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Review Article

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Prediction of Solubility and Permeability Class Membership: Provisional BCS Classification of the World's Top Oral Drugs

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Abstract. The Biopharmaceutics Classification System (BCS) categorizes drugs into one of four biopharmaceutical classes according to their water solubility and membrane permeability characteristics and broadly allows the prediction of the rate-limiting step in the intestinal absorption process following oral administration. Since its introduction in 1995, the BCS has generated remarkable impact on the global pharmaceutical sciences arena, in drug discovery, development, and regulation, and extensive validation/discussion/extension of the BCS is continuously published in the literature. The BCS has been effectively implanted by drug regulatory agencies around the world in setting bioavailability/bioequivalence standards for immediate-release (IR) oral drug product approval. In this review, we describe the BCS scientific framework and impact on regulatory practice of oral drug products and review the provisional BCS classification of the top drugs on the global market. The Biopharmaceutical Drug Disposition Classification System and its association with the BCS are discussed as well. One notable finding of the provisional BCS classification is that the clinical performance of the majority of approved IR oral drug products essential for human health can be assured with an *in vitro* dissolution test, rather than empirical *in vivo* human studies.

KEY WORDS: BA/BE; biopharmaceutics classification system; biowaiver; intestinal absorption; molecular biopharmaceutics; oral drug product.

INTRODUCTION

The rate and extent of drug absorption from the gastrointestinal (GI) tract are very complex and affected by many factors. These include physicochemical factors (e.g., pKa, solubility, stability, diffusivity, lipophilicity, polar–nonpolar surface area, presence of hydrogen bonding functionalities, particle size, and crystal form), physiological factors (e.g., GI pH, GI blood flow, gastric emptying, small intestinal transit time, colonic transit time, and absorption mechanisms), and factors related to the dosage form (e.g., tablet, capsule, solution, suspension, emulsion, and gel) (1–4). Despite this complexity, the work of Amidon *et al*. (5) revealed that the fundamental events controlling oral drug absorption are the permeability of the drug through the GI membrane and the solubility/dissolution of the drug dose in the GI milieu. These key parameters are characterized in the Biopharmaceutics Classification System (BCS) by three dimensionless numbers: absorption number (A_n), dissolution number (D_n), and dose number (D_0). These numbers take into account both physicochemical and physiological parameters and are fundamental to the oral absorption process (6,7). Based on their solubility and intestinal membrane permeability characteristics, drug substances have been classified into one of four categories according to the BCS (Fig. 1). The BCS is one of the most significant prognostic tools created to facilitate oral drug product development in recent years; the validity and broad applicability of the BCS have been the subject of extensive research and discussion (8–13); it has been adopted by the US Food and Drug Administration (FDA), the European Medicines Agency (EMEA), and the World Health Organization (WHO) for setting bioavailability/bioequivalence (BA/BE) standards for immediate-release (IR) oral drug product approval; and the BCS principles are extensively used by the pharmaceutical industry throughout drug discovery and development (14–17). In this review, we describe and discuss the impact of the BCS and its scientific basis on regulatory practice of oral drug products and review the provisional BCS classification of the top drugs on the global market. The Biopharmaceutical Drug Disposition Classification System (BDDCS) and its association with the BCS are discussed as well. One important outcome of the provisional classification is that the clinical performance of the majority of approved IR oral drug products essential for human health can be assured with an *in vitro* dissolution test, rather than empirical *in vivo* human studies.

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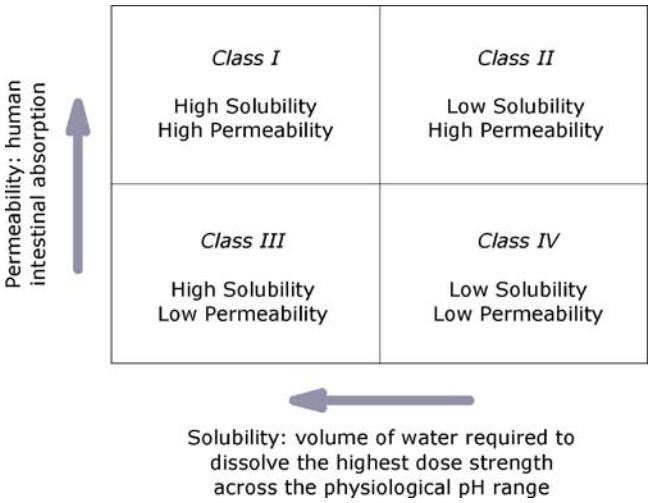

Fig. 1. The Biopharmaceutics Classification System as defined by Amidon *et al.* (5). The BCS classifies drugs by their solubility and permeability properties in order to stand for the most fundamental view of the drug intestinal absorption process following oral administration

BCS IN REGULATORY PRACTICE

Throughout the past decade, the BCS has become an increasingly important tool in drug product regulation worldwide, by presenting a new paradigm in bioequivalence. Bioequivalence (BE) is the critical step that connects the physical drug product with the clinical properties claimed on its label, ensuring continuing quality of the innovative products and the generic products. Before the presentation of the BCS, the BE standard was solely empirical, depending on *in vivo* bioavailability (BA) studies, i.e., plasma levels, AUC, and C_{max}. By revealing the fundamental parameters dictating the *in vivo* oral drug absorption process, the BCS is able to ensure BE by mechanistic tools, rather than empirical observation; if two drug products that contain the same active pharmaceutical ingredient (API) have a similar GI concentration–time profile under all luminal conditions, than a similar rate, and extant of absorption is ensured for these products, i.e., they are bioequivalent. Thus, BE can be guaranteed based on *in vitro* dissolution tests that provide the mechanistic proof for similar bioavailability, rather than empirical *in vivo* human studies. This is the regulatory waiver of *in vivo* BE, based on the scientific and mechanistic rationale provided by the BCS. Initially, waivers of *in vivo* BE were accepted only for Scale-Up and Post Approval Changes (SUPAC), but later, the biowaiver principle was extended to the approval of new generic drug products, thus avoiding unnecessary human experiments and reducing cost and time of developing generic IR oral drug products.

The solubility classification of a given drug is based on the highest dose strength in an IR product. According to the current FDA guidance (18,19), drug substance is considered highly soluble if the highest strength is soluble in 250 ml or less of aqueous media throughout the pH range of 1.2–6.8 (the volume of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 oz) of water). Otherwise, the drug substance is considered poorly soluble. A drug substance is considered highly permeable if the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered poorly permeable. The permeability classification is based either directly on the extent of intestinal absorption of a drug substance in humans determined by mass balance or in comparison to an intravenous reference dose, or indirectly on the measurements of the rate of mass transfer across the human intestinal membrane. Alternatively, animal or *in vitro* models that predict human intestinal absorption, e.g., intestinal rat perfusion models or epithelial cell culture models, can be used. An IR product is characterized as rapidly dissolved if not less than 85% of the labeled drug amount is dissolved 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 USP-simulated gastric fluid without enzymes; (2) pH4.5 buffer; and (3) pH6.8 buffer or USP-simulated intestinal fluid without enzymes. Otherwise, the drug product is considered to be slow dissolving.

Up to now, The FDA has implemented the BCS system to allow waiver of *in vivo* BA/BE testing of IR solid dosage forms for class I, high-solubility, high-permeability drugs. As for class III (high-solubility low-permeability) drugs, as long as the drug product does not contain agents and/or excipients that may modify intestinal membrane permeability, *in vitro* dissolution test can ensure BE. The absorption of a class III drug is likely limited by its permeability, less dependent upon its formulation, and its bioavailability may be determined by its *in vivo* permeability pattern. If the *in vitro* dissolution of a class III drug product is rapid under all physiological pH conditions, its *in vivo* behavior will essentially be similar to oral solution (controlled by gastric emptying), and as long as the drug product does not contain permeability modifying agents (this potential effect is largely mitigated by the large gastric dilution), *in vitro* dissolution test can ensure BE. Hence, biowaivers for BCS class III drugs are scientifically justified and have been recommended (20–24).

PROVISIONAL BCS CLASSIFICATION OF THE TOP DRUGS

Since its introduction in 1995, the validity and broad applicability of the BCS have been the subject of extensive research and discussion, including an effort to draw a BCS classification of many drug products. In this section, we will review the information gathered in the literature on the BCS classification of the top IR oral drug products on the global market. The majority of the data is based on secondary aqueous solubility references and permeability estimations based on correlations with Log *P* and CLog*P*. As such, the classifications are provisional and can be revised as more experimental data become available. Also, it should be well recognized that more extensive solubility, dissolution, and permeability determinations would need to be carried out in order to officially classify these drugs in accordance with current BCS criteria, especially to support a biowaiver application. In addition, the BDDCS and its association with the BCS will be discussed as well.

BCS Classification Based on Literature Data

In order to determine the broad applicability and significance of the BCS, we developed a provisional classification of first the WHO Essential Medicines List (25) and then extended this analysis to the top 200 drugs on the United States, Great Britain, Spain, and Japan lists (26). Values for drug solubility were obtained from standard references (e.g., *Merck Index*, USP etc.), and the maximum dose strengths were readily available in the list being classified, enabling the calculation of the dimensionless dose number (D_0). D_0 is the ratio of drug concentration in the administered volume (250 ml) to the saturation solubility of the drug in water (27), that may also be viewed as the number of glasses of water required to dissolve the drug dose. A dose number equal or lower than 1 indicated high-solubility, and $D_0>1$ signified a low-solubility compound. As for the permeability classification, ideally, this would be based on experimental human jejunal permeability data, or well-defined mass balance studies and/or comparison to an intravenous reference dose. However, since such data is available only for a small number of drugs, the provisional permeability classification was based on correlation of the estimated *n*-octanol/water partition coefficient using both Log *P* and CLog*P* of the uncharged form of the drug molecule (28,29). Log *P* and CLog*P* values were used for permeability classifications as these parameters are readily attainable for most drugs. The correlations were based on a set of 29 reference drugs for which the actual human jejunal membrane permeability data are available. Drugs exhibiting *n*-octanol/water partition coefficient value greater than metoprolol (Log *P* 1.72) were categorized as high-permeability since metoprolol is known to be 95% absorbed from the GI and hence may be used as a reference standard for the low/high class boundary (30). One noticeable short coming regarding the permeability prediction by lipophilicity correlations is that drugs whose intestinal absorption is carrier-mediated, either in the absorptive direction or exsorptive direction, will have their permeabilities underestimated or overestimated, respectively.

Since 1977, the WHO has published a list of essential medicines required for basic health care based on public health relevance, efficacy, safety, and cost-effectiveness. A total of 260 drugs are included in the 12th edition of the WHO list from 2002 (31), 123 of which are orally administered drugs. This list classification was subsequently compared with the classification of the top 200 prescribed drugs in the United States that include 141 orally administered drugs (32). Only 43 IR oral drugs appear in both WHO list and top 200 prescribed US drugs, highlighting differences in treatment priorities, social acceptance, and awareness between the US and the developing countries (25).

Solubility classification of the drugs on the WHO list and the top 200 US list revealed that 67% and 68%, respectively, are categorized as high-solubility ($D_0<1$). This finding was obtained even though a conservative approach was applied for the dose number calculations. A total of 43 and 49 drugs on the WHO list and the top 200 US list, respectively, exhibited solubility lower than 0.1 mg/ml; however, some of these drugs were classified as high-solubility based on the dose number (low dose compounds). This reflects the recent trend towards development of highly lipophilic, but high-potency drugs, leading to low dose that compensate for the poor water solubility (1,33).

Based on Log *P* or CLog*P* and permeability correlations, a total of 43% and 50%, respectively, of the WHO list exhibited higher values than the reference drug metoprolol and, hence, were provisionally assigned as high-permeability drugs. For carrier-mediated absorbed drugs, e.g., glucose, L-leucine, phenylalanine, and L-dopa, permeability classification based on partition coefficient (either Log *P* or CLog*P*) was false-negative (as expected). Based on Log *P* correlations, no false-positives were obtained; however, based on CLog*P* correlations, furosemide and losartan, two low-permeability drugs, were false-positives (25). Indeed, both drugs were reported to be susceptible for efflux transport, furosemide by MRP2 (34), and losartan by P-gp and potentially MRP2 as well (35). Likewise, we have recently found that sulfasalazine is actually a low-permeability drug due to efflux process, even though this drug has Log *P* and CLog*P* values higher than metoprolol (8).

The percentages of the drugs in IR dosage forms on the WHO list that were classified as class I drugs based on D_0 and Log *P* or CLog*P* were 23.6% and 28.5%, respectively (Fig. 2). The corresponding percentage of drugs classified as class III drugs were 31.7% and 35.0% (Fig. 2), respectively, and regulatory approval of biowaiver for this class of drugs is scientifically justified and recommended by WHO (36). Hence, the majority of IR oral drug products on the WHO List of Essential Drugs are candidates for waiver of *in vivo* BE testing based on an *in vitro* dissolution test. The impact of waiving an expensive *in vivo* BE testing and its replacement by rapid and affordable *in vitro* dissolution standards in developing countries is expected to be profoundly significant.

Similar results were obtained in a subsequent classification of the WHO list of Essential Medicines that was based primarily on human fraction absorbed (F_{abs}) literature data for the permeability assignment (37). Out of 61 drugs that could be reliably classified, 34% were classified as class I, 17% as class II, 39% as class III, and 10% as class IV. In this analysis, hence, more than 70% of the classified drugs proved to be candidates for waiver of *in vivo* BE testing based on *in vitro* dissolution test. Of course, other drug product characteristics, such as the therapeutic index and the potential influence of the excipients on the rate and extent of absorption, should also be considered.

In view of the fact that many of the WHO drugs are not on the top 200 drugs lists of the developed countries, a subsequent provisional BCS classification of the orally administered IR solid dosage forms in the top 200 drug products lists from the United States (US), Great Britain (GB), Spain (ES), and Japan (JP) was carried out (26). Criteria for solubility/permeability classification were as described above, i.e., D_0 calculations based on literature data for solubility and partition coefficients correlation for the permeability. More than 50% of the top 200 drug products on all four lists were oral IR drug products, ranging from 102–113 classified drugs/list. The maximum and minimum dose strengths on the US, ES, and GB were similar, indicating commonality with respect to use and efficacy standards. Conversely, significantly lower doses were found on the JP list compared to the other countries, reflecting differences in therapeutic categories and higher

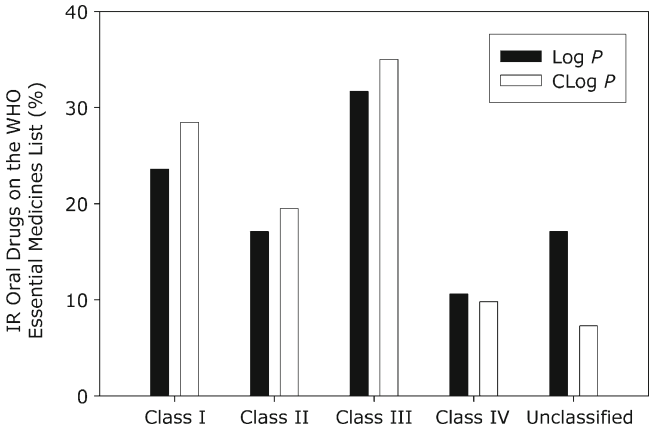

Fig. 2. Provisional BCS classification of the 123 oral drugs in immediate-release solid dosage forms on the WHO Essential Medicines List, based on dose number (D_0) for the solubility criterion and Log *P*/CLog*P* correlations for the permeability classification (25)

emphasis on safety issues. According to the Japanese Guideline for BE studies, the volume used for D_0 calculation is 150 ml; hence, this value was used for the classification of the JP list. A volume of 250 ml was used for the classification of the other three lists (26).

The solubility classification of the top selling drugs in the four countries was very similar (~55% high-solubility drugs per list), despite of the fact that only 34–44 drugs on the JP list were in common with the US, GB, and ES lists. Based on D_0 and CLog*P* correlation, the percentage of drugs that were classified as BCS class I drugs were 31%, 30.4%, 30.2%, and 34.5% on the US, GB, ES, and JP, respectively (Fig. 3). The corresponding percentage of drugs classified as class III compounds were 23.0%, 25.8%, 28.0%, and 19.5% on the US, GB, ES, and JP, respectively (Fig. 3). Thus, BE criteria of the majority of the world's top-selling drugs may potentially be based on a suitable *in vitro* dissolution test procedure. This information should help pharmaceutical manufacturers to avoid unnecessary human experiments and reduce cost and time of the product development. This is of particular interest in countries with considerably limited health care budget. Hence, BCS contributes to the public health worldwide by significantly enhancing the efficiency in drug development and regulatory approval processes.

It should be noted that the solubility criteria specified in the BCS classification guidelines covers the physiologically relevant pH range (typically pH 1.2, 4.5, and 6.8 buffers). However, the solubility values used in the provisional BCS classifications are based on drug solubility in water only. Thus, for ionizable drugs in which the API solid form is a salt, the value of solubility used for the provisional BCS classification may not be the minimum solubility of the drug over the physiological relevant pH range and could, therefore, represent a best case scenario with regard to aqueous solubility. In fact, 31% of the drugs classified as high-solubility on the WHO list are salts, whereas 36% are free-forms. Likewise, 35–39% of the drugs classified as high-solubility on the US, GB, ES, and JP lists are salts, whereas 16–24% are free-forms.

Provisional BCS Classification Based on *In Silico* Calculations

It is well recognized that human permeability data are very expensive and difficult to obtain. In addition, at the very early stage of drug discovery and development, very little amount of the API is available for thorough evaluation of BCS classification. Hence, a reliable BCS classification based solely on an *in silico* approach can be extremely valuable. Certainly, the underlying assumptions and methods used in any computational approach should be carefully evaluated; however, the continuous progress, convenience, and feasibility of *in silico* methods attract increasing interest.

A set of 185 worldwide IR oral drug products was assigned with provisional BCS classification based on two *in silico* solubility estimations and three *in silico* permeability approaches: CLog*P* (BioLoom 5.0 and ChemDraw 8.0), Log *P* (MOE Version 2004.03), and KLog *P* using simplified approach based upon the Crippen fragmentation method that depends strictly on the element type in the molecule (38). An excellent agreement was obtained between the solubility classification based on *in silico* methods and literature values. The *in silico* permeability calculations demonstrated ~75% accuracy in classifying 29 reference drugs with human permeability data and ~90% accuracy in classifying the 14 FDA reference drugs for permeability.

The *in silico* based provisional BCS classification of these 185 drugs showed some interesting trends; for a given solubility classification approach, the BCS classification was not significantly different when different *in silico* partition coefficient methods were used. The classification by the two solubility approaches for a given partition coefficient method, however, exhibited some systematic differences. The *in silico* solubility approach underestimated class I and overestimated class II drugs by an identical average of 4.3 ± 1%, while it overestimated class III and underestimated class IV drugs by an identical average of 7.3 ± 0.7%, compared to the classification using reference literature solubility (38). This work suggests that when the *in silico* method is validated, it is convenient, efficient, and cost-effective in the early preclinical drug discovery setting. Further research should continuously improve the accuracy and reliability of *in silico*-based BCS classification. Methods for more accurate structure-based prediction of solubility and permeability (e.g., polar surface area) should be further developed and evaluated to enable even more reliable *in silico* classifications.

The Biopharmaceutics Drug Disposition Classification System

While solubility measurements are relatively easy to carry out and usually there is a broad agreement when classifying drugs as either high- or low-solubility drugs, intestinal permeability is not as routinely measured, particularly using methods and laboratory practice that would allow granting a FDA *in vivo* biowaiver. Wu and Benet (39) have noticed that the high-permeability characteristics of BCS class I and II drugs allow ready access to metabolizing enzymes within hepatocytes and suggested that there is a good correlation between the extent of drug metabolism and the

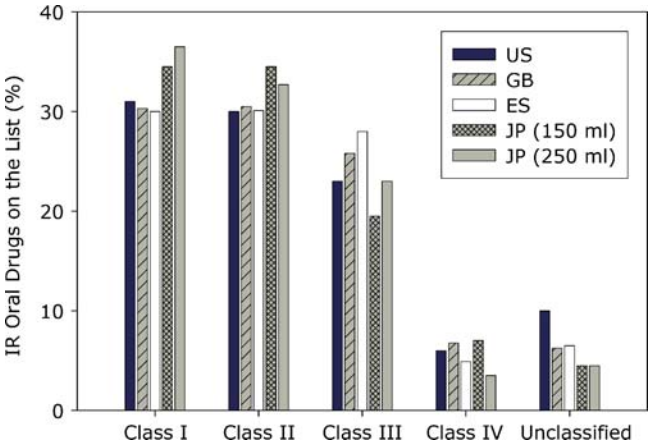

Fig. 3. Provisional BCS classification of oral drugs in IR solid dosage forms on the top 200 US, GB, ES, and JP drugs lists using dose number (D_0) for the solubility criterion and CLog*P* for the permeability classification (26)

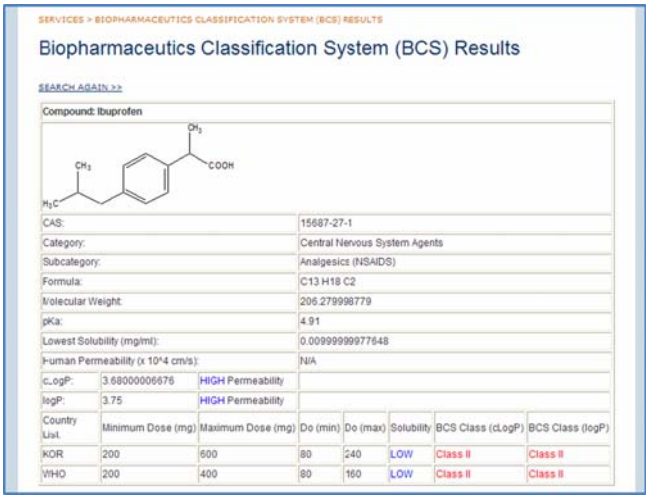

Fig. 5. The provisional BCS classification service as offered by Therapeutic Systems Research Laboratory (TSRL Inc., Ann Arbor, MI) website

permeability as defined in the BCS. This is the BDDCS, claiming that if the major route of elimination of a given drug is metabolism, then the drug is high-permeable and if the major route of elimination is renal and biliary excretion of unchanged drug, then that drug should be classified as low-permeability (40). The cutoff was originally set at ≥50% metabolism but later changed to 70% or 90% of an oral dose in human. Additional implications of the BDDCS, e.g., food effect and significance of transporter/enzyme interplay in drug interactions, were suggested as well (41).

The key questions, to what extent metabolism can be used as a surrogate for intestinal permeability and under what circumstances drug metabolism may not be viable for permeability predictions, were investigated. A total of 168 drugs were classified by the BDDCS based on solubility and metabolism (39). Drugs with ≥50% metabolism were defined as extensively metabolized and thus considered high-permeability drugs. Takagi *et al.* (26) compared this BDDCS classification of 164 drugs with the BCS approach using D_0 and CLog*P*. The BDDCS classification indicated that 59 drugs are class I, 51 class II, 42 class III, and 12 drugs out of the 164 are class IV compounds. The BCS classification based on metoprolol as the reference compound indicated a total of 42, 54, 57, and 11 drugs as class I, II, III, and IV, respectively. Hence, 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. 4). It was shown that the differences could be reduced depending on the choice of permeability (fraction absorbed) or percent metabolism dividing line for high/low classification (26).

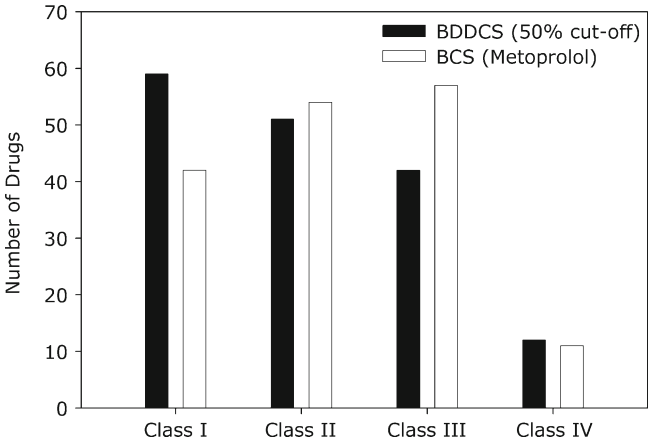

Fig. 4. Comparison of the provisional classification of 164 drugs according to the BDDCS and the BCS. BDDCS classification was carried out using 50% as the cutoff for extensive metabolism and the BCS using metoprolol as the reference permeability drug (26)

More recently, the extent of metabolism of 51 high-permeability drugs was evaluated (42). By using a cutoff of 50% metabolism, 37 drugs (73%) were classified as extensively metabolized and, hence, also high-permeability, according to the BDDCS as well. Hence, 27% of these BCS high-permeability drugs were poorly metabolized compounds, pointing out that high permeability as defined by the BCS does not necessarily dictate extensive metabolism. The authors concluded that the extent of metabolism may be useful in supporting permeability classification only under certain circumstances (42).

While permeability classification based solely upon metabolism might fail to correctly classify drugs that are highly absorbed but are excreted unchanged into urine and bile (e.g., amoxicillin, trimethoprim, lomefloxacin, zalcitabine, and chloroquine), lipophilicity considerations alone would not be able to predict active carrier-mediated transport of drugs. Despite these differences, the two approaches indicate that granting a waiver from *in vivo* BE studies is justified for the majority of drugs (26,39,40).

Additional BCS Classification Sources

In addition to the contributions aiming to provisionally classify different drug lists reviewed so far, several other sources are available as well. Literature search reveals that research articles often offer a BCS classification of the investigated drugs (43–47). Moreover, starting in 2004, a

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