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Bioavailiability Enhancement of BCS Class 4 Drugs: Key for Successful Formulations

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Abstract

Traditionally nearly 40% of the new chemical entities identified by pharmaceutical industry screening programmes have failed to be developed because of low solubility and low permeability which make formulation difficult or even impossible. The solubility issues complicating the delivery of many existing drugs. The various tradition and novel technique that can be used for bioavability enhancement of BCS class 4 drugs are discussed in this article. The traditional techniques discussed in this article includes use of co-solvents, hydrotopymicronization, amorphous forms, chemical modification of drug, use of surfactant, complexation .nano-nization.use of prodrug, alternation of pH, use of ppt.inhibitor solvent deposition. In case of novel drug delivery technologies depends upon the development in recent year for bio-avability enhancement of poor soluble-poor permeable are size reduction. lipid based deliven- system, micellar techniques, micro-particle techniques.

Keywords: Bio-avalibility, Nano-nization, Permeability, dissolution, therapeutic efficacy.

Contents

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1. Introduction

The traditional way of administration of drug in the form of infusion, injection, injection inhalation, topical application, oral deliver is moist convenient and preferred outre for administration of the drug due to its possibility of self administration and improved patient compliance. Oral drug delivery is the simplest and easiest way of drug administration because of acurete dosage, cheapest cost of production, greater stability, less bulky, due the development of different technologies for production of oral drug product leads the generic pharmaceutical companies to the development of bioequivalent oral dosage forms.

2. Bio-Availability

Bio-availability has been defines as relative absorption efficiency of the test dosage forms compared to standard prepration. Thus bio-availability of drug is the percentage of dose that reaches the systemic circulation after administration via. State route bio-availability depends upon several factors, drug solubility in an aqueous environment and drug permeability through lipophilic membranes any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. More than 40% new chemical entities developed in pharma-

industry are practically insoluble in water. The amount of drug reaches at receptor site it is important for to give therapeutic effect. However the poor bi-availability of drug is mejor challenge for design of oral dosage forms. The oral bio-availability depends upon factor like aqueous solubility, drug permeability ,dissolution, rate, first-pass metabolism, certain disease states involving the gutgastric molality and emptying time, drug fomulationm, interaction in the gut lumen, nowel wall and liver. The low bio-availability is the certain and most probabilistatic cause of pooor soluble and permeable.

Bioavailability Study Design

Absolute bioavailability:

Absolute bioavailability compares the bioavailability of the active drug in systemic circulation administration of drug non-intravenously i.e..after oral, rectal, transdermal, subcutaneous, or sublingual administration, and comprising the bioavailability of the same drug administered intravenously.

Relative Bioavailability:

When the systemic bioavailability of a drug after administered orally is compared with that of an oral standard of the same drug (aqueous or non aqueous solutions). It is used to characterize absorption of a drug from its formulation. The importance of solubility and permeability is especially reflected in the adoption of Biopharmaceutics Classification System (BCS) by the FDA in 2000, devised as a scientific basis to grant biowaivers for in vivo bioavailability and bioequivalence studies. The Biopharmaceutics Classification System classifies drugs into four groups: Class 1: high permeability, high solubility; Class 2: high permeability, low solubility-Class 3: low permeability, high solubility; and Class 4: low permeability, low solubility. Low bioavailability is often associated with oral dosage forms of Class 3 and 4 drugs (Class 2 to a lesser extent), i.e. drugs with low solubility, low-permeability, or both.

Objectives and Concept of BCS

The objectives of the BCS are :

a. To improve the efficiency of the drug development and review process by recommending a strategy for identifying expendable clinical bioequivalence test.
b. To recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on in vitro dissolution tests.
c. To recommend methods for classification according to dosage form dissolution along with the solubility-permeability characteristics of the drug product.

The BCS, which is based on scientific principles, presents a new paradigm in bioequivalence. According to the tenets of the BCS, certain drug products can be considered for biowaivers (i.e., product approval based on in vitro dissolution tests rather than bioequivalence studies in human subjects). At first, biowaivers were only applied to scale-up and post approval changes (SUPAC) ,but later the biowaiver principle was extended to the approval of new generic drug products. As a result, unnecessary human experiments can be avoided, and the cost of developing generic products can be significantly lowered . It provides drug designers an opportunity to manipu¬late the structure or physicochemical properties of lead candidates to achieve better "deliverability"

3. Classifications

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability . It allows for the prediction of in vivo pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes (Table 1) based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form

Table 1. The Biopharmaceutics Classification System

Class Solubility	Permeability
I High	High
II Low	High
III High	Low
IV Low	Low

The interest in this classification system stems largely from its application in early drug development and then inthe management of product change through its life cycle. In early drug development, knowledge of the class of a particular drug is an important factor influencing the decision to continue or stop its development. Therefore, an organization wishing to produce oral dosage forms will wish to limit development to molecules with high permeability. Increasingly, these considerations are incorporated from the very earliest phases, with the concept of property-based design being used in combinatorial chemistry to target production of compounds showing optimal

properties. This classification is associated with a drug dissolution and absorption model, which identifies the key param¬eters controlling drug absorption as a set of dimensionless numbers .

Absorption Number (An): Defined as the ratio of the mean residence time to mea n absorption time. It denotes the dimensionless dose/solubility ratio for the particular drug formulation. The dose/solubility ratio indicates whether the capacity of the GI fluid is sufficient to dissolve the entire dose administered.
Dissolution Number (Dn): Defined as the ratio of mean residence time to mean dissolution time.
Dose Number (D0): Defined as the mass divided by the product of uptake volume (250 mL) and solubility of drug.
Class I
The drugs of this class exhibit high absorption number and high dissolution number. The rate-limiting step is drug dissolution, and if dissolution is very rapid, then the gastric-emptying rate becomes the rate-determining step. These compounds are well absorbed, and their absorption rate is usually higher than the excretion rate. Examples include metoprolol, diltiazem, verapamil, and propranolol.
Class II
The drugs of this class have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate-limiting step for absorption except at a very high dose number. The absorption for Class II drugs is usually slower than for Class I and occurs over a longer period of time. In vitro-in vivo correlation (IVIVC) is usually accepted for Class I and Class II drugs. The bioavailability of these products is limited by their solvation rates. Hence, a correlation between the in vivo bioavailability and the in vitro solvation can be found . Examples include glibenclamide, phenytoin, danazol, mefenamic acid, nifedinpine, ketoprofen, naproxen, carbamezapine, and ketoconazole.
Class III
Drug permeability is the rate-limiting step for drug absorption, but the drug is solvated very quickly. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. If the formulation does not change the permeabil¬ity or gastrointestinal duration time, then Class I criteria can be applied Examples include cimetidine, ranitidine, acyclovir, neomycin B, atenolol, and captopril.
Class IV
The drugs of this class are problematic for effective oral administration. These compounds have poor bioavailability. They are usually not well absorbed through the intestinal mucosa, and a high variability is expected. Fortunately, extreme examples of Class IV compounds are the excep¬tion rather than the rule, and these are rarely developed and marketed. Nevertheless, several Class IV drugs do exist .Examples include hydrochlorothiazide, taxol, and furosemide.
BCS Class Boundaries
Class boundary parameters (i.e., solubility, permeability, and dissolution) are for easy identification and determination of BCS class .
Solubility:A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of water over a pH range of 1-7.5 at 37 °C
Permeability:
A drug substance is considered highly permeable when the extent of absorption in humans is greater than 90% of an administered dose, based on mass-balance or compared with an intravenous reference dose .
Dissolution:
A drug product is considered rapidly dissolving when 85% or more of the labeled amount of drug substance dissolves within 30 min using USP Apparatus 1 or 2 in a volume of 900 mL or less of buffer solutions

Methods
Traditonal Technique
a. Micronization
b. Hydrotropy
c. pH adjustment
d. liposomes
e. Spray-freeze drying
Novel Technique
a. Size Reduction
b. Micro-emulsion
c. Mixed missel formation
d. Polymeric micelles
e. Micro-emulstion

f. Sonocrystalisation
g. Nano-emulsion

Solid Dispersion Technique

a. Melting method
b. Solvent method
c. Melting-solvent method
d. Melt-extrusion method

Traditional Techniques

Micronization

The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods such as fluid energy mill, jet mill, rotor stator colloid mill etc. The process is also called as "Micro-milling". Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Micronization of drug is not preferred because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution. Figure 2 depicts the increase in window of absorption of a drug by micronizatiom

The addition of a water-miscible or partially miscible organic solvent is a common and an effective way to increase the solubility of a non-polar drug. This process is known as co solvency and the solvents used in combination to increase the solubility of the drugs are known as cosolvents. The cosolvent system works by reducing the interfacial tension between the predominately aqueous solution and the hydrophobic solute. It is also commonly referred to as solvent blending. Cosolvents such as ethanol.propylene glycol, glycerin, sorbitol and polyoxyethylene glycols can be used. .

Limitation

The toxicity and tolerability level of solvent administered has to be considered while formulation. The precipitation phenomenon to be considers which can be uncontrollable also.

Hydrotrophy

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "'salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism" . Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.

Advantages of Hydrotropic Solubilisation Technique:

a. Hydrotropy is suggested to be superior to other solubilisation method, such as miscibility, micellar solubilisation, cosolvency and salting in, because the solvent character is independent of pH.
b. It has high selectivity and does not require emulsification.
c. It only requires mixing the drug with the hydrotrope in water.
d. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

pH adjustment

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 - 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. lonizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline aswell as lipophilic poorly soluble compounds .Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs.

Advantages:

Simple to formulate and analyze. Simple to produce and fast track.

Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages:

a. Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
b. Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.
c. As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

Liposome

A liposome is a bubble (vesicle) like structure, made out of the same material as a cell membrane. Liposomes filled with drugs, and used to deliver drugs. These are bilayered lipid structure. The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. Structurally, liposomes are concentric vesicles in which aqueous volume is entirely enclosed by a membranous lipid bilayer. Membranes are usually made of phospholipids, which are molecules that have a hydrophilic head group and a hydrophobic tail group. The head is attracted to water, and the tail, which is made of a long hydrocarbon chain, is repelled by water. In nature, phospholipids are found in stable membranes composed of two layers (a bilayer). The polar heads are attracted to water and line up to form a surface facing the water. The tails are repelled by water, and line up to form a surface away from the water. In a cell, one layer of heads faces outside of the cell, attracted to the water in the environment, and another layer of heads faces inside the cell, attracted by the water inside the cell. The hydrocarbon tails of one layer face the hydrocarbon tails of the other layer, and the combined structure forms a bilayer.

The lipids in the membrane are chiefly phospholipids like phosphatidyl ethanolamine and phosphatidylcholine. Phospholipids are amphiphilic with the hydrocarbon tail of the molecule being hydrophobic, its polar head hydrophilic. As the plasma membrane faces watery solutions on both sides, its phospholipids accommodate this by forming a phospholipid bilayer with the hydrophobic tails facing each other. Liposomes can be composed of naturally-derived phospholipids with mixed lipid chains (like eggphosphatidyl ethanolamine), or of pure surfactant components like DOPE (dioleoylphosphatidyl ethanolamine). Liposomes, usually but not by definition, contain a core of aqueous solution; lipid spheres that contain no aqueous material are called micelles, however, reverse micelles can be made to encompass an aqueous environment. Liposomes are drug delivery for both hydrophilic and hydrophobic drugs. Surface of the liposomal microcapsule can be modified to alter their bio distribution and pharmacokinetic and drug distribution according to their size. Liposomes can be made to release the entrapped drug at increased temperatures. Hydrophilic polymers can be grafted with liposomes to certain advantages like reduction of uptake by macrophages.

Limitations

They tend to be uptaken by other lipoidal cell membranes where they are not intended for the action. They need many modification for drug delivery to special organs where lipophilic environment not available. They are not economical for preparation.

Spray freeze drying

The technology involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous-organic emulsion or suspension containing a drug and pharmaceutical excipients sprayed directly into a compressed gas (i.e. C02. helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon, or hydro-fluoro ethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders. The dissolution rate was remarkably enhanced due to high surface area and excellent wet ability. In spray drying method the drug and polymer suspended in a common solvent or solvent mixture and then dried it into a stream of air. Due to the large surface area of the droplets, the solvent rapidly sublimes because the product exceeds glass transition temperature and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying provides large surface area for heat and mass transfer by atomizing a liquid in small droplet. Product have uniform and controllable size as drying takes place at very low temperature enzymatic activity gets minimized. Final product is slow and in form of porous nature gives ready solubility. Process under vacuum result no contact with air hence oxidation minimizes.

Limitations

Process is slow and complicated which is expensive too. Porosity, ready solubility and complete dryness yield very hygroscopic final dosage form. Thermal efficiency of the preparation technology is very low as air should be hot near exhaust to avoid condensation in order to reduce the relative humidity and to deliver the energy necessary for sublimation.

Novel Technique

Size Reduction Technologies

Nano formulations are one of the more complex formulations. Not only must the drug particles be rendered into nanosized but they must also be stabilized and formulated rigorously to retain the nature and properties of the nanoparticles.

Mixed Micelles

In general, amphiphilic, ionic, anionic or ampholytic molecules, which are able to decrease the surface tension of a solvent, arrange in micelles above a certain critical concentration. Micelle formation can only occur above a certain solute concentration, the critical micellar concentration (CMC), and at solution temperatures above the critical micellar temperature (CMT) .

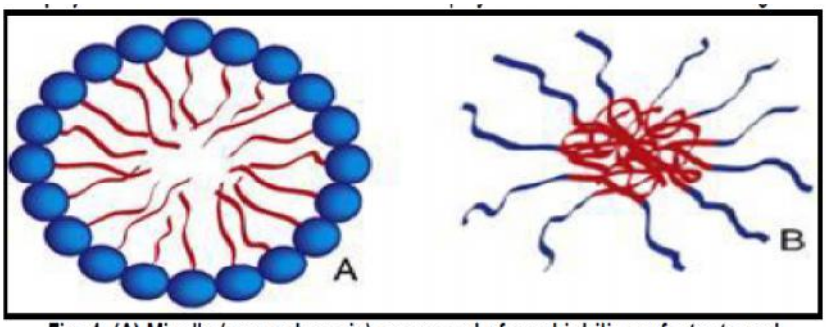

Fig. 4: (A) Micelle (non-polymeric) composed of amphiphilic surfactants and (B) Polymeric micelle composed of amphiphilic block copolymers

Polymeric Micelles

Amphiphilic polymers assemble into nanoscopic supramolecular core-shell structures, termed polymeric micelles. The block copolymers used for formation of polymeric micelles are Pluronics poly (ethylene glycol) ,(PEG)-phospholipid conjugates, PEG-b-poly (ester), and PEG-bpoly (L-amino acids) The polymeric and nonpolymeric micelles are shown in Figure 4.

Microremuision Technology

Microemulsions are thermodynamically stable, isotropically clear dispersions of two immiscible liquids stabilized by interfacial films of surface-active molecules. The microemulsions are formed by simple agitation of oil. water, surfactant and co-surfactant. The co-surfactant together with the surfactant reduces the interfacial tension to very low and even transient negative values.

Sonocrystallization

Sonocrystallization is a novel particle engineering technique to enhance solubility and dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size by using ultrasound. Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. Most applications use ultrasound in the range 20 kHz-5 MHz. Melt sonocrystallization (MSC) is promising technique of sonocrystallization to obtain porous, amorphous material with high stability.

Nanoemulsion

Nanoemulsions are a nonequilibrium, heterogeneous system consisting of two immiscible liquids in which one liquid is dispersed as droplets in another liquid. Emulsions with nanoscopic droplet sizes (typically in the range of 20-200 nm) are often referred to as submicron emulsions. Nanoemulsions are composed of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules. The methods used for the production of nanoemulsions include HPH, microfluidization, ultrasonication and spontaneous emulsification. Commercial products that are nanoemulsions include Estrasorb and Flexogan.

Methods of Preparation of Solid Dispersions:

Melting method

The melting or fusion method, first proposed by (Sekiguchi and Obi 1961) involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

Solvent method:

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties'6

The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

However, some disadvantages are associated with this method such as

a. The higher cost of preparation.
b. The difficulty in completely removing liquid solvent.
c. The possible adverse effect of traces of the solvent on the chemical stability
d. The selection of a common volatile solvent.
e. The difficulty of reproducing crystal form.

Melting Solvent Method (Melt Evaporation)

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight.The 5 -10% (w/w) of liquid compounds can be incorporated into polyethylene glycol6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

Melt extrusion method:

The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.

4. Conclusion

By this article we conclude that, bioavailability of the drug is the most critical factor that have to consider while formulation and development of dosage form which controls the formulation of the drug as well as therapeutic efficacy of the drug. Dissolution of drug is the rate determining step for oral absorption and permeability is also the basic requirement for the formulation and development of different dosage form of BCS class IV drugs. The various techniques described above alone or in combination can be used to enhance the bioavailability of the drug.

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