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Review Article

Biological classification system (BCS); its significance on dissolution study and application in dosage form development

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ABSTRACT

Bioavailability (BA) has an important role in new drug discovery and product development in pharmaceutical field. The solubility and permeability are important parameters of biopharmaceutics and have central role in lead optimization by controlling the pharmacokinetic parameters to give better therapeutic activity. Biopharmaceutical classification system (BCS) is a drug development tool that is based on correlation of solubility and permeability with bioavailability of drug in human body. The principles of BCS are widely applicable in development of new drug and new drug product as the scientific approach for testing of waiver on clinical study and bioavailability of drug and in regulatory approvals of drug. This review article gives an overview of BCS with special emphasis on concept, classification, class boundaries determination, extension and BDDCS with brief idea on applications. Finally, future prospect and limitations are pointed out.

INTRODUCTION

The oral route of drug administration is the route of choice for the formulators and also convincible for patients so that continues to dominate the area oral drug delivery technologies..Oral drug delivery route has two main challenges that is the solubility and permeability of drug. The oral absorption and hence bioavailability of drug is determined by the extent of drug solubility and permeability. The applicability and validity have been the matter of extensive research and discussion since the introduction of the Biopharmaceutics Classification System (BCS)[1, 2].The bioavailability and bioequivalence are depend on the solubility and permeability of drug and it is useful tool for the drug development process provided by U. S. Food & Drug Administration.[3]The Biopharmaceutical classification system (BCS) is a very important tool for decision making for bioavailability of drug during the phases of early drug development.[4] The BCS was first devised in 1995 and became a standard in the regulation of bioequivalence of oral dosage forms.[5, 6]

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The BCS is a scientific framework that classifies a drug substance based on two parameters : its aqueous solubility and intestinal permeability[7]. On combination of these parameters with the in vitro dissolution characteristics of the drug product, the BCS considers three major factors: solubility, intestinal permeability, and dissolution rate, that affect bioavailability from IR solid oral-drug products [8, 9].In BCS, each class has particularly designated rate-limiting step with possibilities for its modification so that the formulator can select and optimize a specific dosage form for the drug substance belonging to a particular class of BCS[10, 11].The target of this review article is to present and discuss BCS with its applications and future prospect.

Concept Behind BCS[12]

The Pharmacotherapeutics response of orally administered drugs mainly depends upon their solubility and tissue permeability characteristics. Depend on the solubility and permeability of drug substances BCS classified the drug substances in four classes. Which are described in **Table: 1.** If solubility is rate limiting step for the bioavailability of drug then we have to improve the solubility by changing the factors which affect the solubility.

Table 1: BCS Classification

Classes/ Parameters	Solubility	Permeability	Rate Limiting step for Bio-availability
Class-1	High	High	None
Class-2	Low	High	Solubility
Class-3	High	Low	Permeability
Class-4	Low	Low	Both

The factors are surface area of particles, surface charges of particles, salt formation, adding surface active agent (Nonionic surface active agent), Polymorphism and changing the dosage form. By changing the all parameters are not affecting the drug solubility then lastly we have to change the drug structure. If permeability is rate limiting step for the bioavailability of drug then we have to improve the drug permeability for better absorption and bioavailability. The factors which affect drug permeability are pH, polymorphism, and dosage form, we cannot change the GI fluid pH but we can provide microenvironment to drug for its better absorption.

Objectives

BCS serves as an important guiding tool for the formulation scientists to select and design the formulation of any drug substance and to explain waiver for in vivo bioavailability and bioequivalence studies maybe requested [16]. The objectives are to recommend a class of immediate release (IR) solid oral dosage form for which bioequivalence may be accessed based on in vitro dissolution tests, to improve drug development and review process efficiency by recommendation of a strategy for identifying clinical bioequivalence test and to recommend methods for classification according to dosage form solubility and permeability characteristics of drug substance[9].

Key Parameters Controlling Absorption

BCS is related with drug dissolution and absorption model, which identifies the key parameters that are a set of dimensionless numbers and control absorption of drug substance: [8, 17].

The Dissolution number is a ratio of mean residence time to mean dissolution time and estimated using equation 2.

Dn=(Tres/Tdiss)=(3.14 R2L/Q) / (ρ r2 /3 D Cs min)...(2)

The Absorption Number (An) is the ratio of the Mean Residence Time (Tres) to the Mean Absorption Time (Tabs) and estimated using equation.

An = (Tres / T abs) = (3.14R2L/Q) (R/Peff) ...(3)

The Dose number is the mass divided by an uptake volume of 250 ml and the drug solubility. It could be estimated using equation.

D0 = Dose/(V0 xCmins) ……(4)

The mean residence time here is the average of the residence time in the stomach, small intestine and the colon.

Where: R = tube radius, L = tube length, Q = fluid flow rate, π = 3.14, D = particle acceleration, ro = initial particle radius, ρ = particle density, Peff = effective permeability, Vo is the initial gastric volume equal to250 ml which is derived from typical bioequivalence study protocols that prescribe drug administration to human volunteers with a glass of water at the time of drug administration and Cs min is minimum aqueous solubility in the physiological pH range of 1-8.

Classification

Class I drugs have a high dissolution number and a high absorption number. The rate limiting step is drug dissolution but in the case where dissolution is very rapid, gastric emptying rate becomes the rate determining step for bioavailability. The absorption rate of these compounds is generally higher than their excretion. So there is no need of bioavailability and bioequivalence studies for such products rendering these compounds highly suitable to design the SR and CR formulations. IVIVC cannot be expected. Examples include Ketoprofen, Diltiazem, Verapamil, Naproxen, Carbamazepine, Propanolol, Metoprolol, etc.[2-4, 18, 19]

Class II drugs exhibit a high absorption number but a low dissolution number. The rate limiting step is in vivo dissolution except at a very high dose number. These drugs exhibit variable bioavailability and need the dissolution enhancement to increase the bioavailability. These compounds are suitable for design the SR and CR formulations and In vitro- In vivo correlation (IVIVC) is can be found. Examples include Felodipine, Ketoconazole, Mefenamic acid, Nifedinpine, Phenytoin, Danazol,

Nicardipine, Nisoldipineetc. The dissolution can be enhanced by using various methods such as use of surfactants, complexation, produg concept, use of selected polymeric forms, solvates and hydrates, salt of weak acids and weak bases, by buffering the pH of the microenvironment, by increasing surface area using different techniques like micronization, solid dispersion etc.[18, 20-22]

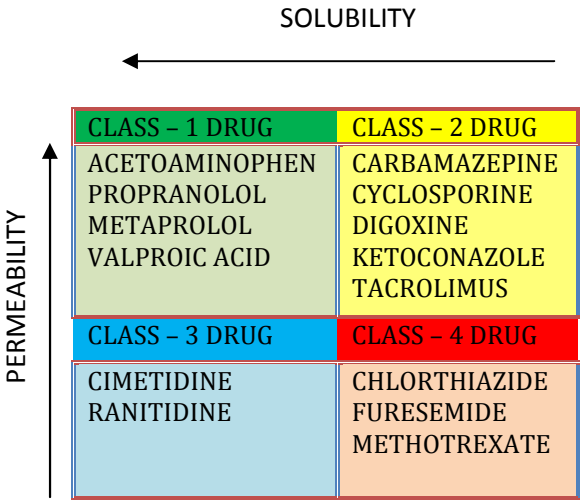

Figure 1: BCS Classification with relevant drugs' example

Class III drugs show low absorption number and high dissolution number. The permeability is rate limiting step for drug absorption exhibiting high degree of alteration in drug absorption. Since the dissolution is rapid, the variation may be due to variation in physiology and membrane permeability rather than the dosage form factors. The bioavailability is lower and need of enhancement in permeability by pH, polymorphism, and dosage form. We cannot change the GI fluid pH but we can provide microenvironment to drug for its better absorption. The controlled release development for these drugs is difficult. The examples are Enalaprilat, Neomycin B, Captopril, Acyclovir, Alendronate, etc. [18, 20]

Class IV drugs are problematic for optimum oral administration exhibiting poor and variable bioavailability. The rate limiting steps for the drug absorption are created by several factors such as dissolution rate, permeability and gastric emptying making them unsuitable for controlled release. The examples are hydrochlorthiazide, taxol, Cefuroxime, Furosemide, Chlorthiazide, Tobramycine etc.[14, 20]

BCS could be reduced into two classes. Class-I Permeation rate limited absorption: Drugs with in-vivo K diss> in-vivo Kpe belong to class I regardless fa. Class-II Dissolution rate limited absorption Drugs with in-vivo Kdiss< in-vivo Kpe belong to class II. Here in-vivo BE studies are required.

Class Boundaries and Determination [23-25]

The solubility, permeability and dissolution are main class boundary parameters useful in identification of drug products.

1. 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. The volume 250 mL estimate by bioequivalence study, Drug product administered the fasting healthy volunteers with glass of 8 ounces of waters.
2. 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.
3. 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.

Solubility Determination

Solubility is the amount of a substance that has passed into solution when equilibrium is attained between the solution and excess (i.e., un dissolved) substance at a given temperature and pressure.

The solubility is determined by adding the excess amount of solid in pre quantify amount of liquid (water or water/buffer) and stir it for 12 hours at 25°C. If all drug dissolve then we can add more repeat this till we got saturated solubility and assay after equilibrium that usually takes 60-72 hrs.[26]The Solubility determination by precipitation method is not appropriate because of the so-called meta stable (solubility) zone leads to false interpretation. The pH–solubility profile of the drug is determined at 37 ± 1°C in aqueous medium in the pH range of1.2–6.8 (per WHO guidelines) or 1–7.5 (per FDA guidelines) with evaluation of sufficient number of samples. For the solubility determination number of pH condition can be based on the ionization characteristics of the test drug substance to include pH=pKa, pH = pKa+1, pH=pKa-1 and pH = 1 and 6.8. A minimum of three replicate

solubility determinations should be carried out in each pH condition but additional replicates may be necessary, depending on study variability, to provide accurate estimation.

The other methods such as acid or base titration methods can be used to support the ability of methods like shake flask method for prediction of equilibrium solubility of the test drug with proper justification.[27]Drug substance and its degradation products should be quantitatively determine by validated stability indicating assay method. Solubility can be measured as either a kinetic or a thermodynamic value. Kinetic solubility measurements are strongly time-dependent and represent the maximum (kinetic) solubility of the fastest precipitating species of a compound. The different kinetic methods are turbidimetric, nephelometric method and UV absorption. The thermodynamic methods such as a scaled-down shake-flask method and a solvent evaporation method are also used.

Permeability Determination

The permeability is directly related to the extent of intestinal absorption of a drug substance in humans or indirectly to the measurements of the rate of mass transfer across the human intestinal membrane.[28]

A drug substance is considered highly permeable when the extent of absorption is 90% or more of an administered dose in humans, compared with an intravenous reference dose or based on mass-balance. In many cases, a single method may be sufficient: (i) when the absolute BA is 85 percent or more, or (ii) when 85 percent or more of the administered drug is excreted unchanged in urine, or (iii) when 85 percent or more of the administered drug is recovered in urine as parent and metabolites with evidence indicating stability in the GI tract. When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable. In case of conflicting information from different types of studies, it is important to note that human data supersede in vitro or animal data.

The methods that are routinely used for the determination of permeability include:[27]

1. Pharmacokinetic study of human
- Mass Balance studies
- Absolute Bioavailability studies

2. Intestinal Permeability Methods
- In vivo intestinal perfusion studies in humans.
- In vivo or in situ intestinal perfusion studies using suitable animal models.
- In vitro permeation studies using excised human or animal intestinal tissues.
- In vitro permeation studies across a monolayer of cultured epithelial cells (e.g., Caco-2 cells or TC-7 cells)

3. Instability in the Gastrointestinal Tract

Pharmacokinetic study of human

Mass Balance studies

Pharmacokinetic mass balance studies using radio labeled drug substances or labeled isotopes can be used to extent absorption of drug. To minimize the error (or minimize the standard deviation) sufficient number of subject should be enrolled. When mass balance studies are used to demonstrate high permeability, additional data to document the drug's stability in the GI tract is required, unless 85 percent or more of the drug is excreted unchanged in urine.

Absolute Bioavailability method

Oral bioavailability determination using administration of intravenous as a reference can be used. To minimize the error of studies, a sufficient number of subject should be studied to get reliable estimate of the extent of absorption. When the absolute bioavailability of a drug is shown to be 85 percent or more, additional data to document drug stability in the GI fluid is not necessary.

Intestinal Permeability Method

The following methods can be used to determine the permeability of a drug substance from the GI tract:
- in vivo intestinal perfusion studies in humans;
- in vivo or in situ intestinal perfusion studies using suitable animal models;
- in vitro permeation studies using excised human or animal intestinal tissues; or
- in vitro permeation studies across a monolayer of cultured epithelial cells.

In vivo or in situ animal models and in vitro methods, such as those using cultured mono layers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane efflux transporters such as P-glycoprotein (P-gp). When the efflux transporters are absent in these models, or their degree of expression is low compared to that in

humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared to a drug transported passively.

For BCS-based permeability determination, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied

A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration-time curve) of a drug is demonstrated in humans.

Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 mL) in the perfusion fluid.

Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 ml) is demonstrated, or on transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp).

3. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the GI fluid prior to intestinal membrane permeation. In addition, some methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human and/or animal GI tract either in vivo or in situ. Documenting the fact that drug loss from the GI tract arises from intestinal membrane permeation, rather than a degradation process, will help establish permeability. Stability in the GI tract may be documented using simulated gastric and intestinal fluids. Obtaining GI fluids from human subjects requires intubation and may be difficult. Therefore, use of simulated fluids such as Gastric and Intestinal Fluids USP may be reasonable.

Drug solutions in these fluids should be incubated at 37oC for a period that is representative of in vivo drug contact with these fluids; for example, 1 hour in gastric fluid and 3 hours in intestinal fluid. Drug concentrations should then be determined using a validated stability-indicating assay method. Significant degradation (>5 percent) of a drug in this study could suggest potential instability.

DISSOLUTION DETERMINATION

According to BCS, a drug product is called rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 min in 900 ml or less dissolution medium using USP Apparatus 1 (basket) at 100 rpm or USP Apparatus 2 (paddle) at 50 rpm. Various types of dissolution medium used are:[24, 28]

1. 0.1 N HCI or simulated gastric fluid (SGF) USP without enzymes
2. pH 4.5 buffer
3. pH 6.8 buffer or simulated intestinal fluid (SIF) USP without enzymes

Selection of the dissolution testing apparatus (USP Apparatus I or II) should be based on a comparison of in vitro dissolution and available in vivo pharmacokinetic data for the drug product. The evaluation of minimum 12 dosage units of a drug product should be evaluated and samples should be collected at a sufficient number of time intervals (e.g., 10, 15, 20,30 and 60 min). The dissolution profiles of the test and reference products should be compared using a similarity factor (f2) to measure of the similarity in the percent (%) of dissolution between the two curves. The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error.

$$f2 = 50 * \log \{[1 + (1/n) \Sigma=1n (Rt - Tt) 2]-0.5 * 100\}$$

Where, Rt is the cumulative percentage dissolved at time point t for reference products, Tt is the cumulative percentage dissolved at time point t for test products and n is the number of pool points (3). The dissolution profiles are considered similar when the value of f2 is >50.

Dissolution Media for Various Classes of BCS

Media for Class I substances

Substances that belong to class I possess good aqueous solubility and are transported through the GI mucosa. Their bioavailability after oral organization is usually close to 100 %, provided they are not decomposed in GIT and do not undergo extensive first pass metabolism [17]. After administration, the dosage form quickly passes into stomach and, usually disintegrates there, so it is logical to use a dissolution medium

that reflects the gastric conditions. Simulated gastrointestinal fluid (SGF) without enzymes is suitable for many immediate release dosage forms of this class. For some capsules, an enzyme (pepsin) may have to be added to the medium to ensure the timely dissolution of the shell [18]. In case of weak acidic drugs simulated intestinal fluid without enzyme may be used due to hampered dissolution of this drug by the SGF medium. Water is less suitable medium than the aforementioned buffers, because it has a nominal buffer capacity zero; therefore, the pH may vary during the test [19]. Milk use dissolution media as simulate fed state condition of body fluid because milk contain similar ratio of carbohydrate: Protein: fat which ratio found in fed state condition of GI fluid. [20, 21]

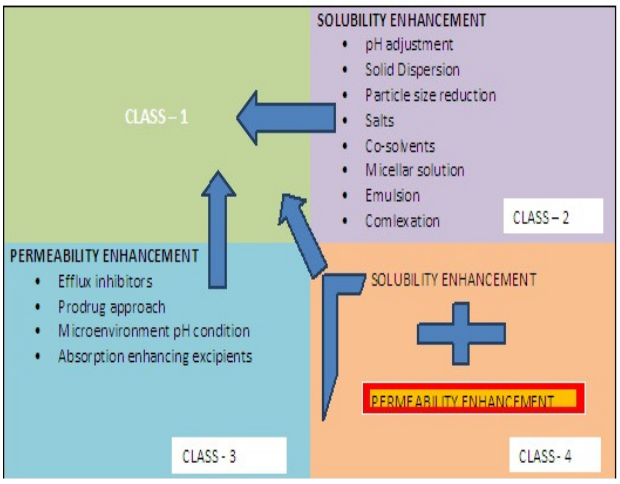

Figure 2: Strategies to get the BCS class I characteristics

Media for Class II substances

Substances that belong to class II possess poor aqueous solubility but are easily transported across the GI mucosa. Suitable bio relevant media for class II drugs are: (a) SGF sp plus surfactant (e.g., Triton X-100), to simulate the fasted state in the stomach. This medium is specifically useful for weak basic drugs, because these are most soluble under acidic condition. Presence of surfactant in the gastric may play a role in the wetting and solubilization of poorly soluble acids in the stomach [22]. (b) Ensure and Milk as dissolution media can improve the drug solubility include the solubilization of drugs in the fatty part of the fluid. Both of these media contains similar ratio of protein/fat/ carbohydrate [20, 21]. (c) FaSSIF (Fasted state simulated intestinal fluid) and FeSSIF (Fed state simulated intestinal fluid) are the recently developed to simulate the intestinal condition. The two media are particularly useful for forecasting the in vivo dissolution of the poorly soluble drugs from different formulations and for assessing potential for foods effects on the in vivo dissolution. The dissolution rate of the poorly soluble drug is often better in FaS SIF and FeS SIF than in the simple aqueous buffers because of the increased wetting of the drug surface and micellar solubilization of the drug by the bile components of these media [19, 23]. (d) Hydro alcoholic mixtures as dissolution media were popular for the dissolution of poorly soluble drugs. Particular significance of these media over the surfactant containing media is that they do not tend to foam, which makes duration and volume adjustment somewhat less frustrating [17, 19].

Media for Class III substances

Despite their good aqueous solubility, class III substances fail to achieve complete bioavailability after oral dosing because of their poor membrane permeability. A simple aqueous media can be used [6,19].

Media for Class IV substances

Class IV drugs combine poor solubility with poor permeability. Therefore, similar to class III drugs, they usually do not approach complete bioavailability. Two compendial media i.e. SGF sp & SIF sp with addition of a surfactant to ensure the complete release of drug from formulation can be used [6, 17, 19].

Model dependent and independent method to compare dissolution profiles

These two methods are used to compare dissolution profile of two or more dosage forms.

BCS Guidance on Bio waivers

The BCS guidance, issued by FDA, recommends that bio waiver may be requested by sponsors for highly soluble and highly permeable drug substances (Class I) in immediate release solid oral dosage forms that show rapid in vitro dissolution.[6] The drug product should meet the following conditions:

1) The drug must be stable in the gastro intestinal tract;
2) The drug must have a wide therapeutic index;
3) The product should not be absorbed in the oral cavity and
4) Excipients should not have any significant effect on the bioavailability of drug.

Table 2: Methods for comparison of dissolution profile

Approach	Method	Parameter/equation
Model-independent	Ratio test procedures	Ratio of percent dissolved
		Ratio of area under dissolution curve
		Ratio of mean dissolution time
	Pair wise procedures	Difference factor (f_1)
		Similarity factor (f_2)
		Index of Rescigno (ξ_1 and ξ_2)
Model-dependent	Zero-order	% diss = kt
	First-order	% diss = 100 $(1 - e^{-kt})$
	Hixson-Crowell	% diss = 100 $[1-(1- kt/4.6416 mg^{1/3})^3$
	Higuchi	% diss = $kt^{0.5}$
	Quadratic	% diss = $100(k_1t^2 + k_2t)$
	Weibull	% diss = 100 $[1 - e^{-(t/\tau)\beta}]$
	Gompertz	% diss = A $e^{-e-k(t-\gamma)}$
	logistic	% diss = A / $[1+e^{-k(t-\gamma)}]$

According to the BCS, in vivo differences in drug dissolution of two pharmaceutically equivalent solid oral products may result in the in vivo differences in the rate and extent of absorption of a drug. The rate and extent of drug absorption is independent of drug dissolution when the in vivo dissolution of an immediate release oral dosage form is fast in comparison with gastric emptying. Therefore, in the case where the inactive ingredients of the dosage form significantly affect the absorption of the active ingredient, demonstration of in vivo bioequivalence may be necessary. For BCS Class I drug substances, assurance of rapid in vivo dissolution can be provided by demonstration of rapid in vitro dissolution using appropriate test methods. So it can be concluded FDA guidance lowers expenditures associated with bioavailability/bioequivalence studies with focus on the development of new chemical entities.[28]

Extension to BCS

Six class Biopharmaceutical Classification System

A modified BCS designed by Bergstrom and co-workers; dividing the drugs into six classes. The classification was based on the solubility, permeability and calculated surface area. The solubility was allotted as "high" or "low" and the permeability was classified as "low", "intermediate," or "high". The non polar surface area of the molecule terminated in good permeability and polar surface area good solubility. It was tentatively concluded that these models may be useful during the early stages of drug discovery to indicate the absorption profiles of the compound and to suggest necessary modifications can be made for optimization of the pharmacokinetic parameters.[29]

Quantitative Biopharmaceutical Classification System (QBCS)

Experience gained with intensive experiments has shown that the process of dissolution can be dependent on the amount of drug present at the site of absorption (dose), in addition to the solubility of drug in the dissolution fluid. The quantitative BCS (QBCS) was designed by Rinaki et al. 2003. The classification was based on the solubility: dose ratio as main parameter. The system sets solubility: dose ratio vs. permeability plane with cut-off values based on physiology for classification of compounds. The experiments results provide convincing evidence that the dissolution process can be dependent on the amount of drug present at the site of absorption (dose), in addition to the solubility of drug in the dissolution medium. As the solubility is a static equilibrium parameter, the dynamic character of the dissolution process cannot be described for the entire dose administered. The dose consideration should be taken into account because the drugs are administered in various doses. According to FDA guidance for the industry, August 2000, the highest dose strength of an immediate release product should be considered for study.[30]The QBCS relies on a (permeability, dose/solubility ratio) plane with cutoff points 2 × 10−6 cm/s to 2 × 10−5 cm/s for permeability and 0.5 to 1.0 for the dose solubility ratio. Permeability estimates, (P app that is the apparent permeability) were derived from Caco-2 cell studies and a constant intestinal volume content of 250 ml was used to express the dose solubility ratio as a dimensionless quantity (q). Drugs are classified into four quadrants of a plane, around the cutoff points, according to their P app , and q values, establishing four categories, that is, I (P app > 10−5 cm/s, q ≤ 0.5), II (P app > 10−5 cm/s, q > 1), III (P app < 2 × 10−6 cm/s, q ≤ 0.5), and IV (P app < 2 × 10−6 cm/s, q > 1). A region of borderline drugs (2 × 10−6 < P app < 10−5 cm/s, 0.5 < q< 1.0) has also been defined. For category I, complete absorption is anticipated, whereas, categories II and III exhibit dose/solubility ratio - limited and permeability -and limited absorption, respectively. For category IV both permeability

and dose/solubility ratio control drug absorption.

Table 3: Quantitative Biopharmaceutical Classification System

BCS Class	P*app**(cm/sec)	q*
I	P*app*>10^{-5}cm/sec	q≤ 0.5
II	P*app*>10^{-5}cm/sec	q>1
III	P*app*<2 C 10^{-6}cm/sec	q ≤ 0.5
IV	P*app*<2 C 10^{-6}cm/sec	q.>1

*Papp- apparent permeability and q- Dose/solubility

Table 4: Chirality and BCS Classification

Class	Solubility	Permeability	Chiral Conversion *
I	High	High	A High*
			B Low*
II	Low	High	A High
			B Low
III	High	Low	A High
			B Low
IV	Low	Low	A High
			B Low

*Chiral Conversion- an active form of drug is converted into an inactive form in blood stream. For racemic drugs, the fraction of dose of active enantiomer reaching the receptor site is more relevant for pharmacological response.
*High- higher amount of active enantiomer is converted to inactive form.
*Low- lower amount of active enantiomer is converted to inactive form.

Third Dimension to BCS

Gohel MC, has suggested that, since living body is a highly chiral environment. So, once the drug meant for oral use dissolves in gastro intestinal fluid and subsequently permeates through the membrane, it enters into general circulation. The drug may undergo chiral conversion in blood. Therefore, in such cases, the pharmacological action will depend upon the amount of unchanged active enantiomer reaching the receptors. So, we can add a third dimension was added to BCS, i.e. chiral conversion for the drugs where only one form (R or S) is active and the other form is inactive. The drugs that fall under Class IB will show superior action as compared to Class I A. [25]

REGULATORY APPLICATIONS OF THE BCS: [7]

The widespread use of BCS in pharmaceutical field is partly due to its inclusion in various guidance documents as cited below.

INDs/NDAs

BCS-based biowaivers are applicable to the to be marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles. This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class I), and the formulations pre- and post-change are pharmaceutical equivalents. BCS-based biowaivers are intended only for bioequivalence (BE) studies. They do not apply to food effect bioavailability (BA) studies or other pharmacokinetic studies.

ANDAs

BCS-based biowaivers can be requested for rapidly dissolving immediate release (IR) test products containing highly soluble and highly permeable drug substances, provided that the reference listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference listed drug product. This approach is useful when the test and reference dosage forms are pharmaceutical equivalents.

Post approval Changes

BCS-based biowaivers can be requested for significant post approval changes (e.g., Level 3 changes in components and composition) to a rapidly dissolving immediate release (IR) product containing a highly soluble, highly permeable drug substance, provided that dissolution remains rapid for the post change product and both pre- and post change products exhibit similar dissolution profiles. BE studies are presently being conducted for NDA of new drug, ANDA of generic products, scale up & post approval changes.BCS is a simple tool in early drug development to determine the rate limiting step in oral absorption process.

In future, this increased awareness of proper biopharmaceutical characterization of a new drug may result in drug molecules with a sufficiently high solubility, permeability & dissolution that will automatically increase the importance of BCS as a regulatory tool.

Industrial Implementation of the BCS

In 1995 Amidon et al. devised a bio-pharmaceutics classification system (BCS) to classify drugs based on their aqueous solubility and intestinal permeability. It was then

recognized that dissolution rate has a negligible impact on bioavailability of highly soluble and highly permeable (BCS Class I) drugs when their formulation's dissolution is sufficiently rapid. As a result, various regulatory agencies including the United States Food and Drug Administration (FDA) now allow bioequivalence of formulations of BCS Class I drugs to be demonstrated by in vitro dissolution (often called a bio-waiver).

Potential Cost Savings

The potential savings is a function of the potential number and likely cost of bioequivalence studies saved (not performed).To examine the potential savings, the number of bioequivalence studies performed by the pharmaceutical industry per year was examined. Thus, it is estimated that the pharmaceutical industry spends between 90 and 150 million dollars a year on bioequivalence studies. Approximately 25% of all compounds were classified as highly soluble and permeable with approximately another 41% having insufficient data to allow classification. Using the 25% estimated, there is the potential to save one quarter the annual expenditures on bioequivalence studies, $22 to $38 million dollars/year. Additional indirect savings can occur if bioequivalence studies are rate limiting to drug development. For example, suppose that results of a bioequivalence study are needed before proceeding with development of a compound with eventual peak sales of one billion dollars/year. It is not unreasonable to assume that results of in vitro dissolution can be obtained 6 weeks earlier than results from an in vivo bioequivalence trial. This time savings translates into a potential additional $110 million dollars in sales from a 6 week earlier approval. Further, by not having to run a human bioequivalence trial, clinical resources are freed to be applied elsewhere.

Pulmonary Biopharmaceutical Classification System (PBCS)

The BCS remains the simplest and most common guiding principle for predicting drug absorption, but it is limited to the gastrointestinal tract. The pulmonary Biopharmaceutics Classification System (PBCS) consider the specific biology of the lung as well as particle deposition, aerosol physics, and the subsequent processes of drug absorption and solubility.

Biopharmaceutics Drug Disposition Classification System (BDDCS)[31, 32]

BDDCS is the well-known extension of BCS developed by Chi Yuan Wu and co-workers in 2005. They demonstrated that the effects various factors such as efflux transporters, food, absorptive transporters and renal or biliary routes of elimination on drug absorption and bioavailability for IR oral solid dosage forms is higher than the permeability. In the BDDCS, permeability is replaced by extent of metabolism and drugs are classified on the base of solubility and extent of metabolism. According to classification, if the drug is mainly eliminated by metabolism, then the drugs show high permeability. If the drug is mainly eliminated as unchanged drug by biliary or renal route, then the drugs show low permeability. Formerly, “Extensive metabolism” was defined as ≥ 50% metabolism of an oral dose in humans in vivo but now “extensive metabolism” mean ≥ 70% metabolism of an oral dose in vivo in humans whereas the “poor metabolism” mean excretion of ≥ 50% of the dose unchanged.

BDDCS Classification

BDDCS[33, 34]divides the drugs in four classes described below:

Class 1: High Solubility, Extensive Metabolism: Class 1 compounds may be substrates for both efflux and uptake transporters in vitro in cellular systems because of high solubility and high permeability. The penetration of the compounds through the blood-brain barrier is affected by efflux transporters. The high passive permeability of the compound may be overcome by the transporters if the systemic concentration of the compounds is lower.

Class 2: Poor Solubility, Extensive Metabolism: Thesecompounds will pass through the membranes of gut due to high permeability. The uptake transporters will have no effect onabsorption while the efflux transporters will affect the rate of absorption and extent of oral bioavailability.

Class 3: High Solubility, Poor Metabolism: Because of high solubility, the drug will be sufficiently available in lumen of gut. The poor permeability can be overcome by an uptake transporter.

Class 4: Low Solubility, Poor Metabolism: The role of uptake and efflux transporter is crucial for these compounds due to the low solubility and low permeability

CLASS – 1	CLASS – 2
HIGH SOLUBILITY & HIGH METABOLISM	LOW SOLUBILITY & HIGH METABOLISM
CLASS – 3	CLASS – 4
HIGH SOLUBILITY & LOW METABOLISM	LOW SOLUBILITY & LOW METABOLISM

Figure 3: Major route of drug elimination

Transporters effect in oral dosing

Transporter effects will be minimal for Class 1 compounds. The high permeability-solubility of such compounds allows large concentrations in the gut to saturate any transporter, both efflux and absorptive, or alternatively the intestine is sufficiently leaky that small molecular weight, soluble, non polar compounds readily pass the membrane. That is, Class 1 compounds may be substrates for both uptake and efflux in cellular systems under the right conditions, but transporter effects will not be important clinically. Efflux transporter effects will predominate for Class 2 compounds. The high permeability of these compounds will allow ready access into the gut membranes, but the low solubility will limit the concentrations coming into the enterocytes, thereby preventing saturation of the efflux transporters.

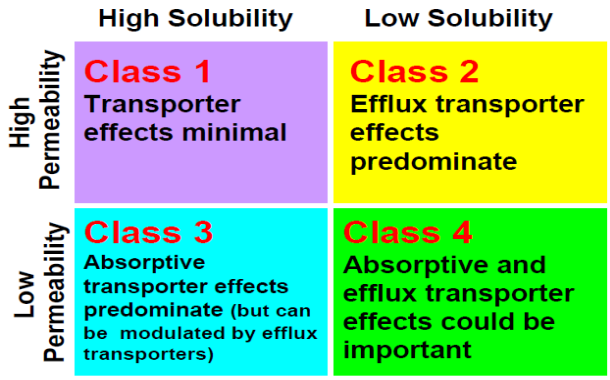

Figure 4: Effect of transporter on various classes

Transporter-enzyme interplay will be primarily important for Class 2 compounds that are substrates for CYP 3A and Phase 2 gut enzymes (e.g. glucuronosyltransferases) where efflux transporter effects can control the access of the drug to the gut enzymes. Absorption of Class 2 compounds is primarily passive and a function of lipophilicity. A series of cellular studies in our laboratory with CYP3A4-transfectedCaco-2 cells demonstrated that transporter enzyme-interplay was an important component of metabolic extraction of Class 2 substrates in that transporters were shown to control access to the enzymes. Inhibition of the efflux pump, P-glycoprotein, with no effect on CYP 3A enzyme, will cause decreased extraction ratio of Class 2 drugs in the intestine resulting in increased AUC, but increased extraction ratio in the liver resulting in decreased AUC. Following oral dosing, major significant interactions will occur for Class 2 drugs that are substrates for intestinal enzymes (e.g. CYP3A, UGTs) and efflux transporters (e.g. P-gp, MRP2, BCRP) since concomitant inhibition of the intestinal enzyme and the efflux transporter both lead to less gut metabolism that synergistically increase systemic AUC. It is not surprising that drugs removed from the market due to drug-drug interactions predominate for orally dosed drugs that are substrates for CYP3A and P-gp. Absorptive transporter effects will predominate for Class 3 compounds. Sufficient drug will be available in the gut lumen due to good solubility, but an absorptive transporter will be necessary to overcome the poor permeability characteristics of these compounds. However, since influx of Class 3 (and Class 4)compounds will be rate limited by an absorptive transporter, the counter effects of efflux transporters will not be saturated and can also be important.

Post Absorption Effect and Intravenous Dosing

Post intestinal absorption and following intravenous dosing both uptake and efflux transporters can be important determinants of Classes 2, 3 and 4 compounds. Thus, for 95% of NMEs transporters can have significant effects on drug absorption, disposition& drug interactions. Inhibition of hepatic uptake transporters can lead to significant increases of drug levels in the systemic circulation for Class 2 compounds that will not be predicted by in vitro microsomal metabolic interactions. The translation of pharmacogenetic differences in metabolic enzymes (genetic polymorphisms) that do not always result in the expected difference in vivo. Phenotype-genotype discordance (as well as changes in the relationship as a function of disease states) may be explained by the effects of transporters on metabolic clearance.

Applications of BCS

The principles of BCS are widely applicable in design of new dosage forms, inclinical pharmacology and also as the scientific approach

for testing of waiver on bioavailability and in regulatory approvals in drug manufacturing.

BCS in Early Drug Development

During the early phase in drug development, BCS can play an important role in selection of drug candidate. The knowledge of BCS class of specific drug impacts the decisions related with development process. The rate-limiting step of particular drug is indicated by its BCS class that may be dissolution, permeability or gastric emptying and according to that solubility and permeability can be set as selection criteria.[1, 35]For the Class I drugs having favorable absorption and rapid dissolution properties, gastric emptying is the rate limiting step. So formulation development is fast and cost effective for this class drugs, provided that no issues of stability or production problems. IVIVCs cannot be found for IR formulations of class I drugs.

The absorption of class II drugs is controlled by rate of dissolution and level A IVIVC, can be found as class II drugs have high permeability, drug solubility enhancement methods can be applied such as nanoparticles, microemulsion, etc.[35, 36] There is also a need of time and specialization to develop an appropriate dissolution method that can discriminate critical formulation or manufacturing variables of the product affecting in vivo drug dissolution.

The permeability is the rate limiting step in absorption of BCS III drugs and it is difficult to solve it by formulation factors because of difficulty in development of specific permeability enhancers.[35]The bioavailability may be increased by pro drug approach to improve availability of drug to the target tissue.[36]But when the appropriate drug concentrations for therapeutic effect can be achieved with the parent drug and cost effective conventional formulations, the pro drug concept may not needed. An IVIVC cannot be found for BCS III drugs.[37] The development of dissolution method for class III drugs is easier in comparison with that of class II drugs.

The rate-limiting step in drug absorption for class IV drugs can be solubility, dissolution or permeability resulting in variability of absorbed dose. The tolerated level of variability depends on the therapeutic index and indication of the drug.[37]

Generics Approval

The classification of drug as per BCS is performed according to the FDA guidelines during the early stage of clinical studies. The BCS can work as useful tool for development of standard for dissolution of product and reduction in requirement of in vivo bioequivalence. By application of BCS knowledge, the formulation scientist can determine the potential for IVIVC and significantly reduce the in vivo studies.[38]

BCS in Oral Drug Delivery Technology

The BCS provides information of the solubility and permeability characteristics of the drug facilitating the decision of development of specific drug delivery technology. For the class I drugs, the major challenge is to achieve a predetermined release rate with appropriate pharmacokinetic and/or pharmacodynamic profile. According to that, the formulation approaches may include control of rate of release and certain physicochemical properties of drugs such as pH-solubility profile of drug. For class II drugs, development of the systems are based on micronization, use of surfactants and complexing agents such as cyclodextrins, , lyophilization, emulsions and microemulsion systems, etc. Class III drugs require the technologies that help to overcome the fundamental limitations of permeability. A major challenge for development of drug delivery system is posed by class IV drugs. The formulation includes use of solubility enhancers and parenteral route as route of choice for drug administration.[29]

BCS in Biowaiver

The term Biowaiver means to achieve waive off for carrying out costly and time-consuming bioavailability and bioequivalence studies. BCS provides biowaivers for Class I, II and III drug with some specifications. The USFDA BCS guidance recommends biowaiver for class I drugs or an immediate release drug product. For waiver of an in vivo relative bioavailability study, dissolution should be greater than 85% in 30 minutes in the three recommended dissolution media. But in the case when both the reference and test products dissolve 85% or more of the labeled amount in <15 min in all 3 recommended dissolution media, a profile comparison is unnecessary. The biowaivers for BCS class II drugs may be allowed for drugs with weak acidic nature and drugs with weak basic nature. The weakly basic drugs show high solubility in the higher pH in intestine and so complete

absorption take place e.g. Diclofenac Sodium and Diclofenac Potassium. The weakly basic drugs show high solubility in lower pH in stomach and absorption occur. The biowaiver based on BCS is applicable for IR oral solid dosage forms that contain one or more of the API(s), if the required data support the similarity of the pharmaceutical product and reference product. As per EMEA BCS guidance, biowaivers are applicable for the IR drug product of BCS class I with very rapid (> 85 % within 15 min)in vitro dissolution characteristics. The biowaiver is also applicable for the drug substance of BCS Class III with very rapid (> 85 % within 15 min) in vitro dissolution of the test provided that there is no effect of excipients on membrane transporters.[24, 39-41]

Additional Considerations for Requesting A Biowaiver

When requesting a BCS-based waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors can affect their request or the documentation of their request:

A. Excipients

In general, using excipient that are currently in FDA-approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on BA of the drug may be requested by the Agency. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product.

B. Prodrugs

Permeability of prodrugs will depend on the mechanism and (anatomical) site of conversion to the drug substance. When the prodrug-to-drug conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and pH-solubility data on both prodrug and drug can be relevant.

Exception for BCS

BCS-based biowaivers are not applicable for the following:

Narrow Therapeutic Range Drugs

BCS classification guidance cannot use for narrow therapeutic drug because it is predict the drug bioavailability by permeability (Basically predict the permeability by passive mechanism in BCS system but in body rather than passive mechanism different mechanism are there to transport the drug.) which should not always true so it is risk to predict the bioavailability of narrow therapeutic drug may it precipitate toxicity. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin.

Products Designed to be absorbed in the Oral Cavity

A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage form sintended for absorption in the oral cavity (e.g. sublingual or buccal tablets).

BCS – THE FUTURE PROSPECT

By looking the way how the present framework gains increased recognition, the future application of the BCS is most likely important. The future revision of the BCS guidelines revision by the group of the academic scientists, industrial experts and the regulatory agencies will result in increased chances of applicability in development of drug with desired characteristics. A special emphasis should be given to the use of BCS in determination of the rate limiting step in the process of oral absorption during early phases of drug development and provision of important information to formulation scientists about the overall drug development process. As the understanding of knowledge about biopharmaceutical characteristics of new drug entities, the drug molecules with desired features will be developed in future and the importance of the BCS as a regulatory tool over time.[44]

Limitation of BCS

BCS based biowaivers are not applicable for the following:

The drugs with narrow therapeutic index

Dosage form meant for absorption in the oral cavity e.g. sublingual or buccal tablets.

Effects of food, efflux transporters, absorptive transporters, and elimination routes such as renal or biliary are important factors to determine overall drug absorption and

bioavailability for IR oral dosage form swhich are not considered in BCS.[38]

CONCLUSION

The *in vivo* pharmacokinetics of drugs depends largely on the solubility and permeability. The BCS has proven to be an extremely useful guiding tool for the prediction of the *in vivo* performance of drug substance and development of new drug delivery systems to suit the performance of the drug in the body, as also for the regulation of bioequivalence of the drug product during scale-up and post approval. BCS as guiding tool is an attempt of FDA to provide an appropriate approach for testing and approve quality of drug product with rationalization of critical absorption components. The principles of BCS are applicable to predict in vivo activity of drug and allow opportunity to develop suitable delivery system as per desired characteristics. The BCS eliminates unnecessary exposure of drug to healthy volunteers and provides cost effective methods in early stages of drug discovery and drug development. As there is increased awareness of biopharmaceutical characterization of new drugs, the future importance of BCS can't be neglected. In the future, the BCS concept will probably be used increasingly in the early development of new drugs, including for analog selection as well as for initial formulation approaches.

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