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Review Article

BIOPHARMACEUTICS DRUG DISPOSITION CLASSIFICATION SYSTEM: AN EXTENSION OF BIOPHARMACEUTICS CLASSIFICATION SYSTEM

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ABSTRACT
The Biopharmaceutics Classification System (BCS) was developed for prediction of *in vivo* pharmacokinetic performance of drug products from measurements of permeability and solubility. If the permeability criteria changed with metabolism criteria than it may be useful in predicting overall drug disposition, including routes of drug elimination and the effects of efflux and absorptive transporters on oral drug absorption, importance of food effects, and transporter effects on post absorption systemic drug concentrations following oral and intravenous dosing known as Biopharmaceutics drug disposition classification system (BDDCS). The drugs that have high permeability but poor metabolism are generally hydrophilic molecules with low molecular weight are likely to be absorbed by active transport mechanisms. Suggesting that drugs have extensive metabolism are highly absorbed. BDDCS using elimination criteria may expand the number of Class 1 drugs eligible for a biowaiver of in vivo bioequivalence (BE) studies and provide predictability of drug disposition profiles for Classes 2, 3, and 4 compounds.
KEYWORDS: BCS, BDDCS, Solubility, Permeability, Metabolism, Biowaiver

INTRODUCTION

BCS is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. The objective of BCS is to predict the *in vivo* pharmacokinetic performances of drugs from measurements of permeability and solubility. It allows estimation of the contributions of three major factors, viz. dissolution, solubility and intestinal permeability. Dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extension of drug absorption thus BCS becomes a fundamental tool in drug development. The BCS was developed primarily in the context of immediate release (IR) solid oral dosage forms. BCS recommends method for classification according to dosage form dissolution along with the solubility–permeability characteristics of the drug product.[1, 2] BCS guidelines are provided by U.S. Food and Drug Administration (USFDA), World Health Organization (WHO) and European Medicines Agency (EMEA).[3] The classification system is based on fick's first law applied to a membrane: Jw= Pw*Cw; Where Jw is the drug flux through intestinal wall at any position and time, Pw is permeability of membrane; Cw is drug concentration at intestinal membrane surface.[4, 5]

Classes of BCS

Drug substances are classified in four classes of BCS as shown in figure 1 by Amidon *et al*.

Class I (High Permeability, High Solubility)

These compounds are well absorbed and their absorption rate is usually higher than excretion. 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. Examples: Metoprolol, Diltiazem, Verapamil, Propranolol

Class II (High permeability, Low solubility)

The bioavailability of these products is limited by their solvation rate. Drugs have a high absorption number but a low dissolution number. The absorption for class II drugs is usually slower than class I and occurs over a longer period of time.

Examples: Danazol, Ketoconazole Glibenclamide, Mefenamic acid, Nifedipine and Itraconazole.

Class III (Low permeability, High solubility)

The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time then class I criteria can be applied. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is an aspect to alteration of physiology and membrane permeability rather than the dosage form factors.

Examples: Cimetidine, Acyclovir, Neomycin B, and Captopril.

Class IV (Low permeability, Low solubility)

These compounds have a poor bioavailability and not good absorbed over the intestinal mucosa properly. Such drugs show evidence of a lot of problems for effective oral administration. Examples: Hydrochlorothiazide, and Taxol.[6, 7, 8]

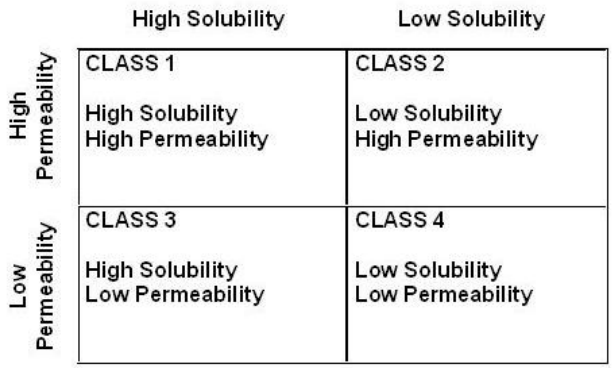

Figure.1: The Biopharmaceutics Classification System

BASIC ELEMENTS OF BCS

BCS drug classification requires knowledge of solubility and permeability data. The determination of drug permeability is typically based on experimental permeability data or well-defined mass balance studies.

Solubility

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 Bioavailability (BA) & Bioequivalence (BE) study) request. According to USFDA BCS guidance 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 to 7.5. As per WHO guidance an API is considered highly soluble when the highest dose (if the API appears in 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 at 37ºC ± 1ºC. EMEA BCS guidance states that a drug substance is considered highly soluble if the highest single dose administered as IR formulation is completely dissolved in 250 ml of buffers (pH 1.2, 4.5 and 6.8) at 37ºC ± 1ºC.[9-13]

Permeability

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. According to USFDA BCS guidance, 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. WHO guidance suggest that 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. According to EMEA BCS guidance if a drug substance has linear and complete absorption then it is considered highly permeable.[10-14]

Dissolution

According to USFDA BCS guidance an IR drug product is considered rapidly dissolving when not 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 of 0.1 N HCl or simulated gastric fluid USP without enzymes, buffer (pH 4.5) and buffer (pH 6.8) or simulated intestinal fluid USP without enzymes. According to WHO BCS guidance a product is considered to be very rapidly dissolving when not 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 of HCl solution (pH 1.2), acetate buffer (pH 4.5) and phosphate buffer (pH 6.8). EMEA BCS guidance mention that the 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 of 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.[10-13]

APPLICATIONS OF BCS IN BIOWAIVER OF DRUG

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. Biowaiver means to obtain waive off for carrying out expensive and time-consuming BA and BE studies. BCS provides biowaivers for Class I, II and III drug with some specifications. This waiver is for both pre- and post approval phases. The USFDA BCS guidance recommends for biowaiver if the drug substance is highly soluble and highly permeable (Class I drugs) or an immediate release drug product. For waiver of an in vivo relative BA study, dissolution should be greater than 85% in 30 minutes in the three recommended dissolution media. 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. The drug should not be a narrow therapeutic index drug, 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 and the drug must be stable in gastrointestinal tract along with the product is designed not to be absorbed in oral cavity are also biowaiver in USFDA BCS guidance documents. Biowaivers for drugs belonging to BCS class II may be granted for drugs with weak basic nature and drugs with weak acidic nature. The drugs with weak basic nature exhibit high solubility in lower pH (stomach) and permeability is not limitation. Hence they will be absorbed before they reach the higher pH region (intestine). The drugs with weak acidic nature exhibit high solubility in the higher pH region (intestine) with permeability being no limitation so well absorbed in higher pH region and owing to greater absorbing surface area e.g. Diclofenac Sodium and Diclofenac Potassium. BCS-based biowaiver is 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. EMEA BCS guidance document suggests that the biowaivers are applicable for the IR drug product if the drug substance has been proven to exhibit high solubility and complete absorption (BCS class I), very rapid (> 85 % within 15 min) in vitro dissolution characteristics of the test and where excipients are not suspect of having any relevant impact on bioavailability. The biowaiver is also applicable for the drug substance exhibit high solubility and limited absorption (BCS class III), very rapid (> 85 % within 15 min) in vitro dissolution of the test. The class III drug substance excipients have to be qualitatively the same and quantitatively very similar to exclude different effects on membrane transporters.[11-13,15-17]

Limitation of BCS

BCS based biowaivers are not applicable for the following:

i. Narrow therapeutic range drug products.
ii. BCS based biowaivers have limited application for the class II drugs and not applicable for class III.
iii. Dosage form meant for absorption in the oral cavity e.g. sublingual or buccal tablets.
iv. Effects of food, absorptive transporters, efflux transporters, and routes of elimination (renal/biliary) were important determinants of overall drug absorption and bioavailability for immediate release oral dosage forms, which are not considered in BCS.[18]

EXTENSION TO BCS

Six class BCS

Bergstrom et al. 2003 developed a modified BCS, in which they categorized the drugs into six classes based on the solubility and permeability. The solubility was classified as "high" or "low" and the permeability was allotted as "low", "intermediate," or "high". This new classification was developed based on the calculated surface area descriptors on the one hand and solubility and permeability on the other. Surface areas related to the nonpolar part of the molecule resulted in good predictions of permeability. It was tentatively concluded that these models would be useful for early indication with regard to the absorption profiles of the compound during the early stages of drug discovery so that the necessary modifications can be made to optimize the pharmacokinetic parameters.[19]

Quantitative BCS (QBCS)

Rinaki et al. 2003 developed quantitative BCS (QBCS) using the solubility: dose ratio as core parameter for classification. The QBCS uses a solubility: dose ratio vs. permeability plane with scientifically, physiologically based cut-off values for compound classification. The 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. It was discussed that solubility is a static equilibrium parameter and cannot describe the dynamic character of the dissolution process for the entire dose administered. Thus, a single solubility value is too little for the purpose of BCS, because the drugs are administered in various doses; therefore, the dose consideration should be taken into account. FDA guidance for the industry, "Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system", states that the highest dose strength of an immediate release product should be considered for study.[20]

Pulmonary BCS

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.[21]

BIOPHARMACEUTICS DRUG DISPOSITION CLASSIFICATION SYSTEM (BDDCS)

BDDCS is the most popular extension of BCS given by Chi-Yuan Wu and Leslie Z. Benet, 2005. They communicated the effects of food, absorptive transporters, efflux transporters, and routes of elimination (renal/biliary) on overall drug absorption and bioavailability for immediate release oral dosage forms is more than the permeability. It was suggested that classifying molecules based on the extent of metabolism is less ambiguous as compared to permeability or extent of absorption. They proposed that BDDCS could provide a very simple replacement for permeability. They suggested that if the major route of elimination for a drug was metabolism, then the drug exhibited high permeability, while if the major route of elimination was renal and biliary excretion of unchanged drug, then that drug should be classified as low permeability. The initially proposed, “Extensive metabolism” was defined as ≥ 50% metabolism of an oral dose in vivo in humans. It is now proposed that the “extensive metabolism” be ≥ 70% metabolism of an oral dose in vivo in humans whereas the “poor metabolism” is ≥ 50% of the dose be excreted unchanged.[22, 23]

BDDCS Classification

Four classes have been defined in BDDCS as shown in figure 2.

Class 1: High Solubility, Extensive Metabolism: The high permeability/ high solubility of such compounds allows high concentrations in the gut to saturate any transporter, both efflux and absorptive. Class 1 compounds may be substrates for both uptake and efflux transporters in vitro in cellular systems, but transporter effects on absorption will not be important clinically. Efflux transporters may have, however measurable effect on the penetration of the compounds through the blood-brain barrier. If the systemic concentration of the compounds is lower, transporters may overcome the effect of the high passive permeability of the compound. These compounds can also be involved in transporter mediated drug-drug interactions.

Class 2: Poor Solubility, Extensive Metabolism: These high permeability compounds will pass through the gut membranes and uptake transporters will have no effect on absorption. However, the low solubility will limit the concentration at the enterocytes, thereby preventing saturation of the efflux transporters. Consequently, efflux transporters will affect the extent of oral bioavailability and the rate of absorption of Class 2 compounds.

Class 3: High Solubility, Poor Metabolism: For Class 3 compounds, the drug availability will be sufficient in the gut lumen due to good solubility, but an uptake transporter will be necessary to overcome the poor permeability of these compounds. Apical efflux transporters may also be important for the absorption of such compounds when sufficient penetration is achieved via an uptake transporter.

Class 4: Low Solubility, Poor Metabolism: Because of the low permeability and low solubility of these compounds both uptake and efflux transporters play an important role in the oral bioavailability of compounds of the class.[24, 25]

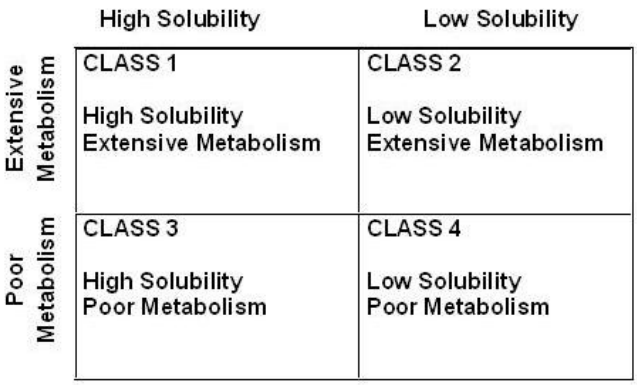

Figure 2: Biopharmaceutics Drug Disposition Classification System

Characteristics of BDDCS Class

In BDDCS class 1 and class 2 drugs are predominantly eliminated by metabolism. Class 3 and 4 drugs are eliminated unchanged via urinary or biliary excretion. The transporter effect will be negligible for class 1 drugs. Efflux and absorptive transporter have predominantly effect on class 2 and class 3 compounds, respectively.

FACTORS GOVERNING DRUG CLASSIFICATION AS PER BDDCS

Effect of transporter

Class 1 Compounds

The gut lumen of the gastrointestinal tract is sufficiently

leaky so that small molecular weight, soluble, non-polar compounds (i.e. Class 1 compounds) readily pass through the membrane. Alternatively, the high permeability/high solubility of Class 1 drugs allows high concentrations in the gut to saturate any transporter, both efflux and absorptive. That is, Class 1 compounds may be substrates for both uptake and efflux transporters in vitro in cellular systems under the right conditions, but transporter effects will not be important clinically.

Example: Acetyl salicylic acid.

Class 2 Compounds

Class 2 drugs (high permeability) will allow ready access into the gut membranes making intestinal uptake transporters generally unimportant due to the rapid permeation of the drug molecule into the enterocytes. Absorption of class 2 compounds is primarily passive and a function of lipophilicity. However, the low solubility of these compounds will limit the concentrations coming into the enterocytes, thereby preventing saturation of the efflux transporters. Consequently, efflux transporters will affect the extent of oral bioavailability and the rate of absorption of class 2 drugs. Moreover, there will be little opportunity to saturate intestinal enzymes due to the low solubility. Thus, changes in transporter expression, and inhibition or induction of efflux transporters will cause changes in intestinal metabolism of drugs that are substrates for the intestinal enzymes. Examples: Artemether, Artesunate

Class 3 and Class 4 Compounds

Class 3 and Class 4 compounds 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, intestinal apical efflux transporters may also be important for the absorption of such compounds when sufficient enterocyte penetration is achieved via an uptake transporter. Since influx of compounds will generally be rate limited by an absorptive transporter, the counter effects of efflux transporters will not be saturated and can also be important. Examples: Ascorbic acid, Doxycycline.[26]

Food effects

Class 1

High fat meals will have no significant effect on class 1 drugs, despite the fact that many class 1 drugs are transporter substrates, because the high gut permeability and high solubility in intestinal fluid possessed by this class of drugs dictate that transporter effects will be minimal. High fat meals may delay stomach emptying, so cause an increase in peak time.

Class 2

High fat meal increases the extent for class 2 compound. Efflux transporter inhibition results in decreased extraction of the drug and additional solubilization of drug in intestinal lumen. Peak time increases due to slowing of stomach emptying and decreases due to inhibition of efflux cycling.

Class 3

High fat meal will decreases the extent for class 3 compound. Transporter inhibition results in the reduction of area under curve (AUC).

Class 4

The compounds of this class were found difficult to predict.

Post absorption effects and intravenous dosing

For intravenous dosing, drug concentration at elimination level will be low due to diluting effect of volume of distribution, as compared to concentration of drug in intestine.

Potential drug-drug interaction predicted by BDDCS

Class 1

Metabolize in the intestine and liver. Drug interaction occurs primarily with transporter enzyme.

Class 2

Metabolic, efflux transporter and efflux transporter enzyme interplay in intestine. Metabolic efflux transporter, uptake transporter and transporter enzyme interplay in liver. Drug–drug interactions mediated by transporter interaction and often involve transporter enzyme. Inhibition of hepatic uptake transporter can lead to significantly increased in systemic drug concentration.

Class 3 and Class 4

Uptake transporter, efflux transporter and uptake-efflux transporter interplay. Inhibition of hepatic and renal uptake transporter can lead to significantly increased systemic drug concentration.[27]

APPLICATIONS OF BDDCS IN BIOWAIVER OF DRUG

BDDCS may also increase the number of class 1 drugs that would become eligible for biowaivers. The BDDCS, like BCS, proposes to classify drug molecules into four classes, defining the extensive metabolism criterion as ≥50% (±10%) metabolism of an oral dose in vivo in humans. Based on this criterion, a few drugs that were previously BCS class 1 were re classified as BDDCS class 3 and thus would not be eligible for biowaivers. The BDDCS approach could be helpful in successfully classifying drugs in class 1, thereby increasing their eligibility for biowaiver. It has been suggested that the matrix of drug metabolism in BDDCS can be used to substantiate the classification of permeability by BCS. Takagi et al. compared 164 BDDCS classifying with the BCS approach using D0A and CLogP. The BDDCS classification indicated that out of 164 drug compounds 59 drugs are class I, 51 class II, 42 class III, and 12 drugs are class IV compounds whereas BCS classification based on metoprolol as the reference compound suggested 42, 54, 57, and 11 drugs as class I, II, III, and IV, respectively. Further the excellent agreement between BDDCS and BCS was obtained for the classification of class II and IV drugs but not for class I and III (Fig. 3). Afterward the extents of metabolism of 51 drugs were studied to examine the use of drug metabolism for predicting permeability. All compounds were classified as high permeability based on BCS, but only 73% of the compounds were found to exhibit extensive metabolism. Lipophilicity accounts for significant metabolism of many highly permeable drugs. Fourteen out of 51 drugs have poor metabolism, suggesting that high permeability as defined by BCS does not necessarily dictate extensive metabolism. The drugs that have high permeability but poor metabolism are generally hydrophilic molecules with low molecular weight and are likely to be absorbed by active transport mechanisms. Based on the present data and literature information, it was concluded that the extent of absorption is mostly complete (or ≥90%) if the drug is subject to a high degree of metabolism (e.g., ≥90%).[28, 29, 30]

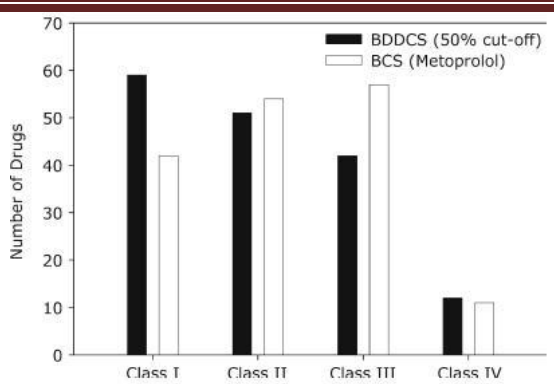

Fig. 3: Comparison of the provisional classification of 164 drugs according to the BDDCS & BCS

Prerequisites for developing *In Vitro* & *In Vivo* Correlation (IVIVC) according to BDDCS

1. Metabolic factors

A drug must pass sequentially from the gastrointestinal lumen, through the gut wall, and the liver, before entering in the systemic circulation. This sequence is an anatomic requirement because blood perfusion virtually all gastrointestinal tissues drain into the liver via the hepatic portal vein. Drug loss may occur in the GIT due to the instability of the drug in the GIT and/or due to complexation of drug with the components of the GI fluids, food, formulation excipients or other co-administered drugs. In addition, the drug may undergo destruction within the walls of the GIT and/or liver.

2. Drug loss in GIT

Any reaction that completes with the absorption of a drug may reduce oral bioavailability of a drug. Reaction can be both enzymatic and non-enzymatic. Acid hydrolysis is a common non-enzymatic reaction. Enzymes in the intestinal epithelium and within the intestinal microflora, which normally reside in the large bowel, metabolize some drug. The reaction products are often inactive or less potent than the large molecule.

BDDCS assist in predicting route of drug elimination, effect of efflux and absorptive transporters on oral drug absorption. The BDDCS also assist in the prediction of effect of transporter enzyme and Drug –Drug interaction potential. The major differences between BCS and BDDCS have also been shown in table 1. The disposition data for several essential medicines as per WHO's guidance documents were compiled from several sources by Khandelwal A. et al. 2007 as reported in table 2, which reveals a correlation between BCS and BDDCS category for certain drugs.[31]

Table 1: Differences between BCS and BDDCS

S. No.	BCS	BDDCS
1	It takes into account solubility and permeability criteria to classify drugs.	It takes into account solubility and metabolism criteria.
2	It is more ambiguous.	It is less ambiguous.
3	Less numbers of drugs are available for biowaiver.	More numbers of drugs are available for biowaiver.
4	It is not applicable in condition where food and transporter interaction occur.	It is applicable in condition where food and transporter interaction occur.

Table 2: Drug Disposition data for a few drugs from WHO Essential Medicines List[31]

Drug Name	Dose (mg)	Solubility (mg/ml)	Dose No.	Bioavailability (%)	Metabolism	BCS	BDDCS
Acetylsalicylic acid	500	4.6	0.6	Limited data	Extensive	3	1
Benznidazole	100	0.4	1	96	Extensive	3	1
Biperiden HCl	2	0.0251	0.32	36	Extensive	1	1
Clomifene citrate	50	1	0.2	90	Poor	1	3
Didanosine	400	27.3	0.06	44	Poor	3	3
Ethambutol	400	100	0.016	N.A.	Poor	3	3
Ethosuximide	250	100	0.01	N.A.	Extensive	3	1
Folic acid	1	0.1	0.04	N.A.	Poor	3	3
Glibenclamide	5	0.01	16	N.A.	Extensive	2	2
Levothyroxine sodium	0.1	0.15	$3 \cdot 10^{-3}$	70	Poor	1	3
Lumefantrine	120	1	0.48	N.A.	Poor	1	3
Methyldopa	250	10	0.1	25	Extensive	3	1
Nicotinamide	50	100	$2 \cdot 10^{-3}$	High	Extensive	3	1
Nifurtimox	250	33	0.02	N.A.	Extensive	3	1
Nitrofurantoin	100	0.19	2.11	S	Extensive	4	2
Norethisterone	1	0.01	0.4	N.A.	Extensive	1	1
Paracetamol	500	0.1	20	75	Extensive	4	1
Penicillamine	250	100	0.01	Limited data	Extensive	3	1
Praziquantel	600	0.4	6	80	Extensive	2	2
Proguanil	100	1	0.4	N.A.	Extensive	1	1
Propylthiouracil	50	1	0.2	N.A.	Extensive	3	1
Retinol palmitate	110	0.01	44	55	Extensive	2	2
Salbutamol sulfate	4	33	$5 \cdot 10^{-4}$	44	Poor	3	3
Stavudine	40	83	$2 \cdot 10^{-3}$	100	Poor	3	3
Sulfasalazine	500	0.01	200	N.A.	Extensive	2	2

N.A. Not Applicable

CONCLUSION

BCS is an important tool for predicting in vivo pharmacokinetics of the drug from in vitro test such as solubility and permeability. BCS has taken into account three major factors, dissolution, solubility and intestinal permeability, acts as a guiding tool for development of various oral drug delivery technologies. As BCS facilitates to waive off expensive in vivo test both time and capital are saved. But due to limitations of BCS to categories drug into biowaiver group, a new classification system known as BDDCS was coined by Wu and Benet 2005. In BDDCS permeability component replaced by metabolism component, prove to be useful tool in predicting over all drug dispositions, effect of food and transporter. The BDDCS expand the number of class 1 drugs eligible for waiver of in vivo bio-equivalence studies, and provide new insight for other classes.

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