

Pharmaceutics Research Laboratory, Department of Pharmaceutical Sciences, Dr. H. S. Gour University, Sagar (M.P.), India

Biowaiver: an alternative to *in vivo* pharmacokinetic bioequivalence studies

V. MISHRA, U. GUPTA, N. K. JAIN

Received July 10, 2009, accepted August 3, 2009

Prof. Narendra K. Jain, Pharmaceutics Research Laboratory, Department of Pharmaceutical Sciences, Dr. H. S. Gour University, Sagar (M.P.), 470003, India
jnarendr@yahoo.co.in

Pharmazie 65: 155–161 (2010)

doi: 10.1691/ph.2010.9231

Bioequivalence is a vital concern in drug development even more significant in the case of Narrow Therapeutic Index (NTI) drugs. In clinical development of New Chemical Entities (NCE), bioequivalence studies necessitate to be performed when the formulation of the pharmaceutical dosage form has been changed. *In vivo* pharmacokinetic data can be used as surrogate parameters for *in vivo* solubility and permeability data. The Biopharmaceutics Classification System (BCS) has emerged as a helpful tool in product development by alluding to the *in vivo* performance of the active substance. The bio-relevance of the BCS properties and the *in vitro* release are best expressed through a correlation between *in vitro* and *in vivo* data. Recently BCS has been implemented for waiving bioequivalence studies on the basis of the solubility and gastrointestinal permeability of drug substance and can be strategically deployed to save time and resources during generic drug development. The BCS has been adopted as a very useful tool for *in vivo* drug design and development worldwide, particularly in terms of regulatory standards. A BCS-based biowaiver has become an important and cost-saving tool in approval of generic drugs.

1. Introduction

Bioavailability (BA)/bioequivalence (BE) parameters are generally required for approval of new and generic drugs. Bioequivalence based on plasma drug concentration has become the most frequently used and successful biomarker of safety and efficacy of a drug. According to the FDA's regulations (codified in Title 21 of the Code of Federal Regulations, 21 CFR) bioavailability is defined as the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action and bioequivalence can be defined as the absence of a significant difference in the rate and extent to which the active ingredient in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in a properly designed study. A generally accepted practical definition of bioavailability is understood to be the extent and the rate at which a drug is delivered from a pharmaceutical dosage form and becomes available in the general circulation (FDA 2000a). BE studies verify that the active ingredient will be absorbed in the body to the same rate and extent as the innovator drug and support products being considered therapeutically equivalent and interchangeable with the innovator drug. Two oral dosage forms are considered to be bioequivalent if both rate and extent of absorption are the same.

From a pharmacokinetic (PK) point of view, BA data present an estimate of the fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the

BA data for a solution, suspension, or intravenous dosage form. However, BA studies can provide information related to distribution, elimination, the effects of nutrients on absorption of the drug substance, dose proportionality, and linearity in PK of the active or inactive moieties. BA data may also provide information about the properties of a drug substance prior to entry into the systemic circulation, such as permeability and the influence of pre-systemic metabolism and p-glycoprotein or other transporters.

BA for orally administered drug products may be documented by developing a systemic exposure profile obtained by measuring the concentration of active or inactive moieties over time in samples collected from the systemic circulation. BA studies conducted early in the Investigational New Drug (IND) period provide useful information related to formulation development, the rate and extent of absorption, PK, and pharmacodynamics (PD) of the investigational drug and its metabolites (Dressman et al. 2001).

2. Biopharmaceutics Classification System

Guidance of Food and Drug Administration/Center for Drug Evaluation and Research (FDA/CDER) for BA and BE outlines methods for classifying drugs and immediate release solid oral drug products according to permeability, solubility and dissolution properties based upon the Biopharmaceutics Classification System (BCS). In an effort to speed up the drug regulatory process, the FDA has provided guidance in the form of the BCS with which to identify expendable clinical bioequivalence tests (FDA 2000b). BCS forms a scientific framework for classifying a drug substance based on

its aqueous solubility and intestinal permeability (Amidon et al. 1995). Classifying drugs according to the BCS has resulted in an improved Scale-Up and Post Approval Changes (SUPAC) guidance, a dissolution guidance, and an FDA guidance on waiver of *in vivo* bioequivalence studies for BCS Class I drugs in rapid dissolution immediate-release (IR) solid oral dosage forms (FDA 2000c).

The FDA promoted the BCS as a scientific approach to permit waiver of *in vivo* BA and BE testing for immediate release solid dosage forms for Class 1 compounds (highly soluble and highly permeable drugs), when such drug products also exhibit rapid dissolution. In brief, bioequivalence is achieved if the generic product shows the same rate and extent of bioavailability with rate evaluated in terms of $C_{\max}$ and extent measured in terms of AUC. The criteria include a 90% confidence interval around point estimates of the ratios of $C_{\max}$ and AUC, test/reference, falling within 0.8–1.25 on a log normal distribution (FDA 2000c).

BCS has been developed to provide a scientific approach to allow for the prediction of *in vivo* pharmacokinetics of oral IR drug products by classifying drug compounds based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form (Amidon et al. 1995; Yu et al. 2002). BCS forms a general approach which is based on the fact that *in vivo* dissolution differences in the gastrointestinal tract are a primary reason for observed differences in bioavailability of two IR solid oral dosage forms containing the same drug substance (Amidon et al. 1995).

The classification framework of the BCS is believed to be useful in the earliest stages of drug discovery research. Its applications improve the prediction of oral absorption and disposition of new molecular entities. In addition, the BCS has proven to be an asset to the FDA by creating a framework for which to allow a waiver of *in vivo* bioequivalence studies for a limited number of suitable Class 1 compounds. Thus BCS has been developed primarily for regulatory applications, but it has also several other applications in both the preclinical and clinical drug development processes and has gained ample recognition within the research-based industry (Yu et al. 2002; Polli et al. 2004; Lennernäs and Abrahamsson 2005). So the intent of the BCS is to provide a regulatory tool for the replacement of certain BE studies by conducting precise *in vitro* dissolution tests.

3. Experimental approaches for classification of a drug

The following experimental approaches are suggested for classifying a drug according to the BCS.

3.1. Determination of solubility class

The purpose of the BCS approach is to determine the equilibrium solubility of a drug under estimated physiological conditions. For this purpose, determination of pH solubility profiles over a pH range of 1–8 is suggested. Buffers that react with the drug should not be used. The solubility class is determined by calculating what volume of an aqueous media is sufficient to dissolve the highest probable dose strength. A drug is considered highly soluble when the highest dose strength is soluble in 250 mL or less of water over the pH range of 1–8.

The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water which is the minimum volume anticipated in the stomach at the time of drug administration during the study protocols.

Yu et al. (2004) described that Disk Intrinsic Dissolution Rate (DIDR) method which generally correlated with the BCS solubility classification with 0.1 mg/min/cm^2 as a class boundary unless the dose was either extremely low or high where a discrepancy may exist between the solubility and DIDR methods. The variables in producing the drug disk, i.e. compression pressure, dissolution medium volume, and die position had no significant effect on DIDR, demonstrating the robustness of the intrinsic dissolution methodology. It should be noted that dose is considered in the classification of solubility while intrinsic dissolution does not consider the effect of dose. Thus, when the dose is either extremely high or extremely low, a discrepancy between the current solubility classification and the DIDR may occur. For example, a compound with the solubility of $1 \mu\text{g/mL}$ may be classified as a high solubility compound if the dose is 0.25 mg or less based on the solubility classification while it is likely classified a low solubility compound if directly based on DIDR. On the other hand, a compound with the solubility of 4 mg/mL may be classified as a low solubility compound if the dose is 1000 mg or more based on the solubility classification while it is likely classified a high solubility compound if directly based on DIDR. Further, when the dose is extremely high, the *in vivo* absorption may be solubility limited (Yu 1999).

3.2. Determination of permeability class

The research carried out to constitute the BCS has provided new quantitative data of great importance for modern drug development especially within the area of drug permeability (Lennernäs 1998).

A drug substance is considered highly permeable when the extent of absorption in humans is determined to be more than 90% of an administered dose based on a mass balance determination, or in comparison to an intravenous reference dose in the absence of evidence suggesting instability in the gastrointestinal tract. An IR drug product is considered rapidly dissolving when not less than 85% of the label amount of the drug substance dissolves within 30 min using the USP Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 mL, or less, (1) in each of Simulated Gastric Fluid USP without enzymes; (2) a buffer (pH 4.5); and (3) Simulated Intestinal Fluid USP without enzymes.

For the determination of the permeability of a drug from the gastro-intestinal tract various methods can be used: (1) *in vivo* intestinal perfusion studies in humans; (2) *in vivo* or *in situ* intestinal perfusion studies in animals; (3) *in vitro* permeation experiments using excised human or animal intestinal tissues; and (4) *in vitro* permeation experiments across a monolayer of cultured human intestinal cells.

The permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurements of the rate of mass transfer across the human intestinal membrane. Animal or *in vitro* models capable of predicting the extent of intestinal absorption in humans may be used as alternatives, for example, *in situ* rat perfusion models and *in vitro* epithelial cell culture models. A drug substance is considered highly permeable when the extent of intestinal absorption is 90% or higher. Of the several *in vitro* models developed for studying intestinal absorption, the Caco-2 human colon carcinoma cell line has been widely utilized in the *in vitro* model system for evaluating the rate of intestinal drug absorption. The results showed that *in vitro* Caco-2 permeability is related to *in vivo* human intestinal absorption for the model drugs, and this relationship provides a means to distinguish between high- and low-permeability drug substances (Hilgers et al. 1990;

Table 1: Suggested model drugs

Permeability class	Drugs	Feature
High	Theophylline, caffeine, ketoprophen, naproxen,	-
High	Antipyrine, metoprolol	Internal standard (IS)
High	Verapamil	Efflux pump substrate (ES)
Low	Furosemide, amoxicillin, ranitidine, atenolol, polyethylene glycol (400)	-
Low	Mannitol	Internal standard (IS)
Low	Polyethylene glycol (4000)	Zero permeability marker

Wilson et al. 1990; Artursson 1990; Artursson and Karlsson 1991; Yee 1997).

Typical means of assessing permeability in clinical studies include determination of mass balance, systemic (absolute) BA, or intestinal perfusion (Sun et al. 2004; Pelkonen et al. 2001; Lennernas et al. 1997). Nonclinical methods include *in vivo* or *in situ* intestinal perfusion studies in a suitable animal model (e.g., rats), or *in vitro* permeability methods using excised intestinal tissues or monolayers of suitable epithelial cells. The suitability of a given permeability method should be established whereby a rank-order relationship exists between the test permeability values and the extent of drug absorption data in human subjects using a sufficient number of model drugs. For human intestinal perfusion studies, six model drugs are recommended. For *in vivo* or *in situ* intestinal perfusion studies in animals and for *in vitro* cell culture methods, twenty model drugs are recommended (Artursson and Karlsson 1991; Tamura et al. 2003; Han et al. 1998; Walter et al. 1996; Hidalgo et al. 1989).

Careful selection of a high permeability internal standard may simplify the classification of a test drug. A low permeability internal standard is suggested to ensure intestinal membrane integrity. The permeability values of the two internal standards can be used to verify reproducibility of the experimental method. The internal standards should be compatible with the drug being evaluated i.e., they should exhibit no physical or chemical interactions. Model drugs and chemicals suggested for use in establishing suitability of a permeability method are included in Table 1. The permeability of these compounds is determined based on data available to the FDA. Potential internal standards (IS) and efflux pump substrates (ES) are also identified.

Yang et al. (2007) determined the permeability and solubility of seven β -blockers (acebutolol, atenolol, labetalol, metoprolol, nadolol, sotalol, and timolol) and classified them according to the BCS. Apparent permeability coefficients (P_{app}) were measured using the Caco-2 cell line, and the solubility was determined at 37 °C over a pH range of 1.0–7.5. On the basis of the *in vitro* permeability and solubility data labetalol, sotalol, metoprolol, and timolol were categorized as BCS Class I drugs, whereas acebutolol, atenolol, and nadolol belonged to BCS Class III.

4. Ideology of the Biopharmaceutics Classification System

The concept behind the BCS is that if two drug products yield the same concentration profile along the gastrointestinal (GI) tract,

Table 2: Classification of drugs as per BCS

Class	Features	Examples
I	High permeability. High solubility	Paracetamol, metoprolol, theophylline
II	High permeability. Low solubility	Atovaquone, carbamazepine, danazol, glibenclamide, griseofulvin, ketoconazole, troglitazone
III	Low permeability. High solubility	Acyclovir, atenolol, cimetidine, ranitidine
IV	Low permeability. Low solubility	Chlorothiazide, furosemide

they will result in the same plasma profile after oral administration. This concept can be summarized by the following equation:

$$J = P_w C_w \quad (1)$$

where J is the flux across the gut wall, P_w is the permeability of the gut wall to the drug, and C_w is the concentration profile at the gut wall.

In terms of bioequivalence, it is assumed that highly permeable and highly soluble drugs enclosed in rapidly dissolving drug products will be bioequivalent and if no major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to reveal bioequivalence of two drug products. The BCS, thus enables manufacturers to reduce the costs of approving Scale-Up and Post Approval Changes (SUPAC) to certain oral drug products (rapidly dissolving products of Class I drugs; Table 2) without compromising public safety interests (Dressman et al. 2001). In the BCS, the emphasis is sited on what happens with the formulation in the GI tract. The dose, dissolution and absorption number are estimated on the basis of Fick's first law to evaluate the solubility, dissolution and absorption of the drug respectively.

The main assumption in the BCS is that, if the fraction of the dose absorbed is same, the human body should always do the same with the absorbed compound (i.e. distribution and elimination will not be changed). When a drug exhibits dose linearity i.e. a linear relation between AUC and/or C_{max} with the dose and a reasonably fast dissolution profile, it can be stated that these compounds do not cause problems with respect to absorption. This approach is based on actual measurements of the amount of drug which has actually reached the systemic circulation. It should be noted that the standard pharmacokinetic data used for this approach represent the performance of one particular type of formulation. Alternative formulations can only be bio-pharmaceutically similar when the rate and extent of release of the drug substance from this formulation is equal. Comparison of two different formulations should be done on the basis of dissolution testing, which is basically the same as per the BCS approach. Hence, *in vivo* pharmacokinetic data can be used as surrogate parameters for *in vivo* solubility and permeability profile.

The BCS recommends a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on *in vitro* dissolution tests. It can be used to justify a biowaiver based on the fact that observed differences in the bioavailability of two such IR products containing the same drug result primarily from *in vivo* dissolution differences in the GI tract (FDA 2000c). Thus briefly in the BCS, a drug is classified as belonging to (1) high or low solubility class, (2) a high or low permeability class, and (3) an immediate release dosage

Table 3: Relation between class of drug and routes of drug elimination and effect of food

BCS class	Routes of drug elimination	Effect of food
Class I	Undergo metabolism Transporter effects minimal	Extent- No change T_{max} -Increase
Class II	Undergo metabolism Efflux transporter effects predominate	Extent- Increase T_{max} - ?
Class III	Mostly unchanged drug in urine/bile Absorptive transporter effects predominate	Extent- Decrease T_{max} - Increase
Class IV	Mostly unchanged drug in urine/bile Absorptive and efflux transporters predominate	Extent- ? T_{max} - ?

form is categorized as belonging to a rapid or slow dissolving class (Amidon et al. 1995). Classification of drugs is given in Table 2. All poorly water soluble drugs are classed as BCS II or IV. The BCS-defined class boundaries for drug substances can be summarized as:

- Rapidly dissolving – $\geq 85\%$ of labeled amount of drug dissolves within 30 min in vitro.
- Highly soluble – highest dose strength soluble in ≤ 250 mL water at pH range 1–7.5.
- Highly permeable – absorption in humans $\geq 90\%$ of an administered dose.

Poorly-soluble marketed drugs are clearly good candidates for reformulation using the emerging range of different technologies available to target the issues (Dimond 2005).

Another merit of the BCS in a development context is that it provides very clear and easily applied rules in determining the rate-limiting factor in the gastrointestinal drug absorption process. Therefore, the BCS framework can be used in the selection of candidate drugs for full development, route of drug elimination, predictions as well as elucidations of food interactions (Table 3) (Wu and Benet 2005) and choice of formulation principle, including suitability for oral extended release (ER) administration and the possibility of defining in vitro - in vivo correlations (IVIVCs) from dissolution testing of solid formulations (Polli et al. 2004; Fleisher et al. 1999).

Thus the need for a tool to reliably correlate *in vitro* and *in vivo* drug release data has remarkably increased. Such a tool shortens the drug development period, economizes the resources and leads to improved product quality. The BCS works as a drug developmental tool that allows estimation of the contribution of three fundamental factors including dissolution, solubility and intestinal permeability, which govern the rate and extent of drug absorption from solid oral dosage forms (Amidon et al. 1995). BCS forms a fundamental guideline for determining the conditions under which IVIVCs are expected and also used as a tool for developing the *in vitro* dissolution specification.

The classification is dealing with drug dissolution and absorption model, which considers the key parameters controlling drug dissolution and absorption as a set of dimensionless numbers: the absorption number, the dissolution number, and the dose number (Amidon et al. 1995; Dressman et al. 1998).

Table 4: Relation between class of drug and IVIVC

BCS class	Absorption rate control	<i>In vitro-in vivo</i> (IVIV) correlation
I	Gastric emptying	If dissolution rate is slower than gastric emptying rate then IVIVC is possible
II	Dissolution	If dose is very high and in vitro dissolution rate is similar to in vivo dissolution rate then IVIVC is possible
III	Permeability	Absorption (permeability) is rate determining step so limited or no IVIVC is possible with dissolution
IV	Case to case	Limited or no IVIVC is possible

4.1. Absorption number (A_n)

The absorption number (A_n) is the ratio of the mean residence time (T_{res}) to the mean absorption time (T_{abs}).

$$A_n = T_{res}/T_{abs} = (\pi R^2 L/Q)/(R/P_{eff}) \quad (2)$$

4.2. Dissolution number (D_n)

The dissolution number (D_n) is the ratio of T_{res} to mean dissolution time (T_{diss}).

$$D_n = T_{res}/T_{diss} = (\pi R^2 L/Q)/(\rho r_0^2/3 DC_s^{\min}) \quad (3)$$

4.3. Dose number (D_o)

The dose number (D_o) is calculated using equation:

$$D_o = \text{Dose}/(V_o \times C_s^{\min}) \quad (4)$$

where L =tube length, R =tube radius, $\pi=3.14$, Q =fluid flow rate, r_0 =initial particle radius, D =particle acceleration, ρ =particle density, P_{eff} =effective permeability, V_o =the initial gastric volume and $C_s^{\min}$ =minimum aqueous solubility in the physiological pH range of 1–8.

BCS in conjunction with the numerous compendial and physiological media available could be employed as a fundamental guidance for designing appropriate biorelevant dissolution conditions leading to a more meaningful prediction of *in vivo* performances. The purpose of *in vitro* dissolution studies in the drug development process is to assess the lot to lot quality of a drug product, guide development of new formulations; and ensure continuing product quality and performance after certain changes, such as changes in the formulation, the manufacturing process, the site of manufacture, and the scale-up of the manufacturing process (FDA 1997a).

However, from the standpoint of *in vitro-in vivo* correlation (IVIVC), dissolution serves as a surrogate for drug bioavailability. Thus more rigorous dissolution standards may be necessary for the *in vivo* waiver (Dressman and Reppas 2000). So for the IVIVC purposes, the dissolution profiles of at least twelve individual dosage units from each lot should be determined (Table 4). The goal behind it is to develop product specifications that will ensure bioequivalence of future batches prepared within the limits of acceptable dissolution specifications (FDA 1997a).

5. Biowaivers

Before 1995 *in vitro* dissolution tests were used as a quality control tool to ensure batch-to-batch uniformity of formulations. *In vitro* dissolution tests could be used to waive *in vivo* BE tests. If the drug has high permeability and low solubility (BCS II) or modified-release formulation is used, dissolution rate may control drug absorption thus dissolution tests together with level A IVIVC model can be used as a surrogate for *in vivo* BE studies (FDA 1997b; Uppoor 2001).

In some situations (e.g. BCS Class 1 drugs) a bioequivalence study in human subjects may be replaced by *in vitro* dissolution testing. Alternatively sponsors may want to rely on bioequivalence data generated overseas where it is not known whether the formulations under these studies are based on are the same as the formulations proposed to be marketed. When such a waiver for not providing clinical data or justification for utilizing overseas bioequivalence data is allowed by regulatory authorities this is referred to as a “biowaiver”. The FDA guidance outlines (FDA 2000c) five categories of biowaivers:

- 1) Biowaivers without an IVIVC,
- 2) Biowaivers using an IVIVC: non-narrow therapeutic index drugs,
- 3) Biowaivers using an IVIVC: narrow therapeutic index drugs,
- 4) Biowaivers when *in vitro* dissolution is independent of dissolution test conditions,
- 5) Situations for which an IVIVC is not recommended for biowaivers.

Biowaivers may be granted for manufacturing site changes, equipment changes, manufacturing process changes, and formulation composition changes according to a predictive and reliable IVIVC. The changes may range from minor changes that are not significant to alter product performance to major ones where an IVIVC is not sufficient to justify the change for regulatory decision (Uppoor 2001).

6. A Waiver of *In vivo* BA/BE studies

For the grant of a waiver the drug substance should be highly soluble, highly permeable and rapidly dissolving. For waiver of an *in vivo* BA study, dissolution should be greater than 85% in 30 minutes in the three recommended dissolution media and test as well as reference products should exhibit similar dissolution profiles under the dissolution test conditions as defined for rapidly dissolving products. When requesting a waiver for *in vivo* BA/BE studies for IR solid oral dosage forms, one should consider the following aspects:

6.1. Instability in the GI tract

Stability in gastrointestinal fluids can be documented by (1) pH-stability profiles in the pH range of 1–8 and (2) stability in gastric and intestinal fluids obtained from human subjects or animals. Drug solutions in these fluids can be incubated at 37 °C for about three hours and analyzed using a validated stability indicating assay. Significant degradation or loss (>5%) of a drug in about three hours could suggest potential instability.

6.2. Evaluation of excipients

The BCS biowaiver for *in vivo* bioavailability and bioequivalence studies requires excipients to be in a dosage form should have been used previously in FDA approved IR solid dosage forms and should have a wide therapeutic window and showing rapid and similar dissolution, high solubility and high perme-

ability. The quantity of excipients in the IR product should be consistent with their intended function. Excipients can sometimes affect the rate and extent of drug absorption. When new excipients, or atypically large amounts of commonly used excipients, are used in an IR dosage form, additional information regarding the absence of an impact on bioavailability should be documented. Such information can be supplied via a relative bioavailability study using a simple aqueous solution as the reference product. Large quantities of certain excipients, such as surfactants like sodium lauryl sulfate, may be problematic. A request for biowaiver based on the BCS should include a list of all excipients used in the products, the amount used in the test product, intended functions, a brief summary describing the manufacturing process, and the list of equipment used.

7. Exceptions for BCS-based biowaivers

BCS-based biowaivers are not applicable for narrow therapeutic range drug and product designed to be absorbed in the oral cavity.

7.1. Narrow therapeutic range drugs

Narrow therapeutic range drug products can be defined as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. The drug should not have a narrow therapeutic index (FDA 2000c). This limitation is expected to be applied primarily to NDA and ANDA bioequivalence studies after approval, as well as bioequivalence studies submitted in an ANDA, recognizing that during the IND period an investigational drug may not be clearly identified as a narrow therapeutic index drug. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. All drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are not narrow therapeutic range drugs.

7.2. Products designed to be absorbed in the oral cavity

A request for a waiver of *in vivo* BA/BE studies based on the BCS, would not be considered appropriate for dosage forms intended for retention in the oral cavity (e.g., sublingual or buccal tablets), or for those intended for dissolution in the oral cavity or designed for administration without the aid of water. Permeability class membership of prodrugs may depend on whether conversion to the active moiety occurs in the gastrointestinal tract or following intestinal membrane permeation.

8. Simulation model for biowaivers

According to the biopharmaceutics classification system if drug has high solubility and high permeability (BCS I), *in vitro* dissolution tests can be used to waive *in vivo* bioequivalence studies (biowaiver). The absorption of BCS I drugs is not dependent on drug dissolution or gastrointestinal transit time and the solid dosage form behaves like oral solution. In current scenario biowaivers are determined on the basis of solubility, permeability and dissolution, but the factors correlated with the gastrointestinal tract and the dynamic nature of drug dissolution and systemic pharmacokinetics are not taken into consideration. Pharmacokinetic simulation models can be utilized to study effects of formulation types, different rates of dissolution and gastric emptying on drug concentrations in plasma. Simulated maximum concentration in plasma (C_{max}) and area under the curve (AUC) values of solid dosage forms are compared to

the simulations of oral solution. By definition the absorption of BCS I drugs is not dependent on drug dissolution and/or gastrointestinal transit time (FDA 2000c). Furthermore BCS I drug should have a wide therapeutic window and linear pharmacokinetics. The excipients and formulations must be well-known. In current scenario drugs in other categories of BCS (except BCS I drug) are not acceptable as biowaivers.

Pharmacokinetics of drugs are affected by several factors like physiology of the gastrointestinal (GI) tract, drug solubility, dissolution, permeability, distribution and elimination. Pharmacokinetic simulation models have become attractive tools to study the interplay of these variables so that the risks related to the bioavailability or bioequivalence study or biowaiver decision can be estimated and the most critical factors affecting C_{max} and AUC of certain drug can be ascertained. Kortejarvi et al. (2007) used a pharmacokinetic simulation model to evaluate current biowaiver criteria for BCS I drugs and to explore whether biowaivers can be found among BCS II–IV drugs and simulated BCS I–IV drugs using various parameter combinations. C_{max} and AUC of immediate-release solid dosage forms were compared to oral solution in the simulations. Based on these simulations they suggested that all BCS III drugs are good biowaivers, but half of the BCS I drugs are not.

Various studies also suggested that acidic BCS II (Rinaki et al. 2004) and III drugs (Yu et al. 2002; Blume and Schug 1999; Cheng et al. 2004; Vogelpoel et al. 2004) can be biowaivers. Although it has been shown, that C_{max} and/or AUC of some BCS II and III drugs are not sensitive to the minor differences of dissolution rates. As biowaiver criteria a maximum of 10% difference in AUC and C_{max} , between solid dosage forms and oral solution can be suggested. For a good biowaiver candidate AUC and C_{max} should not be sensitive to formulation type, gastric emptying rate or minor differences in dissolution.

In their simulation model Kortejarvi et al. (2007) assumed that *in vivo* dissolution is identical with the *in vitro* dissolution (i.e. $K_d 4h^{-1}$) as defined in biowaiver guidelines. When solid dosage forms were compared to oral solution, less than 9% difference in C_{max} and less than 3% difference in AUC values of BCS I and BCS III drugs were observed. *In vivo* dissolution rate constant $2 h^{-1}$ was used in these simulations and C_{max} ratios of BCS III drugs (0.91–0.97 or 0.91–0.99, for multiple and single unit formulations, respectively) were found closer to 1.0 than the ratios of BCS I drugs (0.82–0.99 and 0.75–0.99 for multiple and single unit formulations, respectively), although BCS I are the currently accepted biowaivers. C_{max} differences of BCS I drugs with rapid absorption and rapid elimination were the greatest. Systematically the influence of formulation types, physiology of GI tract and drug properties (dissolution, absorption and elimination) against current biowaiver criteria should be studied.

9. Conclusion

Advent of the Biopharmaceutics Classification System (BCS) makes it possible to stream line development for some products via BCS biowaiver. BCS can be strategically deployed to save time and resources during generic drug development. BCS approach should be selectively utilized, carefully considering cost versus benefit for each project. BCS waivers represent scientific understanding of both the formulation and the *in vivo* environment and also accelerate development of new products and regulatory approvals.

An extension of the BCS regulatory guidelines is considered essential before its widespread use in all developmental phases. The current version limits the broad use of BCS since Class I drug substances (high solubility, high permeability) are relatively rare in current pharmaceutical discipline (Lennernäs and

Abrahamsson 2005; Kasim et al. 2004). The future application of BCS will become more important when the present framework gains increased recognition, which will probably be the case if the BCS borders for certain Class II (high permeability, low solubility) and Class III (low permeability, high solubility) drugs are extended. Knowing the BCS category of your compound, you can save both time and money. If your immediate-release, orally administered drug meets specific criteria, the FDA will grant you a waiver of the expensive and time-consuming bioequivalence studies.

Revision of the BCS guidelines by the regulatory bodies in communication with academic and industrial scientists is exciting and will hopefully result in an increased applicability in drug development. Finally, scientists in this field emphasise the usefulness of BCS as a simple tool in early drug development to determine the rate-limiting step in the oral absorption process, which has facilitated the exchange of information between experts involved in the overall drug development process. In the future, this increased awareness of a proper biopharmaceutical characterization of new drugs may result in drug molecules with sufficiently high permeability, solubility and dissolution rate properties that will automatically help to increase the importance of BCS as a regulatory tool.

References

- Amidon GL, Lennernas H, Shah VP, Crison JR (1995) A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm Res* 12: 413–420.
- Artursson P (1990) Epithelial transport of drugs in cell culture: A model for studying the passive diffusion of drugs over intestinal absorptive (Caco-2) cells. *J Pharm Sci* 79: 476–482.
- Artursson P, Karlsson J (1991) Correlation between oral drug absorption in human and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. *Biochem Biophys Res Commun* 175: 880–885.
- Blume HH, Schug BS (1999) The biopharmaceutics classification system (BCS): class III drugs-better candidate for BA/BE waiver? *Eur J Pharm Sci* 9: 117–121.
- Cheng CL, Yu LX, Lee HL, Yang CY, Lue CS, Chou CH (2004) Biowaiver extension potential to BCS Class III high solubility-low permeability drugs: bridging evidence for metformin immediate-release tablet. *Eur J Pharm Sci* 22: 297–304.
- Dimond PF (2005) Using nanotechnologies in biotech and medicine. *Gen Eng News* 25: 21.
- Dressman BJ, Reppas C (2000) *In vitro-in vivo* correlations for lipophilic, poorly water-soluble drugs. *Eur J Pharm Sci* 11: 73–80.
- Dressman J, Butler J, Hempenstall J, Reppas C (2001) The BCS: Where Do We Go from Here? *Pharm Tech* 68–76.
- Dressman JB, Amidon GL, Reppas C, Shah VP (1998) Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharm Res* 15: 11–22.
- FDA Guidance (2000b) The Biopharmaceutics Classification System (BCS). Food and Drug Administration, Rockville, MD.
- FDA Guidance for Industry (1997a) Dissolution testing for immediate release solid oral dosage forms. Food and Drug Administration, Rockville, MD.
- FDA Guidance for Industry (1997b) Extended release oral dosage forms: development, evaluation and application of an *in vitro/in vivo* correlation. Food and Drug Administration, Rockville, MD.
- FDA Guidance for Industry (2000a) Bioavailability and bioequivalence studies for orally administered drug products-general considerations. Food and Drug Administration, Rockville, MD.
- FDA Guidance for Industry (2000c) Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Food and Drug Administration, Rockville, MD.
- Fleisher D, Li C, Zhou Y, Pao LH, Karim A (1999) Drug, meal and formulation interactions influencing drug absorption after oral administration: Clinical implications. *Clin Pharmacokinet* 36: 233–254.
- Han H, de Vruet RL, Rhie JK, Covitz KM, Smith PL, Lee CP, Oh DM, Sadee W, Amidon GL (1998) 5γ-Amino acid esters of antiviral

- nucleosides, acyclovir, and AZT are absorbed by the intestinal PEPT1 peptide transporter. *Pharm Res* 15: 1154–1159.
- Hidalgo I, Raub T, Borchardt R (1989) Characterization of the human colon carcinoma cell line (Caco-2) as a model system for intestinal epithelial permeability. *Gastroenterology* 96: 736–49.
- Hilgers AR, Conradi RA, Burton PS (1990) Caco-2 monolayers as a model for drug transport across the intestinal mucosa. *Pharm Res* 7: 902–910.
- Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernäs H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL (2004) Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. *Mol Pharm* 1: 85–96.
- Kortejarvi H, Urtti A, Yliperttula M (2007) Pharmacokinetic simulation of biowaiver criteria: The effects of gastric emptying, dissolution, absorption and elimination rates. *Eur J Pharm Sci* 30: 155–166.
- Lennernäs H (1998) Human Intestinal Permeability: An Overview. *J Pharm Sci* 87: 403–410.
- Lennernäs H, Abrahamsson B (2005) The use of the Biopharmaceutic Classification in drug discovery and development: current status and future extension in drug bioavailability, estimation of solubility, permeability, absorption and bioavailability. *J Pharm Pharmacol* 57: 273–285.
- Lennernäs H, Lee ID, Fagerholm U, Amidon GL (1997) A residence-time distribution analysis of the hydrodynamics within the intestine in man during a regional single-pass perfusion with Loc-I- Gut: *in-vivo* permeability estimation. *J Pharm Pharmacol* 49: 682–686.
- Pelkonen O, Boobis AR, Gundert-Remy U (2001) *In vitro* prediction of gastrointestinal absorption and bioavailability: an experts' meeting report. *Eur J Clin Pharmacol* 57: 621–629.
- Polli JE, Yu LX, Cook JA, Amidon GL, Borchardt RT, Burnside BA, Burton PS, Chen, ML, Conner DP, Faustino PJ, Hawi AA, Hussain AS, Joshi HN, Kwei G, Lee VH, Lesko LJ, Lipper RA, Loper AE, Nerurkar SG, Polli JW, Sanvordeker DR, Taneja R, Uppoor RS, Vattikonda CS, Wilding I, Zhang G (2004) Summary workshop report: Biopharmaceutics Classification System-implementation challenges and extension opportunities. *J Pharm Sci* 93: 1375–1381.
- Rinaki E, Dokoumetzidis A, Valsami G, Macheras P (2004) Identification of biowaivers among class II drugs: theoretical justification and practical examples. *Pharm Res* 21: 1567–1572.
- Sun D, Yu LX, Hussain MA, Wall DA, Smith RL, Amidon GL (2004) *In vitro* testing of drug absorption for drug developability assessment: forming an interface between *in vitro* preclinical data and clinical outcome. *Curr Opin Drug Discovery Dev* 7: 75–85.
- Tamura S, Tokunaga Y, Ibuki R, Amidon GL, Sezaki H, Yamashita S (2003) The site-specific transport and metabolism of tacrolimus in rat small intestine. *J Pharm Exp Ther* 306: 310–316.
- Uppoor VRS (2001) Regulatory perspectives on *in vitro* (dissolution)/*in vivo* (bioavailability) correlations. *J Control Rel* 72: 127–132.
- Vogelpoel H, Welink J, Amidon GL, Junginger HE, Midha KK, Möller H, Olling M, Shah VP, Barends DM (2004) Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: verapamil hydrochloride, propranolol hydrochloride, and atenolol. *J Pharm Sci* 93: 1945–1956.
- Walter E, Janich S, Roessler BJ, Hilfinger JM, Amidon GL (1996) HT29-MTX/Caco-2 cocultures as an *in vitro* model for the intestinal epithelium: *in vitro-in vivo* correlation with permeability data from rats and humans. *J Pharm Sci* 85: 1070–1076.
- Wilson G, Hassan IF, Dix CJ, Williamson I, Shah R, Mackay M (1990) Transport and permeability properties of human Caco-2 cells: An *in vitro* model of the intestinal epithelial cell barrier. *J Controlled Rel* 11: 25–40.
- Wu CY, Benet LZ (2005) Predicting drug disposition via application of BCS: transport/absorption/ elimination interplay and development of a biopharmaceutics drug disposition classification system. *Pharm Res* 22: 11–23.
- Yang Y, Faustino PJ, Volpe DA, Ellison CD, Lyon RC, Yu LX (2007) Biopharmaceutics Classification of Selected β -Blockers: Solubility and Permeability Class Membership. *Mol Pharma* 4: 608–614.
- Yee S (1997) *In vitro* permeability across Caco-2 cells (colonic) can predict *in vivo* (small intestinal) absorption in man-fact or myth. *Pharm Res* 14: 763–766.
- Yu LX (1999) An integrated absorption model for determining causes of poor oral drug absorption. *Pharm Res* 16: 1883–1887.
- Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, Shah VP, Lesko LJ, Chen ML, Lee VH, Hussain AS (2002) Biopharmaceutics classification system: the scientific basis for biowaiver extensions. *Pharm Res* 19: 921–925.
- Yu LX, Carlin AS, Amidon GL, Hussain AS (2004) Feasibility studies of utilizing disk intrinsic dissolution rate to classify drugs. *Int J Pharm* 270: 221–227.