Review Article

Biopharmaceutical Classification System: Tool based prediction for drug dosage formulation

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Abstract

The Biopharmaceutical Classification System (BCS) has been a predictive tool for assess the prospective effects of formulation on the human, drug oral bioavailability. When used in combination with in vitro dissolution tests, the BCS can maintain the prediction of in vivo product performance and the development. The biopharmaceutical classification system (BCS) is a new perception in the field of pharmaceutical science. This is a helpful tool for the formulation scientists, for the selection and design of the formulation of any drug molecules. The current developments have also enabled us to predict the solubility and permeability character of the drug molecule in the early development stages so that the necessary structural changes can be made to the molecule in order to optimize the pharmacokinetic parameters. The BCS has also got a place in a variety of guidance documents of regulatory importance. The article sheds light on the possible new criteria and class limits proposed for additional biowaivers based on the underlying physiology of the gastrointestinal tract in mandatory cases. The prospective applications of BCS in drug discovery, drug delivery and drug research as well as extension for BCS are discussed including the development of new drugs and oral controlled release products.

Keywords: Biopharmaceutical classification system, drug delivery, biowaivers

Introduction

The oral route of drug administration is the mainly important method for administering drugs for systemic effects. When a new drug is discovered, one of the first questions, a pharmaceutical company asks is whether or not the drug can be successfully administered by the oral route, for its intended effect. The development of dosage forms specially for the prolonged release purpose has been a challenge to formulation scientists, because of many free factors governing the absorption of the drug from the gastrointestinal tract (Khan et al., 2001) and competitive objectives, that is, any action taken to improve one objective or set of objectives may cause another objective or set of objectives to degrade (Sachan et al., 2006). For example, modifying the solubility of the drug substance to lengthen its release in the gastrointestinal tract may cause a reduction in the overall payload of formulation. A trial and error method of formulation does not allow the formulator to know how close a particular formulation is to the optimum solution, and finding the correct cooperate is not straightforward and simple. Hence a fast screen is needed, to enable them to formulate intelligently. For this purpose the drug substances are categorized into four classes based on their solubility parameter and permeabilityto bio-membranes, and such a classification system is called as a Biopharmaceutical Classification System (BCS) (Amidon et al., 1995).

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Aim of Biopharmaceutics Classification System

To improve the efficiency of the drug molecules development and review process by recommending a strategy for identifying expendable clinical bioequivalence test. 2. To recommend a class of immediate-release (IR) solid oral dosage formulations for which bioequivalence may be assessed based on in vitro dissolution tests. 3. To recommend methods for classification according to dosage form on the basis of dissolution along with the solubility and permeability characteristics of the drug molecules (Amidon et al., 1995).

The Biopharmaceutics Classification System (BCS) is not only useful tool for provide waivers for in vivo bioequivalence studies but also for helping in the discovery and prediction for development of new drugs formulation.

It is because BCS is based on a scientific framework elaborate the three rate limiting steps in oral absorption. The three necessary vital steps for a drug to be absorbed are (1) release of drug from dosage systems, (2) maintenance of dissolved state throughout gastrointestinal fluid system, and (3) permeation of drug molecules through GI membrane into hepatic circulation and. There is a fourth step, i.e. enterohepatic metabolism that increases the systemic availability as well as release of metabolites into the systemic circulation.

Within the framework of human pharmaceuticals, drugs molecules can be classified into one of the following four Biopharmaceutical Classification Systems are categories as:

Class I: high solubility, high permeability: generally very well-absorbed molecules

Class II: low solubility, high permeability: exhibit dissolution rate-limited absorption

Class III: high solubility, low permeability: exhibit permeability-limited absorption

Class IV: low solubility, low permeability: extremely poor oral bioavailability

Characteristics of the drugs under BCS (Lobenberg et al., 2000)

Class I: In-vivo these drugs behave like an oral solution has fast dissolution and fast bioavailability. Since the dissolution and absorption of class I drugs is extremely fast, bioavailability and bioequivalence are pointless for the products of such drugs. These drugs are good candidates for controlled drug delivery if they be eligible pharmacokinetic ally and pharmacodynamically for the point. Gastric emptying is often the rate governing limitation in this case. The Class I drugs molecules are not those in which either solubility or permeability is limiting within the target regions of the GI tract. The drug molecules release in such cases can be modulated using controlled release technology. Controlled release technologies for Class I drugs molecules includes number of products like as Multiporous oral drug absorption system, Single composition osmotic tablet system, Microsphere, constant surface area drug delivery shuttle, Diffusion controlled matrix system, Delayed pulsatile hydrogel system, Dual release drug absorption system), Granulated modulating hydrogel system, Intestinal protective drug absorption system, Microparticle Drug Delivery Technology, Pelletized pulsatile delivery system, Bioerodible enhanced oral drug absorption system, Programmable oral drug absorption system, Spheroidal oral drug absorption system, Solubility modulating hydrogel system and Stabilized pellet delivery system.

Class II: Drugs molecules belong contains low solubility and high permeability, therefore, the dissolution rate becomes the principal parameter for bioavailability. These drugs reveal variable bioavailability and need improvement in the dissolution rate by different methods for improvement in bioavailability. These are also appropriate for controlled release development. The technologies under this class include the approaches such as classical micronization, stabilization of high-energy states (including lyophilized fast-melt systems), use of surfactants, emulsion or microemulsion systems, solid dispersion and use of complexing agent such as cyclodextrins. The technologies under this class include: Soft Gel (soft gelatin capsule formulation), Zer-Os tablet technology (osmotic system), Triglas and nanosized carriers such as nanoemulsion, nanosuspension and nanocrystals are treated as hopeful means of increasing solubility and BA of poorly water-soluble active ingredients.

Class III: Drugs molecules of this class permeation through the intestinal membrane form the rate-determining step for these drugs molecules. Since absorption is permeation rate limited, bioavailability is self-governing of drug release from the dosage form. For example, the different ranitidine products having dissimilar dissolution profiles produce super imposable plasma concentration versus time profile in-vivo. These drugs usually show low bioavailability and permeability enhancement is normally required. These drugs are challenging for controlled release development.

Class IV: Drugs molecules of this class show poor and unpredictable bioavailability. The generally bioavailability is governed by numerous factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on. These drugs are usually not suitable for oral drug delivery or else some special drug delivery technologies such as nano-suspensions will be desirable.

Perception behind BCS

The in-vivo presentation of orally administered drugs depends ahead their solubility and tissue permeability character. The release rate or solubility of the drug molecules will not be a governing limit, if the absorption of the drug is permeation rate limited and in such cases the in-vitro dissolution study can be used to express the bioavailability (BA) or bioequivalence (BE) of the drug molecules through in vitro-in vivo correlation (IVIVC). On the other side, if absorption of the drug molecules is dissolution rate limited that way the drug in the gastrointestinal fluid passes freely throughout the bio-membranes at a rate higher than it dissolves or is released from the dosage formulation. The specifically planned in-vivo study will be mandatory in such a case, to access the

absorption rate, and therefore its bioavailability and to reveal the bioequivalence finally. Such a drug molecules is good candidates for controlled delivery provides if they qualify in terms of their pharmacokinetics and pharmacodynamics for controlled release development. Besides if drug molecules having low solubility and a slow dissolution rate, the release will routinely get slower and the dosage form need not have an inbuilt release retardation mechanism, fairly the absorption will now be governed by the gastric emptying rate. Therefore, the dosage form must be able to restrain within the absorption window for a sufficient time so that absorption can take place. In such case, a hydrodynamic ally balanced (floating) system or a mucoadhesive dosage formulation will provide the purpose. Consequently the BCS can work as a guide tool for the improvement of various oral drug delivery technologies (Johnson et al., 2006).

It allows for the prediction of *In-vivo* pharmacokinetics of oral immediate-release (IR) drug molecules by classifying drug compounds into four classes based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form. Biopharmaceutical Classification System (BCS) guidance was provided by US Food and Drug Administration (FDA), to improve the efficiency of drug product development process. The Biopharmaceutical Classification System (BCS) is a system to differentiate the drugs on the basis of their solubility and permeability. It is a guide for predicting the intestinal drug molecules absorption according to Food and Drug Administration. BCS is based on scientific framework relating three rate limiting steps in oral absorption. The three essential steps for a drug to be absorbed are: (1) Release of drug molecules, from dosage forms; (2) Maintenance of dissolved state throughout Gastro-intestinal (G.I) tract; (3) Permeation through G.I. membrane into hepatic circulation. Solubility of drug classification is according to the United States Pharmacopoeia (USP) aperture 2. The intestinal permeability classification is based on a assessment to the intravenous injection. All these factors are very important, since 85% of the most sold drugs in the USA and Europe are orally administered. Until now, application of BCS has been moderately hindered by the lack of a freely available and accurate database summarizing solubility and permeability characteristics of drug molecules. Consequently the facts of BCS help the formulation scientist to develop a dosage form based on mechanistic rather than empirical approaches (FDA Guidelines, 2000).

Important term under BCS

Bioavailability: define as the rate and extent to which the active ingredient or active moiety is absorbed from a drug molecule of product and becomes existing at the site of action.

Bioequivalence: define as the active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar environment in an appropriately designed study.

The Biopharmaceutical Drug Disposition Classification System (BDDCS)

The evaluations of following four steps are uses for oral absorption and, efficacious drugs. as determination of solubility, permeability, and metabolic stability. These oral absorption screening tests are often referred as pharmaceutical profiling. The pharmaceutical researcher in earlier development of the formulation of dosage forms mostly utilizes pharmaceutical profiling data to establish the preliminary BCS classification for the lead compound. Because BCS has ramification in drug approval process from FDA and other regulatory agencies, during the discovery of new drugs molecules, classification of a compound to BCS 2, BCS 3 or BCS 4 communicates to Discovery the need to enhance solubility and/or permeability for following compounds. In the same vein, a BCS classification other than 1 communicates to Manufacturing that may lead to higher formulation risks during drug development. Most importantly, it warns the clinician of the potential for a large unpredictability in exposure and a significant food effect.

The BCS is a vital tool that facilitates product improvement and regulatory decisions. By understanding the solubility of molecules in biorelevant media and its permeability across biological membranes, the rate limiting factors determining the rate and extent of oral drug molecules absorption can be identified. This information can be invaluable for predicting the possible influence of formulation and physiological variables on oral drug bioavailability.

The drugs molecules are classified in BCS on the basis of following parameters:

(1) Solubility, (2) Permeability and (3) Dissolution

The class boundaries for the parameters are:

Solubility determination

The solubility of any drug material can be distinct as the amount of material that has passed into solution when equilibrium is attained between the solution and excess (undissolved substance) at a given temperature and pressure (Lobenberg et al., 2000). A drug material or an active pharmaceutical ingredient (API) is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous medium over a specific pH range

(Johnson et al., 2006). The pH solubility profile of the drug material is determined at 37 6 18C in aqueous medium with pH in the range of 1-7.5 as per United States Food and Drug Administration (USFDA) guidelines, 1.2-6.8 as per World Health Organization (WHO) guidelines (Gothoskar et al., 2005) and 1-8 as per European Medicines Academy (EMEA). A sufficient number of pH conditions must be evaluated to accurately. The number of pH conditions for a solubility determination depends upon ionization characteristics of the test drug material. A minimum of three replicate determinations of solubility in each pH condition should be carried out to expect accurate solubility. Standard buffer solutions described in pharmacopoeias are considered appropriate for use in solubility studies. Other than shake-flask method, can also be used with validation to support the ability of such methods to predict equilibrium solubility of test drug substance. If degradation of drug is observed as a function of buffer composition and/or pH, it should be taken into consideration. The concentration of drug molecules in selected buffers or pH conditions should be determined with a validated solubility indicating assay method that can distinguish between the drug substances from its degradation products (Martinez et al., 2012).

Permeability

The permeability class boundary is based indirectly on the extent of absorption of a drug molecules in humans and directly on measurements of the rate of mass transmit across human intestinal membrane. Otherwise, nonhuman systems able of predicting the amount of drug molecules absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In mass balance studies, unlabeled, stable isotopes or radio labeled drug molecules are used to find out the extent of drug absorption. In absolute bioavailability studies, oral bioavailability is determined and compared against the intravenous bioavailability as reference. Intestinal perfusion models and in vitro methods are recommended for passively transported drugs (Rubas W et al., 1993). An interesting option to intestinal tissue models is the use of in vitro systems based on the human adenocarcinoma cell line Caco-2. These cells provide as a model of small intestinal tissue. The differentiated cells reveal the microvilli typical of the small intestinal mucosa and the integral membrane proteins of the brush-border enzymes. They also form the fluid-filled domes typical of a permeable epithelium. Recent investigations of Caco-2 cell lines have indicated their ability to transport ions, sugars and peptides. These properties have established the Caco-2 cell line as a reliable in vitro model of the small intestine (Davis et al., 2006).

Dissolution

Immediate release drugs formulation is considered rapidly dissolving when no less than 85 % of the labeled amount of the drug molecules dissolves within 15 minutes using USP Dissolution Apparatus- I at 100 RPM or Apparatus - II at 50 RPM in a volume of 900 ml or less in the following media: 0.1 N HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid. According to USFDA BCS guidance (Martinez et al., 2002) an IR drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using USP apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each medium: 0.1 N HCl or simulated gastric fluid USP without enzymes; buffer (pH 4.5); and buffer (pH 6.8) or simulated intestinal fluid USP without enzymes. According to WHO BCS guidance a multisource product (pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent) is considered to be very rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves in 15 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each medium: HCl solution (pH 1.2); acetate buffer (pH 4.5); and phosphate buffer (pH 6.8). A multisource product is considered to be quickly dissolving when no less than 85% of the labeled amount of the drug substance dissolves in 30 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the media: HCl solution (pH 1.2); acetate buffer (pH 4.5); and phosphate buffer (pH 6.8). According to EMEA BCS guidance drug products are considered very rapidly dissolving when more than 85% of the labeled amount is dissolved in 15 minutes, using USP Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 500 ml in each of the media: 0.1 N HCl or simulated gastric fluid without enzymes; buffer (pH 4.5); and buffer (pH 6.8) or simulated intestinal fluid without enzymes and similarity of dissolution profiles should be demonstrated. Lipophilic drugs may be very poorly soluble in water and in simple buffers, but in the GI fluids the bile to a significant extent can often solubilize them. Increases in solubility of one to two orders of magnitude are possible for compounds with log P values of .4. For promising compounds that are both ionizable and lipophilic, extensive solubility experiments in biorelevant media will help to characterize the likely solubility behavior in vivo. Another approach is to use aspirates from human volunteers, although volumes aspirated typically are small and the choice of experiments and apparatus therefore is also limited. Next issue is the use of 250 m (Chiou et al., 2000).

Biowaivers

The term biowaiver is very useful in the regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than through in vivo equivalence testing. Biowaiver means to achiev waive off for carrying out expensive and time-consuming BA and BE studies. A biowaiver has been regarded as an official approval of the waiver for conducting a bioequivalence study in the context of an application for drug molecules approval process. The BCS-based biowaivers related to pre- (IND/NDA and ANDA), post approval phases. BCS-based biowaivers are relevant for immediate-release solid oral drug formulations containing one or more of the API(s) mentioned above if the required data ensure the similarity of the submitted pharmaceutical product and the proper pharmaceutically equivalent comparator product. BCS-based biowaiver has become an important and cost-saving tool in approval of basic (generic) drugs (FDA Guidance 2000).

Presently BCS class I drugs and some class III drugs are suitable for biowaivers. The drug molecules should be highly soluble and highly permeable. An IR drug product should be quickly dissolving. The drug molecules should not be a narrow therapeutic index drug. Excipients used in the dosage formulation should have been used earlier in FDA approved IR solid dosage forms. Used for waivers of an in vivo relative bioavailability study, dissolution should be greater than 85% in 30 min in the three recommended dissolution media (acidic media, such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, a pH 4.5 buffer; and a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes). Used for waivers of in vivo bioequivalence, test and reference products should exhibit similar dissolution profiles under the dissolution test conditions defined for rapidly dissolving products (Amidon et al., 1995).

Exceptions BCS-based biowaivers are not applicable for the subsequent: Narrow therapeutic range drug molecules products as those containing certain drug molecules that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labelling indicates a narrow therapeutic range designation. Examples like digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs molecules subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs. Drug products designed to be absorbed in the Oral Cavity: A applies for for a waiver of in-vivo BA/BE studies based on the BCS is not appropriate for dosage forms for absorption through the oral cavity (e.g., sublingual or buccal tablets) (Amidon et al., 1995).

Application of BCS in drug delivery technology

Biopharmaceutical Drug Disposition Classification System (BDDCS) has been used to forecast the drug disposition and potential drug-drug interactions in the intestine and the liver and potentially the kidney and brain. While the solubility criteria for the BCS and BDDCS are the similar. For the BDDCS, the second classification is linked to the reporting of drug metabolism. The assessment of permeability in the BCS is linked to the reporting of intestinal absorption, i.e., a drug molecules is considered to be highly permeable when the extent of the systemic absorption (parent drug plus metabolites) in humans is determined to be at least 90% of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose (Martinez et al., 2002). Accordingly, the BCS and BDDCS classification of a drug may differ. Once the solubility and permeability characteristics of a drug are known, the formulation scientist can then, based on BCS, easily decide which drug delivery technology will best and help in getting the optimum pharmacokinetic characteristics. The major task in the development of drug delivery systems for class I drug is to achieve a targeted release profile associated with the particular pharmacokinetic and pharmacodynamic properties. Formulation approaches include both the control of release rate and physiochemical properties of drugs like the pH-solubility profile of the drug. The systems that are developed for class II drugs are based on the micronization, lyophilization, addition of surfactants, and formulation as emulsions and microemulsion systems, use of complexing agents like cyclodextrins, and so on. Class III drugs are required for technologies that address the fundamental limitations of absolute or regional permeability. Peptides and proteins constitute, solely, the class III drugs; these are now the center of focus for research in drug delivery. The class IV drugs present a major challenge for the development of drug delivery systems and the route of choice, due to their poor solubility and permeability characteristics. These are often administered by parenteral route with the formulation containing solubility enhancers (Takagi et al., 2006).

Conclusion

The BCS is the tool for the prediction of in vivo performance of the drug molecules, and development of drug delivery system to suit that performance. BCS principles offer a reasonable process for testing and approving drug molecules product quality. BCS applications used for Class 2 and 3 are challenging, but at the same time provides opportunities for lowering regulatory burden with scientific rational. BCS also provides an possibility to predict drug disposition,

transport, absorption, elimination.

Conflict of interest

Authors do not declare any conflict of interest.

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