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Bioavailability improvement of BCS Class II & III drugs by some formulation strategies: A Review

*Adarsh Kumar Singh[1], Gaurish Narayan Singh[2], Pranav Upadhyay[3] Rajeev Shukla[4]

[1,2,3,4] Sheat College of Pharmacy Gahani Varanasi UP India

Authors

[2]Gaurish Narayan Singh

Asst. Professor (Pharmaceutics)

[3]Prof (Dr.) Pranav Upadhyay

HOD of Pharmaceutics

[4]Prof. Rajeev Shukla

Director

Pharmaceutical Chemistry

*Corresponding Author

Adarsh Kumar

M.Pharm (Pharmaceutics)

Abstract:

Drug product regulation comes under Biopharmaceutical Classification System (BCS); it is an important tool for categories the drug products into different groups. Bioavailability of drug is major problem of BCS class II & III IV drugs due to is low solubility and low permeability therefore researchers has investigated the various formulation approaches in order to improve bioavailability. BCS class II drugs shows poor bioavailability due to its low solubility and BCS class III drugs also shows poor bioavailability due to its low permeability across the lipid membrane of cells in the body. So that BCS Class III drugs mostly given from parenteral route. This article reviewed some formulation approaches in order to improve bioavailability and which will be better for longer period of time as futuristic approach as well. This review will be able to describe comprised formulation strategies for enhancement of bioavailability.

Keywords: BCS Class II & III, Bioavailability, Permeability, Solubility, Biopharmaceutical.

1. Introduction

Oral route of administration of drug formulation is most preferred route among others. Hence, many drugs faces problem of solubility and permeability via GI tract route [1]. For clinical application, mostly oral rout is preferred for administration of drug. Through oral rout of administration of drugs, some drugs have good bioavailability due to their high solubility and high permeability whereas bioavailability of some drug shows poor bioavailability due to their limitation of solubility and permeability [2]. In this orally delivery of drug, the two main rate limiting step in drug absorption, one is solubility of drug another is intestinal permeability of drug. To regulate drug product worldwide, FDA has introduced Biopharmaceutical Classification System, according to which drugs are categorized into four categories in context with their solubility and intestinal permeability. From inception in 1995, BCS become important tool to control and regulate drug product. In the field of pharmaceutical sciences, BCS has made an impact on drug discovery and development [3]. BCS drugs are categorized in such a manner like BCS class I (high solubility & high permeability), BCS Class II (low solubility & high permeability), BCS Class III (high solubility & low permeability), BCS Class IV (low solubility & low permeability). In this review we have focused on mainly BCS class III drugs [4].

BCS Class 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]. Manyformulation 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.

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.

Formulation approaches importing lipophilic nature of drug

Double Emulsion:

"Emulsions of emulsions" is known as multiple emulsion which is very complex system. Double emulsion is one among multiple emulsion. It is simplest form of emulsion among multiple emulsion in which primary emulsion is again-emulsified into dispersion system. Double emulsion type formulation increases the absorption of oil based droplet from intestine and have provided bioavailability enhancer of BCS class III drugs such as protein and peptidomimetics [8]. These type of emulsion are always safer for oral administration because of no any addition of organic solvent during preparation and also easy to prepare. In this preparations, the drug is present in inner core of hydrophilic layer which protect and work as reservoir chamber. Although, industrial application of double emulsion is very less due to its instability during shelf life. Koga et al., 2015 formulated multiple emulsion in order to enhance bioavailability and he has found that intestinal absorption improved with this formulation [9]. They reported that double emulsion of Calcein as model drug shows intestinal absorption in rat was significantly higher than that of controlled Calcein [10].

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 performedby them revealed

that the niosomal dispersion significantly improved the oral bioavailabilityof acyclovir by more than 2-fold increase as compared to the free drug solution [12].

Self- double emulsifing systems (SDEDDS)

SDEDDS are formulations that can spontaneously emulsify in the gastrointestinal aqueousfluid 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 orhard 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].

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].

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].

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 mentionedabout formulation of gastroretentive floating tablet of atenolol to increase the gastric retention, to extend the drug release, and to improve the bioavailability 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].

Conclusion

In conclusion as many drugs comes under BCS class III drugs categories such as Aminoglocosides, Antihypertenssives, macrolides, antibiotics, antihyperglycemics etc. Since oral route is very conventional route of administration hence it is mandatory to improve bioavailability along with reduction of dose. Lipid based formulation approaches have shown great importance in drug delivery of lipophilic drugs. Similarly, drug with lipophilic in nature can be impart to as in hydrophilic in nature so that can get better permeability of membrane. Intestinal membrane permeability can be increased by making prolongation in gastric residence time so that it can produce better permeability along with better bioavailability.

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