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RESEARCH ARTICLE

LIPID BASED DRUG DELIVERY SYSTEMS: A STRATEGY FOR ENHANCING THE ORAL BIOAVAILABILITY OF POORLY WATER-SOLUBLE DRUGS

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ABSTRACT

The poor oral bioavailability of manydrugs is mainly due to the poor aqueous solubility, chemical instability and preabsorptive metabolism. Numerous approaches have been developed for enhancement of oral bioavailability and are currently in the clinical application. Even though, some drugs do not meet the required clinical application due to the patient compliance and ineffective therapeutic levels. Vesicular delivery systems are considered as alternative delivery for the enhancement the bioavailability of this category of drugs. The enhanced bioavailability of the liphophilic drugs from the vesicular systems mainly due to the increased effective surface area of the drug in the presence of lipids, surfactants and co surfactants, enhanced lymphatic uptake, altered gastric motility and by virtue of their small particle size. Extensive literature is available for the properties, applications, and preparation and evaluation methods. This review mainly dealt with the reported drug loaded various vesicular systems such as liposomes, niosomes, lipid nanoparticles, self-emulsifying delivery system, nanosuspensions.

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INTRODUCTION

Oral route of administration of drugs is the preferred choice of drug delivery, principally due to better patient compliance, ease of administration, and cheaper in terms of cost of production. The oral bioavailability and thus the efficacy, is an indication of the solubility of drug in the gastrointestinal fluids and its intestinal membrane permeability (Lipinski, 2002). Earlier, lower bioavailability of oral dosage forms was only considered to be the aspect of physicochemical properties of the drug. In later phase due to advancement in technologies of drug delivery systems, numerous biochemical, biological, and receptors level interactions came into light as causes for such experimental results (Palmer, 2003). The prevalent application of combinatorial chemistry and high-throughput screening in the process of drug discovery during the period of past two decades has made new molecular entities (NME) highly insoluble in aqueous media.

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Orally administered drugs are obliged to dissolve in gastrointestinal (GI) fluids preceding their absorption into the body (Prajapati and Patel, 2007). In view of the fact that in many instances the drug dissolution step is proved to be the rate limiting step, suitable formulation design can be a functional approach to improve the dissolution and thus the oral bioavailability of such molecules. The drug dissolution in the gastrointestinal tract (GIT) will be influenced by the characteristics of the GI components like volume of GI fluids, pH, surfactant concentration, and also the physico-chemical properties like pKa and log P of the drug. Numerous factors like molecular size, lipophilicity of the drug, in addition to its affinity to influx or efflux transporter proteins. Modification physicochemical properties like particle size reduction, salt formation may always do not work due to the limitations. In case of salt forms problems like feasibility of salt formation of neutral compounds, form conversion from salt to original acid or base form may lead to aggregation in GIT. Particle size reduction is not advantageous in case of very fine powders with poor wetting properties. Various strategies like solid dispersions (Narendar *et al*., 2016, Carmen *et al*., 2015), cyclodextrins (Ettireddy *et al*., 2017), buccal delivery (Palem *et al*., 2011; Chinna *et al*., 2016), gastro retentive delivery (Desai and Bolton, 1993; Reddy *et al*., 2012), floating tablets

(Dudipala *et al,* 2011) and nanoparticulate delivery systems were employed to overcome these issues concerned to poor bioavailability (Pitta *et al*., 2018). In this review, attempts were made to discuss about the strategies to enhance the oral bioavailability of drugs using various liposomal drug delivery systems such as liposomes, niosomes, lipid nanoparticles (solid lipid nanoparticles and nanostructures lipid carriers), and nanosuspensions and self-emulsifying drug delivery systems. Previously, some reports are published for the development of various nanodelivery systems for independent drugs such as Candesratancilexetil (Kishan, 2017), Zaleplon (Doodipala *et al*., 2016)

Liposomes: Liposomes are spherical shape bilayervesiclesobtainedfrom the combination of cholesterol and phospholipids (Allen, 1997). They are the most promising drug delivery systems owing to their physicochemical and biocompatibility properties. The physical and stability properties of liposomes differ considerably and depends on lipid composition, surface charge, size, and the method of preparation used for making (Abolfazl *et al*., 2013). Furthermore, the rigidity and the charge of the bilayer membrane are mainly influenced by the composition of the bilayer (Karthik *et al*., 2012). It has been also reported that,saturation and source of the phosphatidylcholine (PC) species could impact the vesicle rigidness. Unsaturated PC from natural source, like egg or soybean phosphatidylcholine, resulted in much more permeable and less stable bilayers, while the saturated phospholipids with long acyl chains (dipalmitoylphosphatidylcholine etc.,) form a rigid and impermeable vesicular construct (Shehata *et al*., 2008). Liposomes and prolipiosmes are used to improve the oral bioavialbility by increasing the residence time in the gastro intestainal tract (GIT), surface modification promote uptake and avoiding first-pass metabolism. Various reported liposome and proliposome formulations are presented in Table 1.

Niosomes: Niosomes are multi-lameller structuresimilar to liposomes and are composed of non-ionic surfactant (Cosco *et al*., 2009; Rampal *et al*., 2011).Niosomes are now widely studied as an alternative approach to liposome. There are different types of surfactants thathave the ability to form vesicles, entrap and retain the hydrophilic and hydrophobic solute particles. Theyprimarily consist of two types of components, i.e., nonionic surfactant and the additives. The additives used in the preparation of niosome are cholesterol and the charged molecules (Toshimitsu *et al*., 1994). Cholesterol is a critical component of the cell membrane and its presence improves the rigidity of the bilayer. The presence of cholesterol in the membrane also plays an important role in imparting fluidity and permeability to the cell membrane. As a carrier system for both small and large molecule, niosomes protects the drug molecules from premature degradation and inactivation due to untoward immunological and pharmacological effects (Aranya *et al*., 2003).Niosomehave also been used to overcome challenges with drugsolubility, stability and degradation. Table 2 describes the various reported niosomal formulations.

Lipid nanoparticles: Solid lipid nanoparticles and nanostructured lipid carriers are the extensively used lipid based nanoaprticles. Solid lipid nanoparticles (SLNs) are sub-micron colloidal carrier nanoparicles with particle size range from 50-1000 nm (Muller, 2000). SLNs are mainly composed of solid lipids, which are stable as solid at room temperature. Stability and aggregation of particles are reduced by the incorporation of surfactant and co-surfactant, respectively. The commonly used solid lipids include triglycerides (Dynasan-112, Dynasan-114, Dynasan-116 and Dyanasan-118) mixed glycerides (Compritol ATO 888, glyceryl monbehenate) and monoglycerides (stearic acid, glyceryl monostearate) (Mukherjee *et al*., 2009). SLNs have the advantages of biocompatibility, reduced toxicity, used for incorporation of both hydrophilic and liphophilic drugs and enhanced oral bioavailability and also pharmacodynamicacticivity (Gorre *et al*., 2017). The enhanced oral bioavailability of drugs might be due to enhanced surface area by the addition of surfactants, by virtue of small particle size, presence of lipids promote the gastric motility and also promote the lymphatic transport by reducing the first-pass metabolism and also tumor targeting (Narendar and Goverdhan, 2018). Drug loaded SLNs for enhancement of oral BA are showed in Table 3.

Nanostructured lipid carriers: Nanostructured lipid carriers (NLCs) are considered as modified form of solid lipid nanoparticles. The difference between the SLNs and NLCs is replace one part of the solid lipid with liquid lipid and observed for improved properties (Muller *et al*., 2002). In general, the NLCs made of 1:3 to 1:4 ratio of liquid lipid to solid lipid and along with surfactants and cosurfactants. NLCs minimize drug expulsion, increase the drug encapsulation and stability of loaded drug compared with SLNs (Radtke *et al*., 2005). Preparation of NLCs mainly involves in the selection of liquid lipid and solid lipid and their respective ratios, selection of surfactants and cosurfactants, in some instances miscellaneous agents such as viscosity modifiers, antioxidants and preservatives (Ana *et al*., 2016).NLCs like SLNs also help in controlled and sustained drug delivery (Westesen *et al*., 1997), increased gastric residence time (Garcia-Fuentes *et al*., 2003). Various drugs loaded NLCs are depicted in Table 4.

Nanosuspension: Nanosuspensions are submicron colloidal dispersions of nano-sized drug particles stabilized by the surfactants (Muller *et al., 2000)*Nanosuspensions consists of poorly water-soluble drug without any matrix material suspended in dispersion (*Rabinow, 2004).*Nanosuspensionsare useful for molecules with poor solubility and/or poor permeability, which poses a significant challenge for formulators. The reduction in particle size gives nanosuspensions a possibility to administer drugs intravenously. These suspensions can also be lyophilized to obtain a solid matrix. It also has the advantages of liquid formulations over others (Liversidge and Cundy, 1995). They are suitable for hydrophilic drugs, higher drug loading is possible, the dose of the active can be reduced, aid in enhancing the physical and chemical stability of drugs (Karri *et al*.,2015) and also provides passive drug targeting (*Grau et al., 2000; Keck and Müller, 2006)*. List of drugs developed as nanosuspensions are reported in Table 5.

Self-emulsifying drug delivery systems: Self-emulsifying drug delivery systems (SEDDS) are one of the approaches to improve the oral bioavailability of poorly soluble drugs by presenting the drug in the form of small droplets of oil and maintaining it in a dissolved state throughout its transit time in gastrointestinal tract (GIT) (Pouton, 1985). The composition of SEDDS consists of oil and surfactant. They can formoil-in-water emulsions upon the natural agitation provided within the gastrointestinal movements.

Table 1. List of reported liposomes for improved oral bioavailability

Drug	Type of Formulation	Components	Pre-Clinical Study/ Subject	Outcome	Reference
Vincristine	Liposome	Dihydrosphingomyelin	In vivo/ Rats	Increase in half-life and residence time	Johnston *et al*., 2007
Dehydrosilymarin	Proliposome	Soybean phospholipids, cholesterol	In vivo/ Rabbits	2.28-folds increase in bioavailability	Chang *et al*., 2011
Zaleplone	Proliposome	Soyphosphatidylcholine (HSPC) and cholesterol	In vivo/ Rats	2 to 5 fold increase in bioavailability	Karthik *et al*., 2012
RaloxifeneHCl	Proliposome	Soyphosphatidylcholine and cholesterol	In vivo/ Rats	3-fold increase in bioavailability	Ashok *et al*., 2013
Heparin	Liposome	Soyphosphatidylcholine and cholesterol	In vivo/ Rats	Bioavailability increased by 3-times	Lavanya *et al*., 2016
Valsartan	Proliposome	Dimyristoylphosphatidylglycerol sodium (DMPG) and cholesterol	In vivo/ Rats	2-fold increase in bioavailability	Nekkanti *et al*., 2016

Table 2. List of reported niosomes for improved oral bioavailability

Drug	Components	Pre-Clinical Study/ Subjects	Outcome	Reference
Aciclovir	Cholesterol, span 60, Dicetylphosphare	In vivo/ Rabbits	2-fold increase in bioavailability	Ismail *et al*., 2007
Griseofulvin	Span 20, 40, 60, cholesterol, DCP	In vivo/ Rats	Increase in MRT	Jadon *et al*., 2009
Clarithromycin	Span 20, 40, 60, and 80 and cholesterol	In vivo/ Rats	1.5-fold increase in bioavailability	Gyati *et al*., 2016
Diltiazem	Span 60 or Brij-52 wif cholesterol	In vivo/ Rats	Increased AUC	Ammar *et al*., 2017
Gliclazide	Span 60 and cholesterol	In vivo/ Rats	Reduction in blood glucose level	Tamizharasi*et al*., 2009

Table 3. Various drug loaded solid lipid nanoparticles

Drug	Lipid	Outcome	Reference
Baicalin	Stearic acid	Enhanced bioavailability	Hao *et al*.,2012
Carvedilol	Poloxamer	Improved BA	Vinay Kumar *et al*., 2012
Raloxifene hydrochloride	Compritol 888 ATO	Bioavailability enhanced	Burra *et al*., 2013
Nisoldipine	Tripalmitate	Improved BA	Narendar and Kishan, 2015
Rosuvastatin calcium	Dynasan 114, Dynasan116, Dynasan 118	Improved BA	Suvarna *et al*., 2015
Felodipine	Dynasan 114, 116 and 118	Improved BA	Usha *et al*., 2015
Lacidipine	Dynasan 114, 116 and 118	Improved oral BA	Sandeep *et al*., 2016
Candesartan cilexetil	Dynasan 114, Dynasan116, Dynasan 118	Improved BA	Reddy and Veerabrahma, 2016
Rosuvastatin calcium	Dynasan 112	Improved BA	Dudhipala and Veerabrahma, 2017
Zaleplon	Dyansan 114	ImrovedbA	Reddy and Janga, 2017
Olmesartanmedoxomil	GMS and SA	Improved BA	Arun *et al*., 2018

Table 4. Various drug loaded solid lipid nanoparticles

Drug	Lipid	Outcome	Ref
Chlorambucil	Stearic acid and oleic acid	Improved drug action	Sharma *et al*., 2009
Curcumin	Soylecithin and Poloxamer 188	11.93-foldbioavailability enhancement	Min Fang *et al*., 2012
Carvedilol	Stearic acid and Oleic acid	3.95-foldbioavailability enhancement	Mishra *et al*., 2016
Raloxifene hydrochloride	Glyceryl monostearate and Capmul MCM C8	3.57-fold bioavailability enhancement	Shah *et al*., 2016
Vincristine sulfate	Hyaluronic acid	1.8-foldbioavailability enhancement	Xuan *et al*., 2017
Atorvastatin	Capryol, lecithin	3.6-foldbioavailability enhancement	Mohammed *et al*., 2017
Nisoldipine	Dynasan 114	Improved drug action	Narendar *et al*., 2018

Table 5. Nanosuspensions of drugs as oral delivery vehicle

Drug	Components	Pre-Clinical Study/ Subject	Outcome	Reference
Curcumin	SLS and PVP	In vivo/ Rats	6.8-foldincrease in bioavailability	Gao *et al*., 2016
Efaverinz	Sodium lauryl sulfate and PVP K30	In vivo/ Rats	2.19-fold increase in bioavailability	Patel *et al*., 2014
Furosemide	PVP	In vivo/ Rats	1.38-fold increase in bioavailability	Bhanu and Malay, 2014
Felodipine	PVA and HPMC	In vivo/ Rats	Enhanced AUC	Sahu and Dasu, 2014
Cefdinir	SLS and PVP	In vivo/ Rats	1.75-fold increase in bioavailability	Thota *et al*., 2014
Cefdinir	Zirconium oxide	In vivo/ Rats	3-foldincrease in bioavailability	Sawant *et al*., 2016
Curcumin	SLS and PVP	In vivo/ Rats	4.2-foldincrease in bioavailability	Li *et al*., 2016
Olmesartnmedoxomil	SLS	In vivo/ Rats	2.45-foldincrease in bioavailability	Nagaraj *et al*., 2017

Table 6. List of reported SEDDS formulations

Drug	Components	Size (nm)	Outcome	Reference
Cinnarizine SNEDDS	Sesame oil/ Cremophor RH 40 Oleic acid Brij 97 (Co-surfactant) Ethanol	28.1 ± 0.96	Approximately increased by 25% compared to conventional tablets	Larsen *et al.,* 2012
Silymarin SMEDDS	Ethyl linoleate/Tween 80/ethyl alcohol	10-20	48.82-fold compared to drug suspension	Iosio*et al.,* 2011
Rosuvastatin calcium SNEDDS	Cinnamon oil /labrasol; CapmulMCMC8	120-170	2.45-fold compared to drug suspension	Balakumar*et al*., 2013
Curcumin SMEDDS	Ethyl oleate/ emulsifier OP + Cremorphor EL (1:1) ,co-surfactant (PEG 400)	21.4 ± 1.5	3.86-fold compared to drug suspension	Jing *et al.,* 2009
Amiodarone and talinolol SNEDDS	Triglyceride (trilaurin for amiodarone and tricaprin (for talinolol) / polyoxyl 40-hydroxy castor oil, Tween 20, and Span 80 and lecithin	10±0.03 (for Amiodarone) 45±0.07 (for tricaprin)	2 and 3 fold increase for Amiodarone and Talinolol respectively	Anna *et al.,* 2013
Lercanidipine	Capmul and Tween 80	147 ±3	Enhanced drug release	Kalakuntla*et al.,* 2012
Zaleplon SNEDDS powder	Neusilin US2	138 ±6	3.5-fold	Yadav *et al.,* 2013

In such a system, the lipophilic drug is incorporated in solution, in small droplets of oil in solution from. The large interfacial area generated by these smaller size of droplets, facilitates drug diffusion into intestinal fluids (O'Driscoll 2002). Additionally increased fraction of absorption by lymphatic transport, avoids hepatic first-pass metabolism of drugs which are prone to extensive metabolism (Cuiné *et al*., 2007). The SEDDS are the delivery systems which were engineered through a specific combination of selected lipids and emulsifiers in a specific ratio.

In addition, for a specific drug a particular SEDDS should be developed using different excipients with different physicochemical properties to improve overall hydrophilicity of the drug (Kossena *et al*., 2005). On digestion in GIT lipid excipients form different colloidal species (vesicles, micelles and liquid crystalline phases) in the intestinal lumen which further had an impact on dissolution and absorption of drug co-administered (Porter *et al*., 2008). Many of the excipients were reported to aid in lymphatic bypass and also considerably reducing the access to pre-systemic transporter mediated drug efflux like P-glycoprotein (P-gp) (Zhang *et al*., 2003). Table 6 presents the list of different drug loaded SEDDS formulations.

Conclusion

The enhancement of oral bioavailability of drugs mainly depends on aqueous solubility and permeability properties. Various oral drug delivery forms,such as, buccal delivery, floating delivery, etc.approaches have been developed for the enhancement of bioavailability.Some of the drug delivery technologiesenhancing oral bioavailability have been successfully commercialized and many other promising technologies are currently under investigation. Nevertheless, in the coming years, the technologies to enhance oral drug bioavailability of will see tremendous growth to help scientists develop new and improved drug products for better health outcomes. Furthermore, these technologies can also be used to improve the drug formulation and/or delivery of existing and approved active pharmaceutical ingredients for their respective indications or even a new indication which is certainly a possibility with advancement in drug delivery and development technologies.

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