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A Review on Some Formulation Strategies to Improve the Bioavailability of Drugs with Low Permeability and High Solubility (BCS III)

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Abstract

The biopharmaceutical classification system (BCS) has become an increasingly important tool for world-wide regulation of drug products. Regarding improvement of bioavailability BCS class II, III, and IV; formulation approaches can be taken into considerations, though present researches are focussed mainly on BCS II (drugs with low solubility, high permeability), but talking about BCS III they too suffer poor oral bioavailability due to their low permeability through lipid membranes and are mostly subjected to parenteral route for administration. Here we have discussed about some formulation strategies to enhance oral bioavailability of BCS class III drugs which have shown promising abilities in enhancing permeability of drug through gastrointestinal tract.

Keywords: BCS III, oral bioavailability, formulation strategies.

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1. Introduction

Oral administration of drug still remains the preferred one among other routes, for the majority of clinical applications. Some drugs have ideal characteristic-features for good absorption to occur throughout the gastrointestinal (GI) tract, whereas absorption of some drugs by GI route is limited. The two rate limiting steps in absorption of a drug via GI tract involve dissolution and intestinal permeability. For regulation of drug products world-wide, the biopharmaceutical classification system (BCS) has become an increasingly important tool, since its inception in 1995 [1]. The classification system, introduced by the Food and Drug Administration (FDA), has categorized drugs in terms of their solubility and intestinal permeability [2]. The BCS has generated noteworthy impact on the global pharmaceutical sciences arena, in drug discovery, development, and regulation [3]**.** According to BCS classification drugs can be categorized into four groups namely class I (drugs with high solubility and high permeability), class II (drugs with low solubility and high permeability), class III (drugs with high solubility and low permeability)and class IV (drugs with low solubility and low permeability). On the WHO list, 61 out of the 130 orally administered drugs could be classified with certainty. Twenty-one (84%) of these belong to class I, 10 (17%) to class II, 24 (39%) to class III and 6 (10%) to class IV (poorly soluble, poorly permeable) [3]**.**

1.1 BCS III

Class III drugs have low permeability and high solubility. For this class of drug, rate and extent of drug absorption may be variable, in case of quick dissolution, variability can be attributed to gastrointestinal transit and contents and membrane permeability [4]**.**

Ionization of a drug in intestinal fluid may result in its low oral bioavailability. During a pharmacokinetic phase drug transport represent a compromise between the increased solubility of the ionized form and increased ability of non-ionized form of drug to enter the lipid bilayer of cell membrane, many ionic species are present in cell membranes that can repel or bind ionic drugs, also ionic drugs are more hydrated and so are bulkier than non- ionic drugs [5]. Drugs having greater probability of ionization e.g. aminoglycoside antibiotic like gentamicin has five basic amino groups, and chances of that the all will remain unionized simultaneously is quite low, so oral absorption of this drug is low and to attain therapeutic blood concentration, it is to be administered parenterally **[6].**

In literature it is mentioned that since the permeability of BCS class III drugs is low so this group is not sensitive to formulation factors for enhancing oral bioavailability [7]. Many formulation strategies are there to enhance the oral bioavailability of this class of drug, basic concepts include imparting lipophilic character to this hydrophilic drugs, increasing their retention time in GI tract, other approaches include use of penetration enhancers. Here mainly the former two concepts are being discussed.

2. Formulation strategies

The different formulation strategies for enhancement of oral bioavailability of BCS class III drugs overhere is categorized into (a) formulations imparting lipophilic character to drug and (b) formulations that increase gastric retention time of drug.

2.2 Formulations imparting lipophilic character to drug

2.2.1 Double emulsion

Multiple emulsions are complex systems, which can be termed as "emulsions of emulsions" [8]. Among multiple emulsions, a double emulsion is the simplest, in which a primary emulsion is re-emulsified into a dispersion medium. These formulations have proved to be promising oral bioavailability enhancers of protein, peptidomimetic or BCS class III drugs, as these formulations may directly get absorbed as oil droplets from intestine [9]**.** Since there is no organic solvents required in their preparation so, these emulsions are also safer to administer and easier to prepare [10]. In double emulsions the drug is present in the inner hydrophilic core which serves as a protection and storage chamber. Due to their instability during shelf-life their industrial application is limited.

Koga et al., 2010, developed multilayer emulsions capable of enhancing intestinal absorption calcein as a model BCS class III compound, they reported that absorption-enhancing effects of w/o/w emulsions on intestinal calcein absorption in rats was significantly higher than that than that of the calcein control [9]**.**

2.2.2 Niosomes

Niosome is described as a class of molecular cluster formed by self-association of non-ionic surfactants in an aqueous phase, their unique structure presents an effective novel drug delivery system with ability of loading both hydrophilic and lipophilic drugs [11]. Niosomes can prove to be effective delivery system in enhancing oral bioavailability of BCS class III group of drugs. Attai et al., 2007, prepared acyclovir niosomes which were unilamellar spherical in shape, the nonionic surfactant vesicles were prepared by the conventional thin film hydration method, it is reported that niosomal formulation exhibited

significantly retarded release compared with free drug whereas the *in vivo* study performed by them revealed that the niosomal dispersion significantly improved the oral bioavailability of acyclovir by more than 2-fold increase as compared to the free drug solution [12].

2.2.3 Self- double emulsifing systems (SDEDDS)

SDEDDS are formulations that can spontaneously emulsify in the gastrointestinal aqueous fluid forming water-in-oil-in-water (w/o/w) double emulsions with drugs encapsulated in the inner aqueous core. SDEDDS are stable systems, as compared to conventional thermodynamically unstable double emulsions. SDEDDS can be directly filled into soft or hard gelatin capsule which are easy to administer and storage [13].

Formularion of pidotimod SDEDDS is reported by Qi et al., 2013, *in vivo* study results indicated that Plasma concentration–time profiles in rats dosed with SDEDDS showed 2.56-fold increased absorption of pidotimod, compared to the pidotimod solution [13].

2.2.4 Liposomes

The first liposomes i.e. closed bilayer phospholipid systems, were described in 1965 and soon were proposed as drug delivery systems. Over almost 5 decades the pioneering work of countless liposome researchers led to the development of important technical advances such as extrusion for homogeneous size, remote drug loading, long-circulating (PEGylated) liposomes, triggered release liposomes, liposomes containing nucleic acid polymers, ligand-targeted liposomes and liposomes containing combinations of drugs. These advances have led to numerous clinical trials in delivery of anti-cancer, anti-fungal and antibiotic drugs, gene medicines, and anesthetics and anti-inflammatory drugs [14].

Manconi et al., 2013 designed metformin-loaded liposomes coated with chitosan cross-linked with the biocompatible β-glycerolphosphate, the *in vivo* oral bioavailability performed by them suggested that the microcomplexes are effective carriers of the highly water-soluble antihyperglycaemic drug, thus, allowing its controlled delivery and improved oral availability [15].

2.2.5 Solid lipid nanoparticles

The development of liposomes and polymer-based nanoparticles was followed by solid lipid nanoparticles (SLN) which were introduced in the early 1990s as an nontoxic drug and efficient carrier system made up of natural lipids that are solid at body temperature,

physiological lipids and biocompatible surfactants are commonly used to prepare SLN dispersions, making them well tolerated in living systems and so from SLN degradation, no acute toxic effects are expected [16].

In a research work solid dispersion of atenolol was developed with fatty excipients to modify the release and enhance intestinal permeability of the drug the results of *in vitro* permeability revealed that drug-phosphotidylcholine solid dispersion significantly enhanced percentage permeation in comparison with the pure drug, which could be attributed to higher lipophilicity obtained by incorporation of the drug within the solid lipid dispersion, it is also reported that as the amount of phospholipids increased relative to that of drug, the percentage of permeated drug was also increased [17].

2.3 Formulations that increase gastric retention time of drug

Gastroretentive formulations have capability of remaining in the gastric region for long periods and hence significantly can prolong the gastric retention time (GRT) of drugs. Over the last few-decades, several gastroretentive drug delivery approaches are designed and developed, including: sinking systems that is retained in the bottom of the stomach, low floating systems that causes buoyancy in gastric fluid, mucoadhesive systems that acts by bioadhesion to stomach mucosa, others include unfoldable, swellable, superporous hydrogel systems, magnetic systems etc [18].

A gastroretentive sustained release formulation of acyclovir prepared by combination of swelling and mucoadhesive approach was found to be retained in the upper part of the gastrointestinal tract for 480 minutes whereas a immediate release tablet was retained for only 90 minutes as measured *in-vivo*, comparing the relative bioavailability,that of gastroretentive formulationwas 261% of the immediate release formulation [19].

Metformin Hydrochloride is reported to be absorbed mainly in upper part of GIT. It is having narrow absorption window and high water solubility, and it would be more beneficial to retain the drug in stomach for prolonged duration so as to achieve maximum absorption and better bioavailability, in a study it is indicated that the gastroretentive tablets prepared by using sodium alginate and sodium carboxymethylcellulose can successfully be employed as a onceaday oral controlled release drug delivery system [20].

It is mentioned about formulation of gastroretentive floating tablet of atenolol to increase the gastric retention, to extend the drug release, and to improve the bioavailab--ility of the drug, the floating tablets were formulated by using hydrophilic polymers as Hydroxy propyl methyl cellulose (HPMC K4M and HPMC K15M), hydrophobic retardant as a hydrogenated cottonseed oil (HCSO) and sodium bicarbonate as a gas

generating agent to reduce floating lag time [21].

3. Conclusion

A number of important drugs belong to BCS class III, including antibiotics like macrolides, aminoglycosides; antihypertensives; antihyperglycemicsetc, and since oral route is the most desirable root of drug administration so it is always preferred to enhance oral bioavailability of these drugs with an intension of dose reduction. Lipid based drug delivery systems are of great importance in having capabilities of enhancement of oral absorption of lipophilic drugs, similarly imparting lipophilic character to a hydrophilic drug can help in better membrane permeability. Prolonging gastric retention time has also proved to be effective in membrane permeability enhancement of low permeability drugs.

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