skin and mucosa that is GI.[92] Only the free drug, which is in equilibrium with the drug/CD complex, can penetrate lipophilic membranes. CDs can extract components that are lipophilic biological membranes such as the stratum corneum, but neither pre- nor post-applications of hydrophilic CDs affect the skin barrier.[93] CDs generally do not improve the permeability of hydrophilic drugs that are water-soluble lipophilic biological membranes.[94] Several studies have suggested that excessive CD concentrations reduce drug permeability through biological membranes.[90] The physicochemical properties of the drug (such as its solubility in water), the composition of the drug formulation (aqueous or non-aqueous), and the physiological composition of the membrane barrier (e.g., presence of an aqueous diffusion layer), determine whether CDs enhance or interfere with drug delivery through a biological membrane. Most biological membrane barriers are lipophilic and present in an aqueous exterior, which often forms a structured water layer on the membrane surface, sometimes referred to as the unstirred diffusion layer. When drug permeation through the diffusion that is aqueous is the rate-limiting step of drug permeation through the barrier, CDs can often increase permeation. However, in most cases, CDs cannot increase drug permeation through a lipophilic membrane. Excess CD concentrations (more than is needed to dissolve the drug) will interfere with drug permeation through the membrane. In other words, CDs improve drug delivery through aqueous barriers that are diffusion-controlled but may inhibit drug delivery through lipophilic membrane-controlled barriers. One exception, however, is the ability of lipophilic CDs, such as methylated β-CDs,

to penetrate the mucosa and improve drug delivery through biological membranes, such as through the mucosa that is nasal by reducing the barrier function of these membranes. At least, in theory, CDs can enhance drug bioavailability by stabilizing drug molecules at the biological membrane surface. For example, CDs have been shown to prevent insulin aggregation and improve insulin stability at the nasal mucosa. The enhanced bioavailability of insulin by CD after nasal administration is suggested to result from this effect that is stabilizing. Drug stabilization associated with CD complexation does not typically play a very role that is important drug delivery through biological membranes. This effect is solubilizing related to improved drug delivery. However, it is important to optimize CD-containing concerning drug delivery, as CDs may enhance and interfere with drug delivery through biological membranes. Too much or too little CD can lead to inadequate drug bioavailability.

Challenges to pharmaceutical nanotechnology

Pharmaceutical nanotechnology has provided refined diagnosis and focused treatment of disease. However there are some ethical, scientific, social, and regulatory issues posing various challenges in the practical realization of pharmaceutical nanotechnology. Some significant health risk includes cytotoxicity, translocation to undesired cells, acute and chronic toxicity; some unknown, unpredictable and undefined safety issues, environmental impacts of nanomaterials and non-biocompatibility. There are no specific FDA directives. However, only a few marketed products were approved for liposomes, monoclonal antibody-based products, polymer-drug conjugate, polymer-protein conjugate, and some polymeric drugs. All together, these challenges caused the urgent need to regulate these nanotechnology-based products and delivery devices.

CONCLUSION

Poor bioavailability is a major limitation in successful drug delivery by oral route. A lot of research work is dedicated to the oral bioavailability enhancement of poorly absorbed drugs. It is important to understand the reason behind poor bioavailability before designing a delivery system. The positive results obtained with the use of various delivery systems or different approaches of bioavailability enhancement seems to be promising. However, the commercial development of this a product demands a lot more research for overcoming the difficulties such as, scale-up, cost-effectiveness, and instability of a number of formulations.

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