



Novel Vesicular Drug Carriers for Bioavailability Enhancement

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ABSTRACT

The objective of the study is to evaluate the potential of novel vesicular drug carriers for bioavailability enhancement. Novel vesicular drug delivery carriers intend to deliver the drug at a rate directed by need of body during the period of treatment, and channel the active entity to the site of action. Encapsulation of drug in vesicular structures prolongs the existence of drug in systemic circulation and reduces the toxicity, if selective uptake can be achieved. Vesicular drug delivery systems have been used to improve the therapeutic index, solubility, stability and rapid degradation of drug molecule. This system reduces the cost of therapy by bioavailability improvement of medication, especially in case of poorly soluble drugs. Thus a number of novel vesicular drug delivery systems have been developed that enhance the bioavailability and provide sustained or controlled release of drug. The focus of this review is to discuss various lipoidal and non-lipoidal vesicles with special emphasis on the bioavailability enhancement of drugs.

Keywords: Vesicular drug delivery system, lipoidal, non-lipoidal, niosomes, liposomes.

INTRODUCTION

The therapeutic effectiveness of a drug molecule mainly depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. This aspect of the dosage form is referred as physiologic availability, biologic availability or simply bioavailability. Thus the term bioavailability is defined as the rate and the extent to which the ingredient or active moiety reaches to systemic circulation and becomes available at the site of action. As per the definition of bioavailability, a drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biomembrane and extensive presystemic metabolism¹.

Thus, the marvelous pharmaceutical research in understanding the causes of low oral bioavailability has led to the development of novel technologies to address these challenges. One of the technologies is to design a prodrug with the required physicochemical properties to improve the oral bioavailability². For example, the prodrug approach resulted in improved bioavailability of etilevodopa³. For BCS class IV drugs (having poor solubility and poor membrane permeability) and BCS class III drugs (having high solubility but low membrane permeability), prodrug approach is the best option to enhance their bioavailability but it requires extensive studies to establish the safety profile of prodrugs in humans, which ultimately may result in failure. Furthermore, the potential drawback of this approach is the reduced solubility of the prodrug⁴.

In this era, various technologies are in use to enhance the oral bioavailability of drugs, having poor aqueous

solubility. These include the use of micronization, nanosizing, crystal engineering, solid dispersions, cyclodextrins, solid lipid nanoparticles and other colloidal drug delivery systems such as microemulsions, self emulsifying drug delivery systems, self microemulsifying drug delivery systems and vesicular drug delivery systems. The technology which has the potential to solubilize varying quantities of poorly water soluble drugs with the help of lipids, protects the drug from harsh GI environment and prolongs the existence of drug in systemic circulation, is the vesicular drug delivery system⁵.

Novel vesicular drug delivery carriers intend to deliver the drug at a rate directed by the need of body during the period of treatment, and channel the active moiety to the site of action providing targeted and controlled release of drug⁶. Encapsulation of drug in vesicular structures prolongs the existence of drug in systemic circulation and reduces the toxicity, if selective uptake can be achieved. The phagocytic uptake of the systemic delivery of drug loaded vesicular carriers provides an efficient means for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects. This system reduces the cost of therapy by bioavailability improvement of medication, especially in case of poorly soluble drugs. They can incorporate both hydrophilic and lipophilic drugs. This system delays drug elimination of rapidly metabolizable drugs and functions as sustained release system. Vesicular drug delivery system solves the problem of drug instability, insolubility and rapid degradation^{7,8}. Consequently, a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes, pharmacosomes, bilosomes and emulsomes have been developed. In this article, an attempt has been made to discuss various types of vesicular drug delivery systems with special emphasis on

their bioavailability enhancement. Various vesicular carriers used for bioavailability enhancement are classified as:

- A. Lipoidal Biocarriers
- B. Non-lipoidal Biocarriers

Table 1: Types of vesicles for bioavailability enhancement

Lipoidal biocarriers for bioavailability enhancement	
1. Liposomes	2. Pharmacosomes
3. Transferosomes	4. Emulsomes
Non-lipoidal biocarriers for bioavailability enhancement	
1. Niosomes	2. Bilosomes

LIPOIDAL BIOCARRIES FOR BIOAVAILABILITY ENHANCEMENT

Liposomes

Liposomes are the microscopic lipid vesicles ranging from 20 nm to several micrometers in size. These are

composed of one or several lipid membranes surrounding discrete aqueous compartments⁶. These vesicles can encapsulate water soluble drugs in their aqueous space and lipid soluble drugs within the membrane. Depending upon the gel-liquid crystalline transition temperature of phospholipids (i.e., the temperature at which acyl chains melt), liposomal membrane can attain varying degree of fluidity at ambient temperature. Due to their biocompatibility and biodegradability, liposomes and nanoliposomes are being used in applications ranging from drug and gene delivery to diagnostics, cosmetics, long-lasting immunocontraception and food nanotechnology. Liposomes stabilize the encapsulated materials against a range of environmental and chemical changes, including enzymatic and chemical modification, as well as buffering against extreme pH and temperature. Liposomes easily improve the bioavailability of drug molecules having poor solubility and permeability^{9,10}. The drugs incorporated in liposomes for bioavailability enhancement are depicted in Table 2.

Table 2: Drugs incorporated in liposomes for bioavailability enhancement

Drug	Composition	Methods	Applications	Ref
Pentoxifylline	Phosphatidyl choline, cholesterol	Physical dispersion method	To improve the oral bioavailability and provide controlled drug release profile	11
Silymarin	Phospholipids	Ethanol injection method	To improve the oral bioavailability	12
Silymarin	Phospholipids	Ethanol injection method	Increased the bioavailability of silymarin by adopting buccal liposomal drug delivery system	13
Curcumin	Phospholipon 90G, cholesterol and PEG-GSPE	Thin layer evaporation technique	To improve the bioavailability of curcumin in plasma	14
Cyclosporine A	Soybean phosphatidylcholine, sodium deoxycholate	Thin film dispersion method	To enhance the oral bioavailability of cyclosporine A	15
Fenofibrate	Soybean phosphatidyl choline, sodium deoxycholate	Dry-film dispersing method coupled with sonication and homogenization	To enhance the oral bioavailability of fenofibrate	16

Pharmacosomes

Pharmacosomes are amphiphilic complexes of drugs (containing an active hydrogen atom) with lipids. The drugs bound either covalently, electrostatically or by hydrogen bonds to lipids. Depending on the chemical structure of the drug-lipid complex, they are defined as colloidal dispersions of drug covalently bound to lipids existing as ultrafine vesicular, micellar, or hexagonal aggregates. Similar to other vesicular systems pharmacosomes provide an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects, also reduce the cost of therapy by improved bioavailability of medication especially in case of poorly soluble drugs. Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drugs to improve their solubility, bioavailability and minimize the gastrointestinal toxicity of various drugs. So, developing the drugs as

pharmacosomes may prove to be a potential approach to improve the bioavailability of drugs and also to minimize the GI toxicity. The idea for the development of the vesicular pharmacosome is based on surface and bulk interactions of lipids with drug. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH₂, etc.) can be esterified to the lipid, with or without spacer chain^{6,17,18}. The drugs incorporated in pharmacosomes for bioavailability improvement are cited in Table 3.

Transferosomes

Transferosomes are specially optimized, ultradeformable (ultraflexible) lipid supramolecular aggregates, which are able to penetrate the mammalian skin intact. Liposomal as well as niosomal systems, are not suitable for transdermal delivery, because of their poor skin permeability, breaking of vesicles, leakage of drug, aggregation and fusion of vesicles. To overcome these

problems, a new type of carrier system called "transfersome" has recently been introduced, which is capable of transdermal delivery of low as well as high molecular weight drugs²². Each transfersome consists of at least one inner aqueous compartment, which is surrounded by a lipid bilayer with specially tailored

properties, due to the incorporation of "edge activators" into the vesicular membrane. Surfactants such as sodium cholate, sodium deoxycholate, span 80 and Tween 80, have been used as edge activators²³. The drugs incorporated in transfersomes for bioavailability enhancement are listed in Table 4.

Table 3: Drugs incorporated in pharmacosomes for bioavailability enhancement

Drug	Composition	Methods	Applications	Ref
Aceclofenac	Phosphatidyl choline and dichloromethane	Conventional solvent evaporation technique	To improve the water solubility, bioavailability and minimize the gastrointestinal toxicity	19
Diclofenac	Phosphatidyl choline and dichloromethane	Conventional solvent evaporation technique	To improve dissolution and reducing the gastrointestinal toxicity of drug	17
Diclofenac	Phosphatidyl choline and dichloromethane	Conventional solvent evaporation technique	To improve the water solubility which results in improved dissolution and lower gastrointestinal toxicity	20
Aspirin	Phosphatidyl choline and dichloromethane	Conventional solvent evaporation technique	To improve the solubility, bioavailability and dissolution of aspirin	21

Table 4: Drugs incorporated in transfersomes for bioavailability enhancement

Drug	Composition	Methods	Applications	Ref
Curcumin	Tween 80, span 80 and phosphatidyl choline	Hand shaking method	To improve the oral bioavailability of curcumin	24
Sertraline	Span 80, soya lecithin and carbopol 940	Rotary evaporation and sonication method	To enhance the permeation of the sertraline through the skin which enhances the bioavailability	25
Insulin	Soyabean phosphatidyl choline and sodium cholate	-	To enhance the bioavailability of insulin	26

Emulsomes

The emulsome nanocarrier technology is a lipid-based drug delivery system designed to act as a carrier for drugs with poor water solubility. In emulsomes, the internal core is made up of fats and triglycerides, which are stabilized in form of o/w emulsion by addition of high concentration of lecithin. Emulsomes have the characteristics of both liposomes and emulsions. By virtue of solidified or semisolidified internal oily core, it provides better opportunity to load lipophilic drugs in high concentration, simultaneously a controlled release can also be expected and these also have the ability to encapsulate water soluble medicaments in aqueous compartments of surrounding phospholipid layers²⁷. These systems are often prepared by melt expression or emulsion solvent diffusive extraction methods²⁸. Emulsomes protect the drug from harsh gastric environment of stomach before oral administration because the drug is enclosed in the triglyceride lipid core hence increases the solubility and bioavailability of poorly aqueous soluble drugs. As they are composed of lipid core hence used to develop oral controlled delivery of drug. They are economical alternative to current commercial lipid formulations because they reduce the dosing frequency of drugs. Emulsomes-based system showed excellent potential for targeting also²⁹. The formulations could significantly modify providing prolonged action at comparatively low drug doses thereby reduction in the toxicity problem due to complimentary localization of the drug in target cells³⁰. Emulsomes may enhance bioavailability of drugs by changing the biochemical

barrier functions of the GI tract as it is clear that the lipids and triglycerides, which are incorporated in emulsomal preparation may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump and may also reduce the extent of enterocyte-based metabolism³¹. This is a new emerging drug delivery system and therefore could play an essential function in the effective treatment of life-threatening viral infections and fungal infections such as hepatitis, HIV, Epstein-Barr virus, leishmaniasis, etc³⁰⁻³². Kaiser Raza et al prepared dithranol loaded emulsomes with enhanced biocompatibility, efficacy and stability in treatment of psoriasis³³. Paliwal R et al developed and evaluated methotrexate (MTX), an anticancer drug loaded emulsomes for oral lymphatic delivery. The relative bioavailability of MTX was enhanced nearly 5.7 times with optimized emulsomal formulation when compared to plain MTX solution with higher uptake and longer residence time of MTX molecules in lymphatics. Thus, emulsome could be used as lymphotropic carrier for delivery of bioactive(s) and hence for bioavailability enhancement of drugs³⁰.

NON-LIPOIDAL BIOCARRIES FOR BIOAVAILABILITY ENHANCEMENT

Niosomes

These can enhance the bioavailability of encapsulated drug and also provide the drug release in a controlled manner for prolonged period of time³⁴. Niosomes are novel surfactant vesicles, which are microscopic lamellar structures of size range 10-1000 nm formed on admixture



of non-ionic surfactant of alkyl or dialkylpolyglycerol ether class and cholesterol with subsequent hydration in aqueous media^{35,36}. The properties of non-ionic surfactant vesicles can be modified by incorporation of various ingredients into the membrane, for e.g., cholesterol imparts rigidity and orientational order to the niosomal bilayer resulting in stable and less leaky vesicles^{34,36}. Charge inducing agents like dicetyl phosphate, diacylglycerol and stearylamine provide electrostatic stabilization of vesicles and thus show increased entrapment efficiency of vesicles³⁴. Niosomes are also known as amphiphilic vesicles allow the encapsulation of hydrophilic drug in the core cavity and hydrophobic drugs in non-polar region within the bilayer³⁵. The vesicles act as a depot and release the drug in controlled manner³⁷.

The therapeutic performance of drug molecules can be improved by delayed clearance from transmission, protecting the drug from biological environment thus providing targeted drug delivery. These can be prepared by various methods such as ether injection method, hand shaking method, thin film hydration method, sonication, microfluidization, multiple membrane extrusion method, reverse phase evaporation and bubble method. They provide enhanced drug concentration at the site of action after oral, parenteral and topical administration, thus minimize the side-effects. They release the drug by diffusion controlled mechanism³⁸. The drugs incorporated in niosomes for the improvement in bioavailability are enlisted in Table 5.

Table 5: Drugs incorporated in niosomes for bioavailability enhancement

Drug	Composition	Methods	Applications	Ref
Acetofenac	Span 20, 60 and cholesterol	Ether injection technique	To enhance the bioavailability	39
Celecoxib	Span 60, 80; cholesterol and phosphatidylcholine	Thin film hydration technique	Provides prolonged drug release and improved site specificity of drug	40
Acetazolamide	Span 40, 60 and cholesterol	Reverse phase evaporation and thin film hydration technique	Improved the low corneal penetration and bioavailability of acetazolamide	41
Brimonidine tartarate	Span 20, 40, 60, 80, cholesterol; HPMC K 15 M and carbopol 940	Thin film hydration technique	Improved the ocular bioavailability of brimonidine tartarate for the treatment of glaucoma	42
Cefuroxime axetil	Span 40, 60, 80, cholesterol and stearyl amine	Hand shaking method	Prolonged the existence of drug in systemic circulation and increased the bioavailability	43
Gliclazide	Span 60 and cholesterol	Thin film hydration technique	To improve the oral bioavailability and prolonged drug release	44
Griseofulvin	Span 20, 40, 60; cholesterol and dicetyl phosphate	Thin film hydration technique and ether injection technique	Improved the oral bioavailability and provided prolonged drug release	45
Minoxidil	Brij 52, 76; span 20, 40, 60, 80, cholesterol and dicetyl phosphate	Thin film hydration technique	Improved the low skin penetration and bioavailability of minoxidil	46
Ofloxacin	Span 60 and cholesterol	Thin film hydration technique	To improve the low corneal penetration and bioavailability of ofloxacin	47
Orlistat	Span 60 and cholesterol	Reverse phase evaporation technique	To improve the oral bioavailability, stability and provided sustained drug release	48
Paclitaxel	Tween 20, 60; span 20, 40, 60; brij 72, 76, 78; cholesterol and dicetyl phosphate	Thin film hydration technique	To increase the oral bioavailability of paclitaxel	49

Bilosomes

Bilosomes are the novel innovative drug delivery carriers consist of deoxycholic acid incorporated into the membrane of niosomes²⁷. As conventional vesicles (liposomes and niosomes) can cause dissolution and undergo enzymatic degradation in gastro intestinal tract but incorporation of bile salts (commonly used as penetration enhancers) in niosomal formulation could stabilize the membrane against the detrimental effects of

bile acids in GI tract. These bile salt stabilized vesicles are known as bilosomes^{27,50}. Bilosomes show various advantages including biocompatibility as they are produced from naturally occurring lipids. Bile salts along with lipid content increase the bioavailability of enclosed bioactive substance and act as penetration enhancers²⁷. Bilosomes have been found to increase the bioavailability of drugs as they can readily absorbed through small intestine to the portal circulation (hepato circulation). Through this circulation they approach to liver and

release the drug, so also found to be an effective tool in drug targeting to liver⁵¹. This delivery system exhibits inherent adjuvant properties when associated with an antigen. These allow only small quantity of an antigen to be effective and both cellular and humoral immune responses can be induced²⁷. Shukla et al showed that HBsAg loaded bilosomes produced both systemic as well as mucosal antibody responses upon oral administration⁵². Daisy Arora et al developed and characterized mannosylated bilosomes loaded with Hepatitis B surface antigen for dendritic cell targeting to provide enhanced bioavailability with extended humoral, cell mediated and mucosal immune responses⁵⁰.

CONCLUSION

Vesicular drug carriers have been realized as a useful means in today scenario because they are of great significance in the bioavailability enhancement of drugs as it is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug. This system has the potential to solubilize varying quantities of poorly water soluble drugs with the help of lipids, protect the drugs from harsh GI environment and prolongs the existence of drug in systemic circulation. Drugs can be successfully delivered using lipoidal biocarriers such as liposomes, transferosomes, pharmacosomes, and emulsomes and non lipoidal biocarriers such as niosomes and bilosomes. Vesicular drug delivery system has been thrived as a useful tool in formulation, development and research for the improvement of drug solubility, oral absorption, and hence bioavailability.

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