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Biopharmaceutical Classification System :An Account

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Abstract: In 1995, Amidon and coworkers introduced the biopharmaceutical classification system (BCS) to reduce the need for *in vivo* bioequivalency studies, utilization of *in vitro* dissolution tests as a surrogate for *in vivo* bioequivalence studies. The principles of the BCS classification system can be applied to NDA and ANDA approvals as well as to scale-up and post approval changes in drug manufacturing. Therefore, can save significant amount of product development time of pharmaceutical companies and reduces it costs. BCS is a drug development tool that allows estimation of the contributions of three major factors, dissolution, solubility, and intestinal permeability, which affect oral drug absorption from immediate release (IR) solid oral products. Knowledge of BCS helps to the formulation scientist to develop a suitable dosage forms based on mechanistic rather than empirical approaches.
This review article represents principle, goal & guidance of BCS, characteristics of various BCS class drugs, Various type of dissolution media for various BCS class drugs, their importance & methodology of dissolution, and various applications of BCS have been highlighted.
Key Words: BCS; Solubility; Permeability; Dissolution; Bioequivalence.

INTRODUCTION

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability [1]. When combined with the *in vitro* dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid oral-dosage forms [2, 3]. According to the BCS the drugs can be categorized in to four basic groups on the bases of their solubility and permeability GIT mucosa. **(Table 1)**

The solubility classification of a drug in the BCS is based on the highest dose strength in an IR product. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0–7.5; otherwise, the drug substance is considered poorly soluble. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe the administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water [2, 3].

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. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered to be poorly permeable [2, 3].

An IR drug product is characterized as a rapid dissolution product when not less than 85% of the labeled amount of the drug substance dissolves within 30 min using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 mL or less of each of the following media: 1) acidic media, such as 0.1 N HCl or USP simulated gastric fluid without enzymes; 2) a pH 4.5 buffer; and 3) a pH 6.8 buffer or USP simulated intestinal fluid without enzymes. Otherwise, the drug product is considered to be a slow dissolution product [2, 3].

PRINCIPLE CONCEPT BEHIND BCS

Principle concept behind BCS is that if two drugs products yield the same concentration profile along the gastrointestinal (GI) tract, they will result in the same

plasma profile after oral administration. This concept can be summarized by application of Fick's first in the following equation

J = Pw Cw ……. (1)

Where J is the flux across the gut wall, Pw is the permeability of the gut wall to the drug, and Cw is the concentration profile at the gut wall [3].

In terms of bioequivalence, it is assumed that highly permeable, highly soluble drugs housed in rapidly dissolving drug products will be bioequivalent and that, unless major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to demonstrate bioequivalence of two drug products [4, 5].

PURPOSE OF THE BCS GUIDANCE [3]

- Expands the regulatory application of the BCS and recommends methods for classifying drugs.
- Explains when a waiver for in vivo bioavailability and bioequivalence studies may be requested based on the approach of BCS.

GOALS OF THE BCS GUIDANCE [3]

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

The classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers: [1, 6].

- **The Absorption Number (An)** is the ratio of the Mean Residence Time (T_{res}) to the Mean Absorption Time (T_{abs}) and it could be estimated using equation.

$$An = (T_{res} / T_{abs}) = (3.14R^2L/Q)(R/P_{eff}) \ldots\ldots . (2)$$

- **The Dissolution number** is a ratio of mean residence time to mean dissolution time. It could be estimated using equation 2.

$$Dn = (T_{res}/T_{diss}) = (3.14\ R^2L/Q) / (\rho\ r^2/3\ D\ Cs_{min}) \ldots (3)$$

- **The Dose number** is the mass divided by an uptake volume of 250 ml and the drug's solubility. It could be estimated using equation 2.

$$D0 = Dose/(V_{0\,x}\ C^{min}_{s}) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

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

Where: L = tube length, R = tube radius, π = 3.14, Q = fluid flow rate, ro = initial particle radius, D = particle acceleration, ρ = particle density, Peff = effective permeability, Vo is the initial gastric volume equal to 250 ml which is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting 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 [1].

Table 1: IVIVC expectations for IR products based on the BCS Calss [8,9]

Class	Permeability/ Solubility	Absorption rate control step	IVIVC
Class I	High /High	Gastric emptying	IVIVC expected if dissolution rate is slower than gastric emptying rate. Otherwise limited or no correlation.
Class II	High /Low	Dissolution	IVIVC expected if invitro dissolution rate is similar to invivo dissolution rate, unless dose is very high.
Class III	Low /High	Permeability	Absorption is rate determining and Limited or no IVIVC with dissolution.
Class IV	Low /Low	Case by case	Limited or no IVIVC expected

CHARACTERISTICS OF DRUGS OF VARIOUS BCS CLASSES

Class I drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step. Bioavailability and dissolution is very rapid. So bioavailability and bioequivalency studies are unecessory for such product. IVIVC can nte be expected. Thes compounds are highly suitable for design the SR and CR formulations. Examples include Ketoprofen, Naproxen, Carbamazepine, Propanolol, Metoprolol, Diltiazem, Verapamil etc [11, 12, 13, 14].

Class II drugs have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. Thes drug exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. Thes compounds are suitable for design the SR and CR formulations. In vitro- In vivo correlation (IVIVC) is usually expected for class II drugs. Examples include Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedinpine, Felodipine, Nicardipine, Nisoldipine etc. [13, 14].

Method of enhancing the dissolution [14, 15, 16]

- Use of surfacrtants
- Complexation
- By making the produg
- Use of selected polymeric forms
- Use of solvates and hydrates
- Use of salt of weak acids and weak bases
- Buffeirng the pH of the microenvironment

Method of enhancing the dissolution by incraesing the surface area [14, 15, 16]

- Micronization (reduced the particle size to increase the surface)
- Solvent deposition (deposition of poorlyu soluble drugs on inert material)
- Solid despertions (dispersion of poorly soluble drugs in a solid matrix of the water soluble carrier)
- Use of the surfactants(to increasing the surface area by facilitating proper wettitng)

For Class III drugs permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. These drugs are problematic for controlled release development. These drugs showed the low bioavailability and need enhancement in permeability. Examples include Acyclovir, Alendronate, Captopril, Enalaprilat Neomycin B etc. [13, 14].

Following permeation enhancers can be used (14).

- **Synthetics surfactants** eg. SLS,polysorbate 20 & 80,sorbitan laurate,glyceryl monolaurate
- **Bile Salts:** Sodium deoxycholate, Sodium glycocholate, Sodium fusidate etc.
- **Fatty acids and derivatives:** Oleic acid, Caprylic acid, Lauric acid etc.
- **Chelators;** eg Sod EDTA, Citric acid, Salicylates etc.
- **Inclusion complexes:** Cyclodextrins and derivatives etc.
- **Mucoadhesive polymers:** Chitosan, Polycarbophil etc.

Class IV drugs exhibit poor and variable bioavailability. Sevaral factors such as dissolution rate, permeability and gastric emptying form the rate limiting steps for the drug absorption. These are unsuitable for controlled release. Examples include Chlothaizude, Furosemide, Tobramycine, Cefuroxime etc [12, 14].

Absorption Rate limiting process

Release of the drug substances from its dosage form or drug permeation through the intestinal membrane are the rate limiting steps for the absorption and bioavailability. If the permeation through intestinal membrane is rate limiting, the dissolution properties may be negligible importance. Since the dissolution of the class I drug is very fast so the BA/BE studies for this class seem to be unnecessary. The class III drug product are seem to be the better for BA/BE studies as their bioavailability depend on the permeabbility properties. (**Table 1)**

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 administration is usually close to 100 %, provided they are not decomposed in GIT and do not under go 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 with out 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]. Ensure and Milk as dissolution media can improve the drug solubility includes the solubilization of drugs in the fatty part of the fluid. Of these media contains similar ratio of protein/ fat/ carbohydrate.Ues of ensure and milk have been vigorously suggested as a media suitable for simulating fed state in the stomach[20, 21].

Media for Class II substances

Substances that belong to class II possess poor aqueous solubility but are easily transported across the GI mucosa. Suitable biorelevant media for class II drugs are: (a) SGFsp 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 invivo dissolution of the poorly soluble drugs from different formulations and for assessing potential for foods effects on the invivo dissolution. The dissolution rate of the poorly soluble drug is often better in FaSSIF and FeSSIF 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) Hydroalcoholic 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 deaeration 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. SGFsp & SIFsp with addition of a surfactant to ensure the complete release of drug from formulation can be used [6, 17, 19].

Table2: Dissolution Apparatus Used for Novel/Special Dosage Forms [27]

Type of the dosage form	Related apparatus
1. solid oral dosage forms (Conventional)	Basket. Paddle, Reciprocating cylinder or Flow through cell
2. Oral suspensions	Paddle
3. Orally disintegrating tablets	Paddle
4. Chewable tablets	Basket. Paddle, Reciprocating cylinder with glass beads
5. Transdermal-patches	Paddle over disk
6. Topical semisolids	Franz diffusion cell
7. Suppositories	Modified basket. Paddle, Dual chamber Flow through cell
8. Chewable gum	Special apparatus (PhEur)
9. Powders and granules	Flow through cell (Powders/ granules sample cell)
10. Micro particulate formulations	Modified flow through cell
11. Implants	Modified flow through cell

CHOICE OF DISSOLUTION EQUIPMENT

According to the USP different 7 types of official dissolution apparatus are: Apparatus 1- Rotating basket, Apparatus II- Rotating Paddle, Apparatus III - Reciprocating cylinder, Apparatus IV - Flow through cell, Apparatus V- Paddle over disc, Apparatus VI- cylinder, and Apparatus VII -Reciprocating Holder [24]. USP I and USP II are the apparatus most often used for IR dosage forms. USP apparatus III is the most suitable when the pH of the medium is to be altered during the test. For example enteric coated dosage forms. USP apparatus IV is particularly suitable for ER dosage forms [25] . **(Table 2)**

SELECTION OF AGITATION RATE

An appropriate rotational speed must be selected [6]. If rotation speed is very too low, coining may occur, leading to artifactually low rates of dissolution. If the rate of rotation is too fast, the test will not be able to discriminate between acceptable and not acceptable batches [25, 26]. Rotation speed in range 50-75 rpm appear to be suitable in case of paddle method. Dissolution of the class first compound is relatively intensive to variation in this speed range and even for class II compounds the effect is minimal. If the basket method is used a rotational speed 75-100 rpm may be suitable [25, 26].

DURATION OF DISSOLUTION TESTS FOR BCS CLASSES

The duration of dissolution test must be tailored to not only the site of absorption for the drug but also timing of administration. If this is best absorbed from the upper small intestine and is to be administered in the fasted state, dissolution test in a medium simulating fasted gastric conditions with duration of 15 to 30 minutes are appropriate. On the other hand, if a drug is administered with food and well absorbed through the small intestine and proximal large intestine, duration of as long as 10 hours (with appropriate changes to the composition dissolution medium) could be envisaged [6].

Class I drugs show the high solubility that's why, U.S. FDA recommended one point test for IR dosage form in a simple medium and 85 % or more of the drug to be released with in 30 minutes. Similar conditions applied for class III drugs due to having high solubility as similar to that of class I drugs. In case of class II and IV drugs having low solubility (if these drugs designed as extended release formulations) demand at least three specification points, the first after 1-2 hours (about 20-30 % drug release) provide assurance against premature drug release. The second specification point has to be close to 50 % drug release (definition of the dissolution pattern). At last point, the dissolution limit should be at least 80 % to ensure almost quantitative release [25].

METHODOLOGY FOR CLASSIFYING A DRUG SUBSTANCE AND FOR DETERMINING THE DISSOLUTION CHARACTERISTICS OF A DRUG PRODUCT

The following approaches are recommended for classifying a drug substance and determining the dissolution characteristics of an IR drug product according to the BCS:

A. Determining Drug Substance Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at 37 ± 1^0C in aqueous media with a pH in the range of 1-7.5. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. A minimum of three replicate determinations of solubility in each pH condition is recommended. Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products.

B. Determining Drug Substance Permeability Class

The permeability class of a drug substance can be determined in human subjects using mass balance, absolute BA, or intestinal perfusion approaches. In many cases, a single method may be sufficient (e.g., when the absolute BA is 90% or more, or when 90% or more of the administered drug is recovered in urine). When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable.

1. Pharmacokinetic Studies in Humans

a. Mass Balance Studies

b. Absolute Bioavailability Studies

2. Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract:

- *In vivo* intestinal perfusions studies in humans.
- *In vivo* or *in situ* intestinal perfusion studies in animals.
- *In vitro* permeation experiments with excised human or animal intestinal tissue.
- *In vitro* permeation experiments across epithelial cell monolayer

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established. For demonstration of suitability

of a method, model drugs should represent a range of low (e.g., < 50%), moderate (e.g., 50 - 89%), and high (≥ 90%) absorption.

C. Determining Drug Product Dissolution Characteristics

Dissolution testing should be carried out in USP Apparatus I at 100 rpm or Apparatus II at 50 rpm using 900 ml of the following dissolution media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. For capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.

Selection of the dissolution testing apparatus (USP Apparatus I or II) during drug development should be based on a comparison of in vitro dissolution and in vivo pharmacokinetic data available for the product.

A minimum of 12 dosage units of a drug product should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product (e.g., 10, 15, 20, and 30 minutes). When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.

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

Two dissolution profiles are considered similar when the f2 value is > 50.

APPLICATIONS OF BCS IN ORAL DRUG DELIVERY TECHNOLOGY

Once the solubility and permeability characteristics of the drug are known it becomes an easy task for the research scientist to decide upon which drug delivery technology to follow or develop.

1. BCS in the drug development

In early drug development, knowledge of the class of a particular drug is an important factor influencing the decision to continue or stops it development.

BCS classification can be utilized in drug candidate selection at an early phase in drug development, during formulation development, and in regulatory applications [28]. The BCS class of a drug indicates the rate-limiting step for oral absorption: gastric emptying, dissolution or intestinal permeability [1]. In the early development phase, the permeability and solubility boundaries can be set as selection criteria for new drug candidates [29]. *In vitro* methods are utilized to measure solubility and permeability. Solubility is typically measured by the shake-flask method and permeability by Caco-2 cells.

Gastric emptying of the dissolved drug is the rate-limiting step for oral absorption of class I drugs with rapid dissolution. Class I drugs have favorable absorption properties, leading to rapid and complete absorption. Drug absorption can be mediated either by passive transcellular diffusion or by active transport. Even simple, conventional IR formulation assures rapid and complete absorption for this class of drugs. Therefore, formulation development is fast and cheap unless other issues, such as stability or production problems exist. IVIVCs cannot be found for IR formulations of class I drugs if dissolution is faster than gastric emptying. Thus, the dissolution method can be a simple and cheap quality control tool. However, if a BCS biowaiver is utilized in a regulatory application, dissolution should be tested in three different media representing the pH range of the gastrointestinal tract.

Dissolution controls absorption of class II drugs and a point-to-point relationship, i.e., level A IVIVC, can be found between *in vitro* dissolution and *in vivo* dissolution or absorption. Like BCS I drugs, class II drugs have high permeability, and transport may be active or occur by passive transcellular diffusion. If absorption is limited by solubility or dissolution, it may be incomplete. Formulation development may be more challenging than for BCS I drugs if special techniques and skills are utilized to enhance drug solubility or dissolution. For example, nanoparticles, microemulsion, cyclodextrins or lipid formulations can be used [28, 29]. *In vitro* dissolution method development also requires more time and a high level of knowledge if *in vitro* conditions are to mimic drug release and dissolution *in vivo*. Several pH values, agitation speeds, and different apparatuses should be tested. An appropriate method should discriminate critical formulation or manufacturing variables of the product affecting drug dissolution *in vivo*. If successful, a level A IVIVC may be proven and *in vitro* dissolution tests can be used as surrogates for *in vivo* bioavailability and bioequivalence studies.

BCS III drugs have permeability limited absorption. Incomplete absorption due to limited permeability can rarely be solved by formulation factors, because specific and non-toxic permeability enhancers are difficult to develop [28]. Instead, bioavailability may be increased by prodrug derivatization of the parent compound, improving drug distribution to the target tissue [30]. The prodrug can be more lipophilic than the parent drug, facilitating transcellular passive diffusion or, alternatively, the prodrug can be designed to be a substrate for a transporter [31, 32]. In many cases, permeability is high enough to achieve therapeutic drug concentrations in plasma. Then conventional

immediate-release formulation is a good choice. For example, the BCS III drugs ranitidine and cimetidine in immediate-release tablets have bioavailability of 50-60% [33, 34,35,36]. In many cases, the prodrug approach is not needed if therapeutic drug concentrations are achieved with the parent drug and with simple and cheap conventional formulations. An IVIVC can not be found for BCS III drugs when permeability is the rate-limiting step for absorption [37]. The role of the dissolution method is to act as a quality control tool to ensure batch-to-batch consistency. Dissolution method development is thus easier for such class III drugs than for class II drugs or controlled-release products.

BCS IV drugs have low solubility and permeability. The rate-limiting step in drug absorption can be solubility, dissolution or permeability. The fraction of absorbed drug dose may be low and highly variable because class IV drugs have problems in solubility and permeability. Formulation and dissolution methods may be similar to those for class II drugs if dissolution is the rate-limiting factor. For permeability-limited absorption, class IV drugs may be developed like class III drugs. Some class IV drugs may be unsuitable for oral administration if the fraction absorbed is too low and oral absorption is highly variable. However, the tolerated level of variability depends on the indication and therapeutic index of the drug. [37]

BCS biowaivers extensions

During the time period spanning 2000-2007, regulatory agencies have received fewer BCS biowaiver applications than expected. This is the case especially for new generic drug products [39,40,41]. There are a few published revisions to methodologies for classifying drugs in the BCS, and extension of biowaivers to acidic class II and class III drugs has been suggested. Hopefully these will lead to BCS guideline revisions and increase BCS biowaiver applications. Methodology revisions it has been suggested that the solubility boundary for biowaiver candidates should be narrowed from pH 1-7.5 to 1-6.8 and the fraction of the dose absorbed should be reduced from 90% to 85% [42, 38]. Currently, a drug product is considered rapidly dissolving if more than 85% dissolves in 30 minutes. A new criterion of 60 minutes for the dissolving time has been suggested [38]. For acidic drugs, solubility tests in conditions mimicking small intestinal pH may be more appropriate than tests performed at pH 7.5 [43]. To classify drug solubility, the solubility is measured in aqueous buffer using a volume of 250 ml. It has been suggested that the volume should be increased from 250 ml to 500 ml and that surfactants may be added to the medium [38]. However, these revisions need experimental verification before they can use.

BCS II drugs have not been accepted as biowaiver candidates by the regulatory agencies, but acidic BCS II drugs have been suggested as possible candidates for biowaivers in scientific publications [43, 44]. Those publications criticize the current biowaiver guidelines, which are based on equilibrium solubility and dissolution tests, and in which the dynamic nature of drug absorption is not taken into account. Acidic BCS II drugs have low solubility only in the stomach, while solubility in the small intestine is high and the fraction of the dose absorbed can be > 0.9. The extent of oral drug absorption (i.e. AUC) may not be sensitive to minor dissolution rate differences under the alkaline conditions in the small intestine. In contrast, the rate of oral absorption (i.e. Cmax) may be sensitive to differences in the dissolution rates, as was pointed out in simulation studies [45]. Solubility and dissolution of acidic BCS II drugs are site dependent, i.e., solubility is low in the acidic stomach and high in the alkaline small intestine. As discussed previously, gastric emptying of solid drugs is a highly variable process, since house-keeping waves occur every 1.3-2 hours [46]. Thus, drug concentrations at the absorption site may vary and minor dissolution rate differences may cause fluctuations in Cmax values.

For BCS III drugs, biowaivers can not be utilized in regulatory applications in the USA and Europe, but in a report recently published by the WHO, BCS III drugs were accepted as biowaiver candidates [47]. There are many scientific papers published where class III drugs are recommended as biowaiver candidates [42, 48, 49, 50]. For this BCS class, the permeability rate controls absorption and the bioavailability is more dependent on the drug (permeability) than on the formulation (dissolution). The test and reference products will be bioequivalent if absorption is permeability rate limited. Class III drugs may be even better biowaiver candidates than class I drugs, if the effects of excipients on gastrointestinal transit time and permeability can be excluded [50].

BCS III drugs which are substrates of efflux proteins and/or have extensive metabolism in the intestine should not be accepted as biowaiver candidates. These saturable mechanisms are dependent on drug concentration and thus in some cases even minor differences in the concentration can lead to changes in the rate and/or extent of absorption.

2. Approval of the generics

BCS is done in accordance with the FDA guidelines when the potential class I drug condidate enters in human testing. If the compound meets all the criteria a petition is send to FDA asking for the agreement with the compound classification. The goal is to send to the FDA prior to initiation of phase II.

The BCS is used to set drug product dissolution standard to reduce the in vivo bioequivalence requirement. As subsequent R & D proceeds, dissolution studies are done on a new formulation in accordance with the FDA guidance and petition is submitted to FDA requesting waivers of in vivo bioequivalence studies.

The knowledge of BCS can also help the formulation scientist to develop a dosage form based on mechanistic approach rather than empirical approach. This allows determining the potential for invitro-invivo correlation and significantly reducing the in vivo studies.

EXCEPTION FOR BCS:

BCS-based biowaivers are not applicable for the following:

1. Narrow Therapeutic Range Drugs

This guidance defines narrow therapeutic range drug products 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. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors should contact the appropriate review division to determine whether a drug should be considered to have a narrow therapeutic range.

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 is not appropriate for dosage forms intended for absorption in the oral cavity (e.g. sublingual or buccal tablets).

CONCLUSION

BCS principles provide a reasonable approach for testing and approving drug product quality. BCS applications for Class 2 and 3 are challenging, but at the same time provides opportunities for lowering regulatory burden with scientific rational. BCS also provides an avenue to predict drug disposition, transport, absorption, elimination. The BCS is the guiding tool for the prediction of *in vivo* performance of the drug substance and development of drug delivery system to suit that performance.

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