Review Article

Biopharmaceutics Classification System

Chavda HV, Patel CN[1], Anand IS[2]

Departments of Pharmaceutics and Pharmaceutical Technology, [1]Pharmaceutical Chemistry, [2]Pharmacology, Shri Sarvajanik Pharmacy College, Hemchandracharya North Gujarat University, Nr. Arvind Baug, Mehsana, Gujarat - 384 001, India

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ABSTRACT

Biopharmaceutics Classification System (BCS) has provided a mechanistic framework for understanding the concept of drug absorption in terms of permeability and solubility. This article reviews the criteria and issues for classifying drugs according to the BCS. Biowaiver extensions for drug or active pharmaceutical ingredient from different BCS classes with scientific basis are discussed as the current BCS guidelines by World Health Organization, Unites State Food and Drug Administration and European Medicines Agency allows for biowaivers based on conservative criteria. The article sheds light on the possible new criteria and class boundaries proposed for additional biowaivers based on the underlying physiology of the gastrointestinal tract in required cases. The potential applications of BCS in drug discovery, drug delivery and drug research as well as extension for BCS are discussed.

Introduction

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. This classification system was devised by Amidon *et al*.[1] This concept underlying the BCS published finally led to introducing the possibility of waiving *in vivo* bioequivalence (BE) studies in favor of specific comparative *in vitro* testing to conclude BE of oral immediate release (IR) products with systemic actions. The BCS has found international recognition in industry, academic institutions and public authorities.[2] The principle of the BCS is that if two drug 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 the following equation:[3]

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

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 BE, 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 BE of two drug products. The BCS thus enables manufacturers to reduce the cost of approving scale-up and postapproval changes to certain oral drug products without compromising public safety interests.

Correspondence:
Mr. Hitesh Chavda; E-mail: hvchavda@sspcmsn.org

Solubility determination

The solubility of any substance can be defined as the amount of substance that has passed into solution when equilibrium is attained between the solution and excess (undissolved substance) at a given temperature and pressure.[4] A drug substance or an active pharmaceutical ingredient (API) is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous medium over a specific pH range.[5-7] The volume estimate of 250 ml is derived from the typical volume of water consumed during the oral administration of dosage form, which is about 1 glassful, or 8 ounces of water. This boundary value is a refection (a light meal or repast) of the minimum fluid volume anticipated in stomach at the time of drug administration. The pH solubility profile of the drug substance is determined at 37 ± 1°C in aqueous medium with pH in the range of 1-7.5 as per United States Food and Drug Administration (USFDA) guidelines,[5] 1.2-6.8 as per World Health Organization (WHO) guidelines[6] and 1-8 as per European Medicines Academy[7] (EMEA). 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 depends upon ionization characteristics of the test drug substance. A minimum of three replicate determinations of solubility in each pH condition should be carried out to predict accurate solubility. Standard buffer solutions described in pharmacopoeias are considered appropriate for use in solubility studies. Methods other than shake-flask method

can also be used with justification to support the ability of such methods to predict equilibrium solubility of test drug substance. If degradation of drug is observed as a function of buffer composition and/or pH, it should be taken into consideration. The concentration of drug substance in selected buffers or pH conditions should be determined using a validated solubility indicating assay method that can distinguish between the drug substances from its degradation products.

Permeability determination

The methods[4] that are routinely used for determination of permeability include the following:

a. Pharmacokinetic studies in human subjects including mass balance studies[8] and absolute bioavailability (BA) studies[9] or intestinal permeability methods[10]
b. *In vivo* or *in situ* intestinal perfusion[11] in a suitable animal model
c. *In vitro* permeability methods[12] using excised intestinal tissues
d. Monolayers of suitable epithelial cells[13,14] e.g. *Caco-2* cells or *TC-7* cells

In mass balance studies, unlabeled, stable isotopes or radiolabeled drug substances are used to determine the extent of drug absorption. In absolute BA studies, oral BA is determined and compared against the intravenous BA as reference. Intestinal perfusion models and *in vitro* methods are suggested for passively transported drugs. An interesting alternative to intestinal tissue models is the use of *in vitro* systems based on the human adenocarcinoma cell line *Caco-2*. These cells serve as a model of small intestinal tissue. The differentiated cells exhibit the microvilli typical of the small intestinal mucosa and the integral membrane proteins of the brush-border enzymes. They also form the fluid-filled domes typical of a permeable epithelium. Recent investigations of *Caco-2* cell lines have indicated their ability to transport ions, sugars and peptides. These properties have established the *Caco-2* cell line as a reliable *in vitro* model of the small intestine.

Biopharmaceutics classification system[4-7]

It is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is a drug-development tool that allows estimation of the contributions of three major factors, dissolution, solubility and intestinal permeability that affect oral drug absorption from IR solid oral dosage forms.[1] It was first introduced into regulatory decision-making process in the guidance document on immediate release solid oral dosage forms: Scale-up and postapproval changes.[15] The drugs are divided into high/low-solubility and permeability classes. Currently, BCS guidelines are provided by USFDA,[5] WHO[6] and EMEA.[7]

Class boundaries

Solubility[5-7]

The solubility class boundary is based on the highest dose strength of a drug product that is the subject of a biowaiver (drug product approval without a pharmacokinetic BE study) request. According to USFDA BCS guidance[5] a drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. According to WHO guidance[6] an API is considered highly soluble when the highest dose (if the API appears on the WHO Model List of Essential Medicines) or highest dose strength available on the market as a oral solid dosage form (if the API does not appear on the WHO Model List of Essential Medicines) is soluble in 250 ml or less of aqueous media over the pH range of 1.2-6.8. The pH-solubility profile of the API should be determined at 37 ± 1 °C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended. Initial recommendations in the BCS Guidance suggested that the solubility should be measured over a pH range of 1.2-7.5. But successive scientific discussions and publications suggest that a pH range of 1.2-6.8 is more appropriate. According to EMEA BCS guidance[7] a drug substance is considered *highly soluble* if the highest single dose administered as IR formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1-6.8 at 37 ± 1 °C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. A minimum of three replicate determinations at each pH condition is recommended (e.g., shake-flask method or other justified method). Solution pH should be verified before and after addition of the drug substance to a buffer.

Permeability[5-7]

The permeability class boundary is based indirectly on the extent of absorption of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., *in vitro* epithelial cell culture methods). According to USFDA BCS guidance,[5] in the absence of evidence suggesting instability in the GI tract, a drug substance is considered to be *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose. According to WHO guidance[6] an API is considered *highly permeable* when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose. The initial recommendation in the BCS Guidance suggested an absorption value of ≥90% as a prerequisite for classification as highly permeable. However, successive scientific discussions and scientific publications have suggested relaxing the criterion to 85% absorption for classifying an API as highly permeable. An acceptable alternative test method for permeability determination of the API could be *in vivo* intestinal perfusion in humans. When this method is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to that of a reference compound whose fraction of dose absorbed has been documented to be at least 85%, as well as use of a negative control. According to EMEA BCS guidance[7] if a drug substance has linear and complete absorption then it is considered *highly permeable*.

Dissolution[5-7]

According to USFDA BCS guidance[5] an IR drug product is considered *rapidly dissolving* when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using

USP apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each medium: 0.1 N HCl or simulated gastric fluid USP without enzymes; buffer (pH 4.5); and buffer (pH 6.8) or simulated intestinal fluid USP without enzymes. According to WHO BCS guidance[6] a multisource product (pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent) is considered to be very rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves in 15 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each medium: HCl solution (pH 1.2); acetate buffer (pH 4.5); and phosphate buffer (pH 6.8). A multisource product is considered to be rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves in 30 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the media: HCl solution (pH 1.2); acetate buffer (pH 4.5); and phosphate buffer (pH 6.8). According to EMEA BCS guidance[7] drug products are considered *very rapidly dissolving* when more than 85% of the labeled amount is dissolved in 15 minutes, using USP Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 500 ml in each of the media: 0.1 N HCl or simulated gastric fluid without enzymes; buffer (pH 4.5); and buffer (pH 6.8) or simulated intestinal fluid without enzymes and similarity of dissolution profiles should be demonstrated.

Classification

According to BCS, drug substances or APIs are divided into high/low solubility and permeability classes[4-7,16] as follow:

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

In combination with the dissolution, the BCS takes into account the three major factors governing BA, *viz*. dissolution, solubility and permeability. The BCS in accordance with WHO guideline is shown in Figure 1. This classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers.[4]

Absorption number, A_n = mean residence time/mean absorption time

Dissolution number, D_n = mean residence time/mean dissolution time

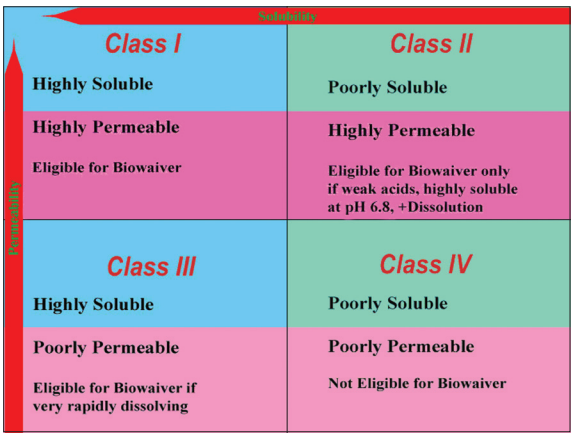

Figure 1: Biopharmaceutics classification system[6]

Dose number, D_o = (maximum dose strength/250)/solubility

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. 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. The absorption for Class II drugs is usually slower than Class I and occurs over a longer period of time. In the case of Class III drugs, permeability is a rate-limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Because the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. Generally, Class IV drugs exhibit problems for effective oral administration. Examples of drugs for different classes are given in Table 1.[3,17-21]

Biowaivers

The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than through *in vivo* equivalence testing.[6] Biowaiver means to obtain waive off for carrying out expensive and time-consuming BA and BE studies.[22] BCS provides biowaivers for Class I, II and III drug with some specifications. This waiver is for both pre- and postapproval phases. BCS-based biowaivers are applicable for immediate-release solid oral dosage formulations containing one or more of the API(s), identified by WHO prequalification of medicines programme (PQP) to be eligible, if the required data ensure the similarity of the submitted pharmaceutical product and the appropriate comparator product. Comparator products used in BCS-biowaiver applications should be selected from the current list of WHO PQP recommended comparator products, including the appropriate fixed-dose combination product. Use of any other comparator has to be duly justified by the Applicant. In the WHO PQP, the biowaivers based on the BCS are intended only to investigate BE and do not apply to other BA or pharmacokinetic studies.[6]

The criteria recommended by USFDA BCS guidance for Biowaiver:[5]

1. The drug substance should be highly soluble and highly permeable (Class I drugs).
2. An immediate release drug product.
3. For waiver of an *in vivo* relative BA study, dissolution should be greater than 85% in 30 minutes in the 3 recommended dissolution media. Two dissolution profiles may be considered similar when compared using similarity factor ($f_2 > 50$) as described in the guidance for industry on dissolution testing. When both the test and the reference products dissolve 85% or more of the labeled amount in <15 min, in all 3 dissolution media recommended above a profile comparison is unnecessary.

Table 1: Examples of some drugs as per biopharmaceutical classification system[3,17-21]

Class I	Class II	Class III	Class IV
Chloroquine	Carbamazepine	Acyclovir	Coenzyme Q_{10}
Diltiazem	Danazol	Atenolol	Cyclosporin A
Metoprolol	Glibenclamide	Captopril	Ellagic acid
Paracetamol	Ketoconazole	Cimetidine	Furosemide
Propranolol	Nifedipine	Metformin	Ritonavir
Theophylline	Phenytoin	Neomycin B	Saquinavir
Verapamil	Troglitazone	Ranitidine	Taxol

4. The drug should not be a narrow therapeutic index drug.
5. Excipients used in the dosage form should have been previously used in a FDA approved IR solid dosage forms. The quantity of excipients in IR product should be consistent with their intended function.
6. The drug must be stable in gastrointestinal tract and the product is designed not to be absorbed in oral cavity.

The criteria recommended by WHO BCS guidance for Biowaiver:[6]

1. Dosage forms of APIs which are highly soluble, highly permeable (BCS Class I) and are rapidly dissolving are eligible for a biowaiver based on the BCS provided:
   a) the dosage form is *rapidly dissolving* and the dissolution profile of the multisource product is similar to that of the comparator product at pH 1.2, 4.5 and 6.8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, $f_2 \geq 50$ (or equivalent statistical criterion);
   b) if both the comparator and the multisource dosage forms are *very rapidly dissolving* the two products are deemed equivalent and a profile comparison is not necessary.

2. Dosage forms of APIs that are highly soluble and have low permeability (BCS Class III) are eligible for biowaivers provided all the criteria mentioned below are met in accordance with WHO BCS guidance and the risk benefit is additionally addressed in terms of extent, site and mechanism of absorption:
   a) the solubility and permeability of the API;
   b) the similarity of the dissolution profiles of the multisource and comparator products in pH 1.2, 4.5 and 6.8 media;
   c) the excipients used in the formulation; and
   d) the risks of an incorrect biowaiver decision in terms of the therapeutic index of, and clinical indications for, the API.

3. Dosage forms of APIs with high solubility at pH 6.8 but not at pH 1.2 or 4.5 and with high permeability (by definition, some but not all BCS Class II compounds with weak acidic properties) are eligible for a biowaiver based on BCS provided that criteria (b), (c) and (d) described in the above section 2 are met, that the API has high permeability (i.e., the fraction absorbed is 85% or greater) and a dose: Solubility ratio of 250 ml or less at pH 6.8, and that the multisource product:
   a) is rapidly dissolving (85% in 30 minutes or less) in pH 6.8 buffer
   b) the multisource product exhibits similar dissolution profiles, as determined with the f_2 value or equivalent statistical evaluation, to those of the comparator product at the three pH values (pH 1.2, 4.5 and 6.8).

Biowaiver extension potential

Biowaiver extension potential for solubility and permeability class boundaries[22,23]

As the solubility class boundary requires that the highest strength of drug substance is soluble in 250 ml or less volume in aqueous media over the pH range of 1-7.5 as per USFDA BCS guidance. The pH range of 1-7.5 may be stringent requirement. Under fasting condition, the pH range in the GI tract vary from 1.4-2.1 in the stomach, 4.9-6.4 in the duodenum, 4.4-6.6 in the jejunum, and 6.5-7.4 in the ileum. In addition, it generally takes approximately 85 minutes for a drug to reach the ileum. By the time the drug reaches the ileum, the dissolution of drug product is likely to be complete if it meets the rapid dissolution criterion, i.e., no less than 85% dissolved within 30 minutes. The researchers redefined the pH range for BCS solubility class boundary from 1.0-7.5 to 1.0-6.8 in alignment with dissolution pH ranges, which are pH 1, 4, 5, and 6.8 buffers. The volume 250 ml seems a conservative estimate of what actually is available *in vivo* for solubilization and dissolution. The physiological volume of small intestine varies from 50-1100 ml, with an average of 500 ml under fasted conditions. When administered with a glass of water, the drug is immersed in approximately 250 ml of liquid in the stomach. If the drug is not in solution in the stomach, gastric emptying would then expose it to small intestinal fluid, and the solid drug would dissolve under the effect of additional small intestine fluid. Because of the large variability of small intestinal volume an appropriate definition of volume for solubility class boundary is difficult to set. Another factor influencing *in vivo* solubility is bile salt micelle solubilization. The intestine is the absorbing region for most of the drug. Many acidic drugs, which have low solubility at low pH, are well absorbed. For example, most nonsteroidal anti-inflammatory drugs are poorly soluble in stomach but are highly soluble in distal intestine and their absolute human BA are 90% or higher, thus exhibiting behavior similar to those of BCS Class I drugs. The criterion of 90% for the fraction of dose absorbed can be considered conservative because the experimentally determined fraction of dose absorbed is seen to be less than 90% for many drugs that are generally considered completely or well absorbed. Therefore, it has been suggested, that there is a potential of redefining BCS permeability class boundary such that a class boundary of 85% might be more appropriate in defining high permeability. Revision of interchangeably and specific BCS guideline by WHO implemented the pH range of from 1-7.5 to 1.2-6.8 for solubility class boundary and permeability class boundary of 85% absorption from 90%. The implementation is sensible only in regulatory environments in which pharmaceutical products and respective manufacturing and control processes are defined.

Biowaiver extension potential for class II drugs[22,23]

Some Class II drugs are consistently and completely absorbed after oral administration. These are typically poorly soluble weak acids with pKa values of ≤ 4.5 and intrinsic solubility (solubility of the unionized form) is of ≥ 0.01 mg/ml. At pH values typical of the fasted state in the jejunum (about pH 6.5), these drugs will have solubility of >1 mg ml, resulting in fast and reliable dissolution of the drug. Currently, these drugs are classified as Class II drugs because they are poorly soluble at gastric pH, in which pH is much less than pKa. Because the small-intestinal transit time is more reliable, and in the fasted state, longer than the gastric residence time (3 h), drugs with these physical characteristics will have sufficient time to be dissolved. As long as these drugs meet the permeability criterion, biowaivers for products that dissolve rapidly at pH values typical of the small intestine could be considered. Therefore, it has been suggested that it is possible to have a biowaiver extension potential to BCS Class II drugs.

Biowaiver extension potential for class III drugs[22,23]

If the dissolution of Class III products is rapid under all physiological pH conditions, it can be expected that they will behave like an oral solution *in vivo*. Because the absorption of Class III drugs is essentially controlled by the gut wall permeability of the drug

and not by the drug's solubility, biowaivers for rapidly dissolving products of Class III drugs also could be justified. The Class III compounds often exhibit site dependent absorption properties, and thus the transit time through the specific region of upper intestine may be critical for BE.

Biowaiver for modified release products[22,24]

Following administration in the fasted (to abstain from food) condition, a modified release product will have left the stomach within about 1 hour and can be expected to arrive in the colon about 3 hours later. If we have to extend the BCS model to oral MR products, we need to recognize the role of intestinal metabolism in the absorption process; a simple measure of permeability is not adequate. It has been found that the drug absorption was diminished in distal intestine and in some cases, so much so that drug as an IR product was terminated following the regional absorption study. It has also been shown that absorption will not always be reduced following delivery to the ileum and colon. In some of the studies it has been shown that BA of drug delivered to the distal small bowel was higher than the reference (solution) formulations. If we are considering a simple mechanistic model of absorption in which permeability and concentration are the key parameter, then this will only be correct if the metabolism rate is constant over the region of intestine to which the drug is delivered. The role of gut wall metabolism and, particularly cytochrome P450 3A4 isozyme activity, has recently become the focus of attention. It has been recently shown that 3A4 activity in man diminishes significantly from the jejunum to ileum. So, if we compare the ratio of parent drug to metabolite following delivery to the different intestinal regions, then the influence of gut wall metabolism can be clearly demonstrated.

Applications of biopharmaceutics classification system

Drug delivery technologies[22,25]

Class I systems

The Class I drugs are not those in which either solubility or permeability is limiting within the target regions of the GI tract. The drug release in such cases can be modulated using controlled release technology. Controlled release technologies for Class I drugs includes number of products such as Macrocap, Micropump, MODAS (Multiporous oral drug absorption system), SCOT (Single composition osmotic tablet system), Microsphere, CONSURF (constant surface area drug delivery shuttle), Diamatrix (Diffusion controlled matrix system), DPHS (Delayed pulsatile hydrogel system), DUREDAS (Dual release drug absorption system), GMHS (Granulated modulating hydrogel system), IPDAS (Intestinal protective drug absorption system), Multipor, Pharmazone (Microparticle Drug Delivery Technology), PPDS (Pelletized pulsatile delivery system), BEODAS (Bioerodible enhanced oral drug absorption system), PRODAS (Programmable oral drug absorption system), SODAS (Spheroidal oral drug absorption system), SMHS (Solubility modulating hydrogel system) and SPDS (Stabilized pellet delivery system).

Class II systems

This class relates to the cases in which solubility or dissolution rate is limiting, and thus significantly affects absorption and BA. The technologies under this class include the approaches such as classical micronization, stabilization of high-energy states (including lyophilized fast-melt systems), use of surfactants, emulsion or microemulsion systems, solid dispersion and use of complexing agent such as cyclodextrins. The technologies under this class include: SoftGel (soft gelatin capsule formulation), Zer-Os tablet technology (osmotic system), Triglas and nanosized carriers such as nanoemulsion, nanosuspension and nanocrystals are treated as hopeful means of increasing solubility and BA of poorly water-soluble active ingredients.

Class III systems

Manipulating the site or rate of exposure or perhaps by incorporating functional agents into the dosage form to modify the metabolic activity of the enzyme systems are included in Class III technologies. The technologies under this class include Oral vaccine system, Gastric retention system, High-Frequency Capsule and Telemetric Capsule.

Class IV systems

Extreme examples of Class IV compounds are exceptions rather than the rule and are rarely developed to reach the market. But a number of examples of Class IV drugs do exist, for example, Cyclosporin A, Furosemide, Ritonavir, Saquinavir and Taxol.

Drug discovery and early development[3,26]

BA and BE play a central role in pharmaceutical product development and BE studies are presently being conducted for New Drug Applications (NDAs) of new compounds, in supplementary NDAs for new medical indications and product line extensions, in Abbreviated New Drug Applications of generic products and in applications for scale-up and postapproval changes.

One of the starting problems with applying the BCS criteria to new drug substances is that, early in preformulation/formulation, the dose is not yet accurately known. Therefore, at this point, the Dose to Solubility ratio (D:S) can only be expressed as a likely range. Compounds with more than 100 μg/ml aqueous solubility seldom exhibit dissolution rate-limited absorption. Alternatively, one can estimate the maximum absorbable dose on the basis of the usual GI fluid volumes available under the anticipated dosing conditions and the drug solubility. In concern with the solubility of the drug, it may be useful to consider the physicochemical properties of the drug when deciding which media to use for the solubility determinations. For example, measuring solubility at all pH values recommended by the BCS is unnecessary for neutral compounds in early development. Later, when formulations are compared, dissolution data for the drug product over the entire GI pH range will be useful in establishing the robustness of release from the formulation under GI conditions. Lipophilic drugs may be very poorly soluble in water and in simple buffers, but in the GI fluids the bile to a significant extent can often solubilize them. Increases in solubility of one to two orders of magnitude are possible for compounds with log *P* values of >4. For promising compounds that are both ionizable and lipophilic, extensive solubility experiments in biorelevant media will help to characterize the likely solubility behavior *in vivo*. Another approach is to use aspirates from human volunteers, although volumes aspirated typically are small and the choice of experiments and apparatus therefore is also limited. Next issue is the use of 250 ml

as the volume in which a dose must be dissolved. This amount is a conservative estimate of the volume of fluid available in the gut under fasting-state conditions and is based on the volume usually ingested along with the dosage form in a pharmacokinetic study. Depending on whether drug administration is to be on an empty stomach or with meals, it is important and reasonable to adjust the volume used to assess the capacity of the GI fluids to dissolve the dose. A suggested starting point would be to use a volume of about 300 ml for the fasted stomach, about 500 ml for the fasting small intestine, and up to 1 l for the postprandial stomach and small intestine. The choice of model for assessing the permeability is also of consideration. The *Caco-2* cells can be used to assess transcellular diffusion and can be standardized to ensure reproducible results, but they tend to underestimate paracellular and active mechanisms, cannot be employed to determine regional permeability within the gut, and tend to overestimate efflux via the P-glycoproteins. *In situ* perfusions in rats, although they are much better in terms of forecasting active transport and can be used to determine regional permeability, but take more time and effort to produce a reliable permeability estimate and so in any case, it is a good idea to have more than one permeability screen at the disposal of the laboratory in order to build confidence and robustness into the screening system. If solubility of the drug is the problem rather than its permeability, formulation efforts should target on improving the dissolution profile. For example, the combined effects of formulating the drug as amorphous solid dispersion and administering it in the fed state tend to shift the solubility-dissolution characteristics from those of a very poorly soluble drug (D:S $>$10,000 ml) to those of a drug product with a D:S within the range of values encountered in the gut after meals. If permeability of the drug rather than solubility is the main problem, formulation approaches are less numerous and less reliable. Even when allowance is made for the differences in solubility and permeability requirements for oral drug product development vis-à-vis biowaiver criteria according to the BCS, further factors still must be considered for new drugs. These factors include the possibility of decomposition under GI conditions and the assessment of first-pass metabolism both in the gut wall and the liver. Appraising decomposition in the gut is relatively simple using biorelevant media and exposure times based on longest anticipated exposure times. For sensitive compounds, appropriate enzymes must be added to the medium in relevant concentrations. The enzymes that can be suitable are pepsin and gastric lipases for the stomach, pancreatic enzymes for the jejunum, and bacterial enzymes for the colon. In the case of first-pass metabolism in the gut wall, it may be possible to screen for metabolites in the permeability model depending on how the model is set up.

Pharmacokinetic optimization in drug research[27]

The two parameters of biopharmaceutics, solubility and permeability, are of pivotal importance in new drug discovery and lead optimization due to the dependence of drug absorption and pharmacokinetics on these two properties. BCS provides drug designer an opportunity to manipulate structure or physicochemical properties of lead candidates so as to achieve better deliverability. With the enormous number of molecules being synthesized using combinatorial and parallel synthesis, high throughput methodologies for screening solubility and permeability have gained significant interest in pharmaceutical industry. Ultimate objective of the drug discovery scientist in pharmacokinetic optimization is to tailor the molecules so that they show the features of BCS Class I without compromising on pharmacodynamics. Considerations to optimize drug delivery and pharmacokinetics right from the initial stages of drug design propelled need for high throughput pharmaceutics. *In silico* predictions and development of theoretical profiles for solubility and lipophilicity provides structure-based biopharmaceutical optimization, while *in vitro* experimental models, microtitre plate assays and cell cultures, validate the predictions. And so, biopharmaceutical characterization during drug design and early development helps in early withdrawal of new chemical entities with insurmountable developmental problems associated with pharmacokinetic optimization. Thus, BCS is helpful in optimizing the new chemical entity characteristics and minimize its chances of rejection.

Extensions to biopharmaceutics classification system

Six classes biopharmaceutics classification system[28]

In accordance with six classes BCS by Bergstrom *et al*. the solubility was classified as “high” or “low” and permeability was classified as “low”, “intermediate” or “high”. This new classification was given based on correlations between the calculated molecular surface area descriptors, on one hand, and solubility and permeability, on the other. The results showed that multivariate data analysis of easily comprehended molecular surface descriptors provides computational tools for prediction of both aqueous drug solubility and drug permeability. Surface areas related to the nonpolar part of the molecule resulted in good predictions of solubility, whereas surface areas describing the polar parts of the molecule resulted in good predictions of permeability. The established correlations were used to perform a theoretical biopharmaceutical classification of WHO listed drugs into six classes, resulting in a correct prediction for 87% of the essential drugs. Of the 23 compounds, 20 (87%) were sorted correctly into their respective Classes I-VI. The three compounds that were wrongly classified were amitryptiline, acyclovir and doxycycline. To overcome this type of false predictions it was suggested that larger data sets covering larger parts of structural space would be needed in development models.

Quantitative version of biopharmaceutics classification system[29]

According to *Rinaki et al*. the quantitative version of BCS (QBCS) was developed using the dose/solubility ratio (q) as the key parameter for solubility classification as it is inextricably linked to the dynamic characteristics of dissolution process. The QBCS uses a q value, apparent permeability (P*app*) plane with scientifically-physiologically based cut-off values for compound classification. The QBCS relies on a plane with cutoff points 2×10^{-6} - 10^{-5} cm/s for the permeability and 0.5-1 (dimensionless) for the dose/solubility ratio axis. Permeability estimates are derived from *Caco-2* studies, and a constant intestinal volume content of 250 ml is used to express the dose/solubility ratio. A physiologic range of 250-500 ml was ued to account for variability in the intestinal volume. Drugs are classified into the four quadrants of the plane around the cutoff points according to their P*app*, q values, establishing four drug 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* $<2 \times 10^{-6}$ cm/s, $q = 0.5$) and IV (P*app* $<2 \times 10^{-6}$ cm/s, $q > 1$). A region for borderline drugs ($2 \times 10^{-6} <$ P*app* $< 10^{-5}$ cm/s $0.5 < q < 1$) was defined.

For category I, complete absorption is anticipated, whereas categories II and III exhibit dose/solubility ratio-limited and permeability-limited absorption, respectively. For category IV, both permeability and dose/solubility ratio are controlling drug absorption.

Fagerholm[30] suggests some improvements after evaluation of BCS. The BCS has a very strict solubility/dissolution limit, a generous P_e limit (≥14-times higher rate constant limit for dissolution than for permeation), and is stricter for drugs with a long half-life. Available human *in vivo*, *in vitro* and *in silico* P_e methods cannot classify P_e for moderately to highly permeable substances sufficiently well, and *in vitro* data often under predict the *in vivo* dissolution potential and rate. Good *in vivo* dissolution and absorption can be expected for most high P_e drug products. It has not been possible to find a highly permeable product with a dose number <385 (<2400 in the fed state) that is clearly incompletely absorbed, and near complete uptake has been shown for a drug product with a dose number of 660,000. The potential implication of these findings is that many true BCS Class I drug products are incorrectly classified. This could be a reason for the limited use of this system. On this basis, it has been suggested that: The limit for high for solubility/dissolution is decreased (to >40 and >95% dissolved within 30 min and 3 h, respectively); the limit for high P_e is increased (to > P_e of metoprolol); accurate P_e models or *in vivo* fraction absorbed data are used; solubility/dissolution tests are performed using real or validated simulated gastrointestinal fluids; *in vitro/in vivo* dissolution relationships are established; the $t_{½}$ is considered; and the rate-limiting step for *in vivo* absorption is determined. A major change could be to reduce the BCS into two classes: Permeation-rate (ClassI) or dissolution-rate (Class II) limited absorption. It is believed that this could give a better balance and increase the number of biowaivers.

Conclusion

The BCS acts as a guiding tool for development of various oral drug delivery technologies. The BCS takes into account three major factors, dissolution, solubility and intestinal permeability, which govern the rate and extent of drug absorption from IR solid dosage forms. BCS provides drug designer an opportunity to manipulate structure or physiochemical properties of lead candidate. The benefits provided by the BCS are minimization of drug exposure to large panel of human subjects and in some cases, shortened drug product development time in addition of large cost savings. BCS relies on black and white definitions of solubility and permeability, are these definitions reliable or realistic, and what about borderline cases? There may be a risk of misclassification. BCS class is based on highest dose, what about smaller doses of the same product? What about controlled-release dosage forms? How early in the development process can we apply the BCS principles? BCS-based are still rarely used probably attributed to uncertainties on both, pharmaceutical companies and regulatory authorities. Substantial differences of biowaiver dossiers and respective assessments contribute to the impression that a common understanding is lacking on a successful use of the BCS concept to support . As our knowledge of GI physiology becomes more sophisticated, *in vitro* dissolution tests will be able to better simulate the conditions in the GI tract. This in turn will lead to more powerful predictions of *in vivo* performance and ultimately to a significant reduction in the number of animal and human studies required to optimize the formulation. Together with screens for other limitations to oral absorption, the BCS paves the way for revolution in the drug-development process.

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