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A Provisional Biopharmaceutical Classification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan

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Abstract: Orally administered, immediate-release (IR) drug products in the top 200 drug product lists from the United States (US), Great Britain (GB), Spain (ES), and Japan (JP) were provisionally classified based on the Biopharmaceutics Classification System (BCS). The provisional classification is based on the aqueous solubility of the drugs reported in readily available reference literature and a correlation of human intestinal membrane permeability for a set of 29 reference drugs with their calculated partition coefficients. Oral IR drug products constituted more that 50% of the top 200 drug products on all four lists, and ranged from 102 to 113 in number. Drugs with dose numbers less than or equal to unity are defined as high-solubility drugs. More than 50% of the oral IR drug products on each list were determined to be high-solubility drugs (55−59%). The provisional classification of permeability is based on correlations of the human intestinal permeabilities of 29 reference drugs with the calculated Log *P* or CLogP lipophilicity values for the uncharged chemical form. The Log *P* and CLogP estimates were linearly correlated ($r^2 = 0.79$) for 187 drugs. Metoprolol was chosen as the reference compound for permeability and Log *P* or CLogP. A total of 62−69.0% and 56−60% of the drugs on the four lists exhibited CLogP and Log *P* estimates, respectively, greater than or equal to the corresponding metoprolol value and are provisionally classified as high-permeability drugs. We have compared the BCS classification in this study with the recently proposed BDDCS classification based on fraction dose metabolism. Although the two approaches are based on different in vivo processes, fraction dose metabolized and fraction dose absorbed are highly correlated and, while depending on the choice of reference drug for permeability classification, e.g., metoprolol vs cimetidine or atenolol, show excellent agreement in drug classification. In summary, more than 55% of the drug products were classified as high-solubility (Class 1 and Class 3) drugs in the four lists, suggesting that in vivo bioequivalence (BE) may be assured with a less expensive and more easily implemented in vitro dissolution test.

Keywords: BCS; solubility; dose number; permeability; partition coefficient; WHO essential drugs; top-selling US, European, Japanese drugs; BDDCS

Introduction

In vivo bioequivalence (BE) tests are the accepted standard for ensuring the therapeutic performance of drug products following manufacturing changes and for approval of generic drug product efficacy claims. BE standards are based on ensuring that reference and test products produce the same plasma concentration−time profiles through demonstrated statistical equivalence of C_{max} and AUC. While the in vivo BE test has been the norm for the past three decades, recently

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a new standard, applicable to a considerable number of drug products, was developed based on the classification of the drugs according to their biopharmaceutical properties.[1] This new standard relies on the Biopharmaceutics Classification System (BCS)[2] and is based on the fundamental properties governing drug absorption, namely, permeability and solubility. Tests based on this new standard can ensure the similarity of absorption, and hence the systemic availability of drug products being compared. The BCS classifies drugs into four categories according to their solubility and intestinal permeability, and has been a useful guide for understanding when and how dissolution tests can help in the design and evaluation of oral dosage forms, and for defining which tests are most suitable for ensuring (in vivo*)* BE. Regulatory agencies have recently implemented BCS-based waivers of in vivo BE studies for immediate-release (IR) solid dosage forms of Class 1, high-solubility, high-permeability drugs, in rapidly dissolving drug products. Waivers for Class 3 drugs (high-solubility, low-permeability) have been scientifically justified and recommended.[3−6] It is important to note that the BCS approach to "biowaivers" does not waive BE, but waives the in vivo BE test, in lieu of a better, more routinely conducted, and more easily implemented dissolution test.

In a previous study, we provisionally classified the oral IR drug products that are contained on the World Health Organization (WHO) Essential Drug List.[7] This analysis indicated that a satisfactory test for ensuring BE for more than 55% of the high-solubility Class 1 and Class 3 drug products on the WHO list may be based on an in vitro dissolution test.[7] Following our analyses of WHO essential drugs, Lindenberg et al.[8] also reported the classification of WHO drugs that formed the basis of a WHO Working Document on the BCS Classification of the Essential Medicines List. In contrast to our report, fraction absorbed data in human studies was the primary source for permeability classification in Lindenberg et al.'s report. Since the Lindenberg report on WHO essential medicines contained a few medicines such as vitamins that were not included in our original report and since some corrections based on errant solubility or octanol−water partition coefficients have been made to the WHO drug classification, we have revised our classification of WHO essential drugs and present it in this report for reference. The conclusions of our previous report are not altered with these corrections. The comparisons in this report are based on this revised WHO classification.

Since many of the WHO drugs are not on the top 200 drug lists of the developed countries, it would be useful to determine similarities in the classification of approved drugs in various regions. We therefore also describe the provisional BCS classification of orally administered drugs in IR dosage forms in the top 200 drug products lists from the United States (US), Great Britian (GB), Spain (ES), and Japan (JP).

The classification of drug solubility is based on the dimensionless dose number Do[9] defined as the ratio of drug concentration in the administered volume to its saturation solubility in water. The classification of drug permeability is based on a correlation of the estimated *n*-octanol−water partition coefficient of the uncharged form of the drug molecule and the measured human jejunal permeability.[10−12] The results of the provisional classification suggest, similarly to the WHO provisional classification, that more than 50%

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of the drugs on the US, GB, ES, and JP lists are candidates for biowaivers.

Recently, Wu and Benet[13] proposed a Biopharmaceutics Drug Disposition Classification System (BDDCS) based upon solubility and extent of metabolism. The authors suggest that it may be more useful to replace the permeability criterion with the major route of drug elimination and propose that designation of the major route of drug elimination "as part or instead of permeability criteria" currently used in BCS classifications may also increase the number of Class 1 drugs that would become eligible for biowaivers. We have therefore also included in this report a comparison of the BDDCS classification of 168 drugs classified by Wu and Benet[13] with those obtained with the BCS approach using three different reference drugs for permeability classification.

Methods

Drug Lists. Lists of the top 200 US, GB, ES, and JP drugs were obtained from IMS Health (Fairfield, CT). Prior to classification, parenteral and modified-release drug products were excluded from the lists based on information obtained from the Electronic Orange Book[14] for the drugs on the US list, from the Japanese Orange Book[15] for those in the JP list, from Medicines.org.uk.[16] for drugs on the GB list, and from PortalFarma.com[17] and information provided by the Spanish agency of medicines[18] for drugs on the ES list. The drugs on the WHO list were obtained from the 14th revised edition of the WHO Essential Medicines core list.[19] The therapeutic categories of drugs on various lists were obtained from appropriate reference literature and drug prescription information sources.

Solubility. Values for drug solubility (mg/mL) were obtained from the Merck Index,[20] the USP DI,[21,22] and Japanese prescription information.[23] For cases where the reported solubility was significantly different in the above three sources, the lowest listed value was used in dose number calculations. For cases wherein specific values of solubility were not available, the lower limit of the range defined in the USP was chosen as a conservative estimate (Table 1). For drugs that were listed as practically insoluble (pi), a more conservative value of 0.01 mg/mL (rather than 0.1 mg/mL in the USP definition), and designated as pi*, was used in dose number calculations. It is noted that, unlike the solubility determinations in aqueous media covering the physiological pH range (typically in pH 1.2, 4.5, and 6.8 buffers) proposed in the FDA,[1] EMEA,[24] and WHO[25] guidelines, the solubility values used in the present classifications are based on drug solubility in water. It is also likely that in some cases the specific values of solubility adopted for ionizable drugs may not be the lowest solubility of the drug over the physiological pH range and could therefore represent a best-case scenario for that drug with regard to solubility considerations.

Table 1. Solubility Definitions

descriptive term (solubility definition)	parts of solvent required for 1 part of solute	solubility range (mg/mL)	solubility assigned (mg/mL)
very soluble (vs)	<1	≥1000	1000
freely soluble (fs)	from 1 to 10	100−1000	100
soluble (s)	from 10 to 30	33−100	33
sparingly soluble (sps)	from 30 to 100	10−33	10
slightly soluble (ss)	from 100 to 1000	1−10	1
very slightly soluble (vss)	form 1000 to 10000	0.1−1	0.1
practically insoluble (pi*)	≥10000	<0.1	0.01

Maximum and Lowest Dose Strengths. Values for maximum and lowest dose strengths were obtained from the Electronic Orange Book[14] for the drugs on the US list, the Japanese Orange Book[15] for those on the JP list, Medicines.org.uk[16] for those on the GB list, and PortalFarma.com[17] and the information provided by the Spanish agency of medicines[18] for those on the ES list.

Dose Number Calculations. The following equation was used to calculate the dose number:

$$\mathrm{Do} = \frac{(M_0/V_0)}{C_s}$$

where M_0 is the maximum dose strength (milligrams), C_s is the solubility (milligrams per milliliter), $V_0 = 250$ mL for

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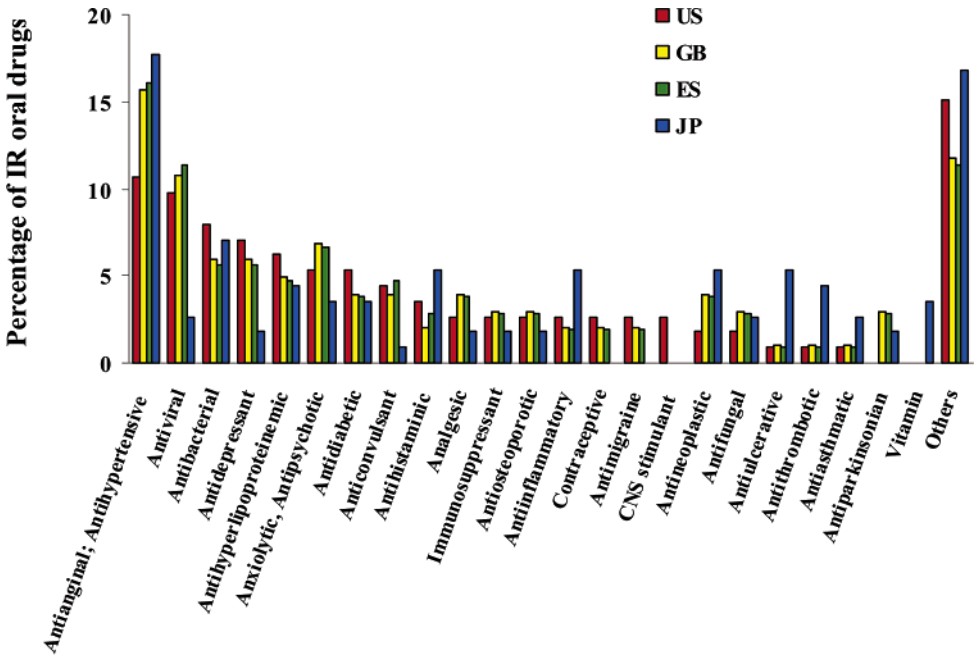

Figure 1. Comparison of the distribution of therapeutic categories on the US, GB, ES, and JP lists.

the drugs on the US, GB, and ES lists, and $V_0 = 150$ mL (according to the Japanese Guideline for BE studies[26]) for drugs on the JP list. Dose numbers were also calculated using the lowest dose strength in order to determine the number of drugs for which the classification would change with dose strength.

Partition Coefficients. Estimates of Log *P* as well as CLogP for the uncharged solute molecule were obtained using algorithms available with ChemDraw Ultra 8.0 software (CambridgeSoft Corp., Cambridge, MA) and chemical structures of the drug as depicted in *The Merck Index*.[20] The algorithm for Log *P* (*n*-octanol−water partition coefficient) is based on atomic contributions to lipophilicity,[27] and that for CLogP values was generated with algorithms based on theoretical treatments developed by Leo.[28]

Correlations of Human Intestinal Permeability with CLogP and Log *P*. The classification of permeability is based on correlations of the experimentally determined human intestinal permeability for 29 reference drugs with estimated CLogP and Log *P* values of the uncharged molecular form. Metoprolol was chosen as the reference compound for permeability since 95% of the drug is known to be absorbed from the gastrointestinal tract.[29] Thus, drugs that exhibit partition coefficients and human intestinal permeability values greater than or equal to the corresponding value for metoprolol are considered high-permeability drugs. Conversely, drugs with estimated partition coefficients and human intestinal permeability values less than the corresponding value for metoprolol are classified as low-permeability drugs. Drugs that exhibit human intestinal permeabilities greater than metropolol but with corresponding CLogP (or Log *P*) values lower than that of metoprolol are termed false negatives. False positives, on the other hand, are drugs with CLogP (or Log *P*) values higher than that of metoprolol but with corresponding experimental human intestinal permeabilities that are lower than that of metoprolol.

Results

Characterization of Molecular Properties of Drugs. The maximum and lowest dose strengths, solubility, dose number, calculated Log *P* and CLogP, and therapeutic categories of the oral drugs in immediate-release dosage forms on the top 200 US, GB, ES, and JP lists are shown in Tables SI1−SI4 (Supporting Information). The number of oral drugs in immediate-release (IR) dosage forms on the US, GB, ES, and JP lists was 113, 102, 106, and 113, respectively. A revised classification of 130 drugs on the WHO essential medicines list is shown in Table SI5 (Supporting Information).

Distribution of Drug Therapeutic Category. The distribution of therapeutic category of the drugs on the US, GB, ES, and JP lists is shown in Figure 1. It is evident from Figure 1 that antianginals and antihypertensives comprise the largest class in all four lists. However, while the overall

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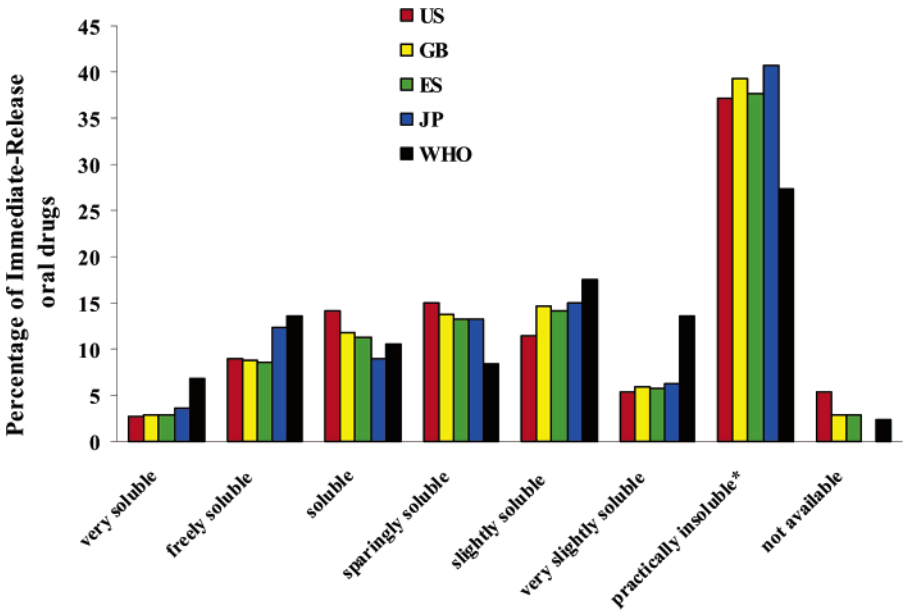

Figure 2. Comparison of the distribution of drug solubility on the US, GB, ES, JP, and WHO lists.

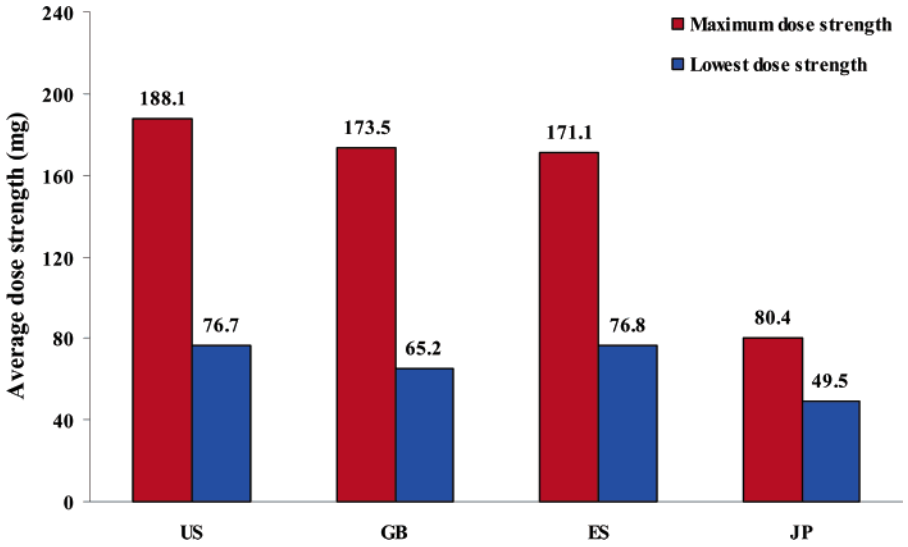

Figure 3. Comparison of average dose strength of the drugs on the US, GB, ES, and JP lists.

distributions of therapeutic categories in the US, GB, and ES are similar to each other, there are distinct differences compared to the distribution in JP. A significantly higher preponderance of vitamins, antihistaminic, antiinflammatory, antiulcerative, antithrombotic, and antiasthmatic drugs is found on the JP top 200 list. On the other hand, the percentages of antiviral, antidepressant, anxiolytic, antipsychotic, and anticonvulsant drugs were lower on the JP list.

Comparison of Drug Solubility. Figure 2 shows a plot of the percentages of drugs on the four lists sorted by solubility categories described in Table 1. Figure 2 also shows the solubility classification of drugs on the WHO list (Table SI5). The plot suggests that with some exceptions the distribution trends in the four lists and the WHO list are similar. A predominant percentage of the drugs on each list (~30−40%) were categorized as practically insoluble* (pi*) drugs (note the lower solubility definition of pi* in Table 1).

Comparison of Dose Strength. A comparison of the average maximum and lowest dose strengths of the drugs in the four lists is shown in Figure 3. Figure 3 clearly shows that the average maximum dose strength of drugs on the JP list is less than half the average maximum dose strength of drugs on the US/GB/ES lists, while the average lowest dose strength is nearly two-thirds of that on the US and ES lists. Figure 4 shows a comparison of the distribution of maximum dose strengths in the four lists. As suggested by Figure 3, the most significant differences are evident at the low and high ends of the range of maximum dose strengths. The maximum dose strengths for 10.6% of the drugs on the JP list were less than 1 mg whereas the corresponding percentages in the other three lists were significantly lower (US,

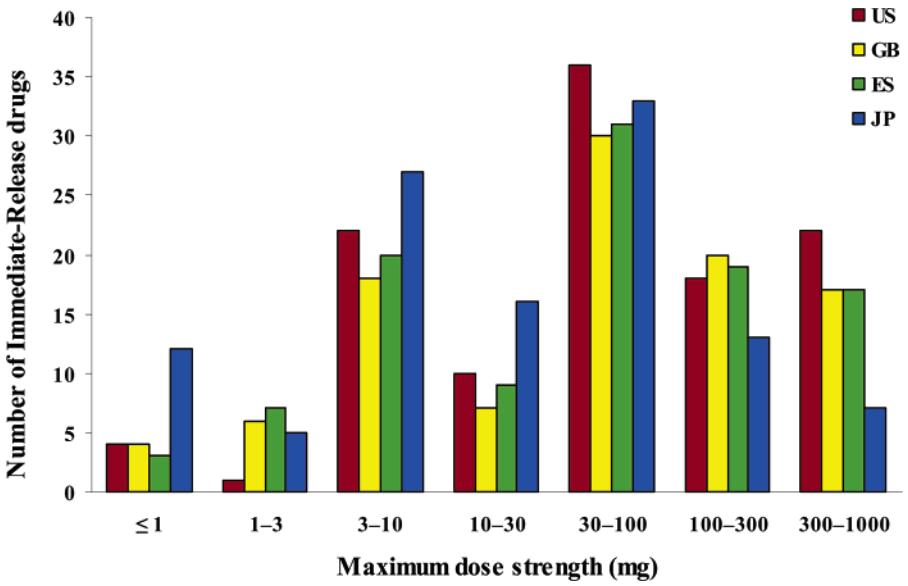

Figure 4. Comparison of the distribution of dose strength of the drugs on the US, GB, ES, and JP lists.

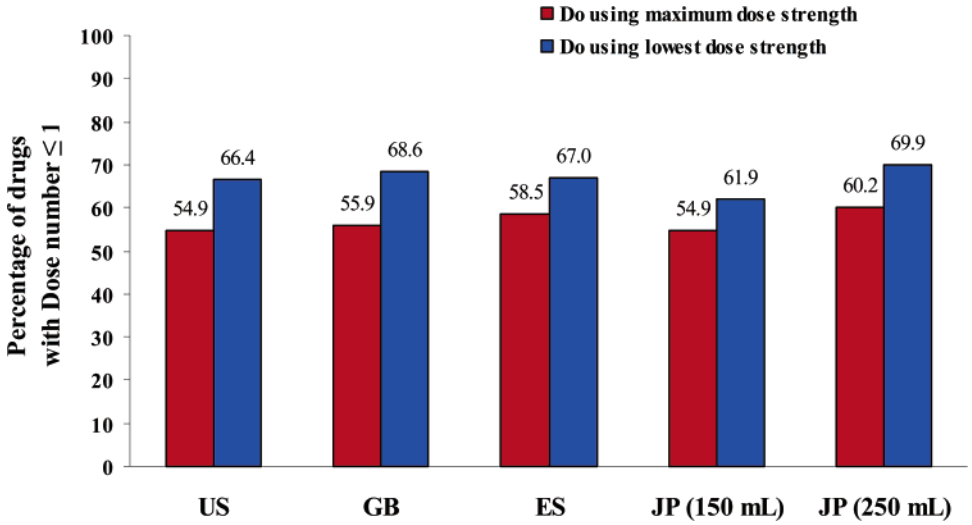

Figure 5. Comparison of the percentage of high-solubility drugs on the US, GB, ES, and JP lists.

3.5%; GB, 3.9%; ES, 2.8%; Figure 4). The percentage of the drugs with maximum dose strengths of >300 mg on the JP list was only 6.2%, which is significantly lower than that in the other regions (US, 19.5%; GB, 16.7%; ES, 16.0%).

Classification of Solubility. Figure 5 shows a comparison plot of the percentage of drugs on the four lists that exhibited dose number Do ≤ 1, and were thus classified as high-solubility drugs. Thus, 54.9−58.5% of the drugs on the lists were classified as high-solubility drugs using maximum dose strengths. The percentage of high-solubility drugs increased to 61.9−68.6% (7−10%) when dose number was calculated using the lowest maximum strength (Figure 5). Figure 5 also shows a comparison of the percentage of high-solubility drugs on the JP list when Do was calculated using 150 mL or 250 mL. As expected, with a higher volume of administration (V_0), the percentage of high-solubility drugs increased from 54.9% to 60.2% when Do was calculated using maximum dose strength and from 61.9% to 69.9% when lowest dose strength was used in Do calculations.

Correlations of Human Intestinal Permeability with CLogP and Log *P*. The experimentally determined human jejunal permeabilities for the 29 reference drugs are listed in Table 2 along with calculated CLogP and Log *P*. A plot of the human jejunal permeability against CLogP (Figure 6) indicated that the classification of permeability based on metoprolol as the reference compound was correct for 19 (metoprolol included) out of 29 drugs (66%). Thus, 8 drugs with CLogP and human intestinal permeability values greater than or equal to the corresponding values for metoprolol (high-permeability drugs; upper right quadrant) and 10 drugs with CLogP and human intestinal permeability values less than the corresponding values for metoprolol (low-permeability drugs; lower left quadrant) are correctly classified. Seven of the incorrectly classified drugs (false negatives; upper left quadrant) are transported by carrier-mediated

Table 2. Estimated CLogP, Log *P*, and Human Jejunal Permeability of Reference Drugs

drug	CLogP	Log *P*	human permeability ($\times 10^4$ cm/s)
α-methyldopa	−2.26	0.39	0.10
amoxicillin	−1.87	−0.58	0.30
antipyrine	0.20	1.01	5.60
atenolol	−0.11	0.50	0.20
carbamazepine	2.38	2.93	4.30
cephalexin	−1.84	−0.67	1.56
cimetidine	0.35	0.79	0.26
creatinine	−1.77	−0.63	0.29
desipramine	4.47	3.94	4.50
D-glucose	−2.21	−2.38	10.00
enalapril	0.67	1.77	1.57
enalaprilat	0.88	1.17	0.20
fluvastatin	4.05	3.41	2.40
furosemide	1.90	0.74	0.05
hydrochlorothiazide	−0.37	−0.15	0.04
ketoprofen	2.76	3.31	8.70
levodopa	−2.82	0.00	3.40
lisinopril	−1.69	0.91	0.33
L-leucine	−1.67	0.34	6.20
losartan	4.11	na[a]	1.15
metoprolol	1.49	1.72	1.34
naproxen	2.82	2.97	8.50
phenylalanine	−1.56	0.78	4.08
piroxicam	1.89	0.29	6.65
propranolol	2.75	2.65	2.91
ranitidine	0.63	na	0.27
terbutaline	0.48	1.16	0.30
valacyclovir	−1.22	−1.06	1.66
verapamil	4.47	5.69	6.80

[a] Not available.

mechanisms, and two (false positives; lower right quadrant) are substrates for efflux transporters (Table 3). A similar plot of the human jejunal permeability against Log *P* indicated that 19 out of 27 drugs (70%) were correctly classified (Figure 7). Of the 8 incorrectly classified drugs, 6 are transported by carrier-mediated mechanisms (Table 3). Antipyrine was an exception in both plots, and piroxicam appears as an additional false negative in the Log *P* correlation plot.

Classification of Permeability. Oral immediate-release drugs with CLogP or Log *P* values greater than or equal to the corresponding value for metoprolol, the reference drug, were classified as high-permeability drugs. Conversely, drugs with CLogP or Log *P* values lower than that of metoprolol were considered to be low-permeability drugs. Thus, a total of 63.2−69.0% and 58.4−59.8% of the drugs on the US, GB, ES, and JP lists were classified as high-permeability drugs based on CLogP and Log *P*, respectively (Figure 8).

BCS Classification of IR Oral Drugs. The drugs in IR dosage forms on the US, GB, ES, and JP lists were provisionally classified into the BCS classes on the basis of Do and CLogP or Do and Log *P* (Tables SI1−SI4). A comparison plot of the percentages of the drugs in IR dosage forms that were classified as BCS Class 1−4 drugs using Do and CLogP is shown in Figure 9. About 30% of the drugs were classified as Class 1 on the US, GB, and ES lists. The percentage of Class 1 drugs on the JP list was slightly higher (34.5%) when Do was calculated using 150 mL and increased further to 36.3% when Do was calculated using 250 mL (2 drugs were reclassified from Class 2 to Class 1). Comparisons of the corresponding percentages of the BCS drug classes on the four lists using Do and Log *P* criteria are shown in Figure 10. Although the distribution of drugs into BCS classes was similar to that obtained with Do and CLogP criteria (Figure 9), a relatively higher percentage of drugs could not be classified due to missing Log *P* values.

BDDCS and BCS. A total of 168 drugs were classified using BDDCS based on solubility and metabolism. Drugs with ≥50% metabolism[30] (Table 3 of Wu and Benet[13]) were defined as extensively metabolized and thus considered high-permeability drugs. The BDDCS classifications of the 168 drugs were compared with those obtained with the BCS approach using Do for solubility classification and CLogP of different reference drugs for permeability classification (aluminum hydroxide, labetolol, lithium carbonate, and penicillins[31] could not be classified using BCS due to unavailability of CLogP values). The permeability classifications were obtained with CLogP estimates alone due to availability of values for a greater number of drugs and also since previous studies had indicated that CLogP is a more accurate predictor of octanol−water partition coefficient.[32] Figure 11 shows a comparison of the BCS classification of 164 drugs with those reported in BDDCS. The classification based on BDDCS indicates that 59 drugs are Class 1, 51 are Class 2, 42 are Class 3, and 12 are Class 4.[33]

The conservative BCS classification based on metoprolol as the reference compound (95% fraction oral dose absorbed[29]) indicates that a total of 42 drugs are Class 1, 54 are Class 2, 57 are Class 3, and 11 are Class 4 drugs (Figure 11). A total of 33 drugs were Class 1 drugs in both BDDCS and BCS using metoprolol as the reference permeability drug. Thus, 26 more drugs were Class 1 in BDDCS but not in BCS. Six of these are actively transported (enalapril, glucose, levodopa, phenylalanine, theophylline, and zidovudine), 2 are listed as high-solubility drugs in BDDCS (ketoprofen and nifedipine), and 3 are borderline Class 1 in BCS (chloramphenicol, colchicine, and ergonovine). A detailed breakdown of the drug classes is shown in Table SI6 (Supporting Information).

(30) In footnote of Table 3 in ref 9, ≥50% defined as extensive metabolism criterion. Elsewhere in text and in Figure 6 of ref 9, ≥70% metabolism listed as extensive metabolism cutoff.

(31) Penicillin V potassium was classified as a BCS Class 1 drug in the WHO provisional classification (see Table SI5).

(32) Machatha, S.; Yalkowsky, S. H. Comparison of the octanol/water partition coefficients calculated by ClogP, ACDlogP and KowWin to experimentally determined values. *Int. J. Pharm.* **2005**, *294*, 85−192.

(33) Ciprofloxacin was dually classified in BDDCS as a Class 3 and Class 4 drug.

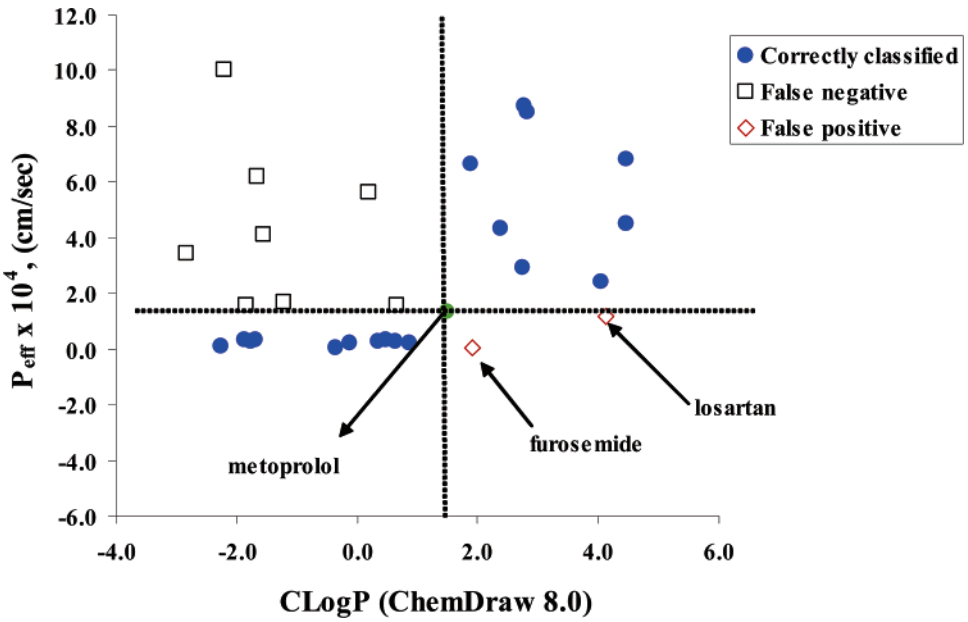

Figure 6. Correlation plot of the human jejunal permeability with CLogP of the reference drugs.

Table 3. Carrier-Mediated Transport or Efflux of Reference Drugs

drug	evidence for transport	permeability classification[a]	
		CLogP based	Log *P* based
α-methyldopa		c	c
amoxicillin		c	c
antipyrine	no evidence of carrier-mediated transport	fn	fn
atenolol		c	c
carbamazepine		c	c
cephalexin	substrate for peptide transporters[52]	fn	fn
cimetidine		c	c
creatinine		c	c
desipramine		c	c
D-glucose	substrate for glucose transporters[53]	fn	fn
enalapril	substrate for peptide transporters[54]	fn	c
enalaprilat		c	c
fluvastatin		c	c
furosemide	secretion in rat jejunum and Caco-2 cells[55]	fp	fp
hydrochlorothiazide		c	c
ketoprofen		c	c
levodopa	substrate for amino acid transporters[56]	fn	fn
lisinopril		c	c
L-leucine	substrate for amino acid transporters[56]	fn	fn
losartan	secretion by P-glycoprotein[57]	fp	na
metoprolol		c	c
naproxen		c	c
phenylalanine	substrate for amino acid transporters[56]	fn	fn
piroxicam	no evidence of carrier-mediated transport	c	fn
propranolol		c	c
ranitidine		c	na
terbutaline		c	c
valacyclovir	substrate for peptide transporters[58]	fn	fn
verapamil		c	c

[a] Partition coefficient comparison with human intestinal permeability classification: c = correctly classified; fn = false negative classification; fp = false positive classification; na = not available.

The BCS classification of the 164 drugs was also carried out using cimetidine (65−70% fraction oral dose absorbed[34,35]), ranitidine (30−70% fraction oral dose absorbed[36−39]), and atenolol (∼50% fraction oral dose absorbed[40]) as the reference permeability drug. The classification based on cimetidine as the reference drug indicates that 61 drugs are Class 1, 58 are Class 2, 31 are Class 3, and 7 are Class 4 (Figure 11). A total of 44 drugs were Class 1 in both BDDCS and BCS. There were 15 additional drugs that

(34) Bodemar, G.; Norlander, B.; Walan, A. Pharmacokinetics of cimetidine after single doses and during continuous treatment. *Clin. Pharmacokinet.* **1981**, *6*, 306−315.

(35) Guay, D. R.; Matzke, G. R.; Bockbrader, H. N.; Dancik, J. Comparison of bioavailability and pharmacokinetics of cimetidine in subjects with normal and impaired renal function. *Clin. Pharm.* **1983**, *2*, 157−162.

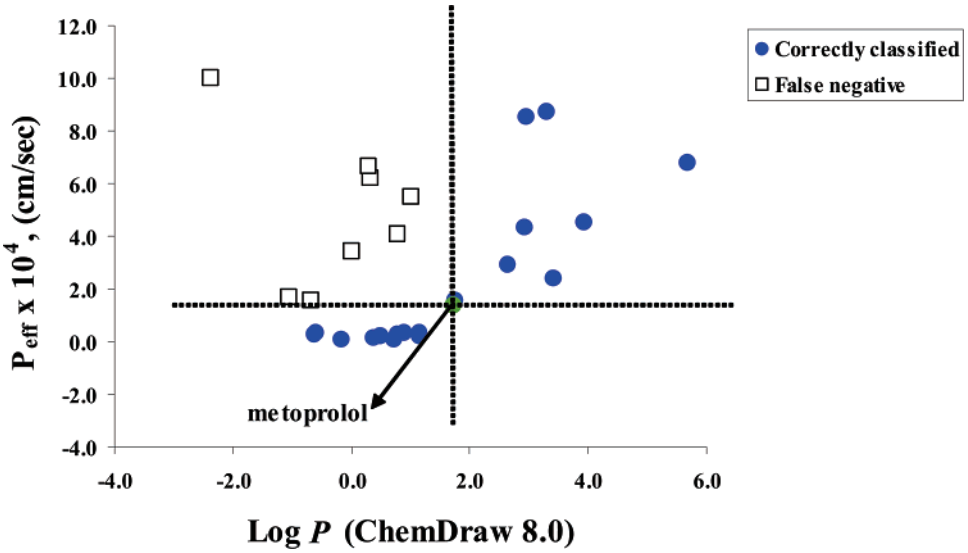

Figure 7. Correlation plot of the human jejunal permeability with Log *P* of the reference drugs.

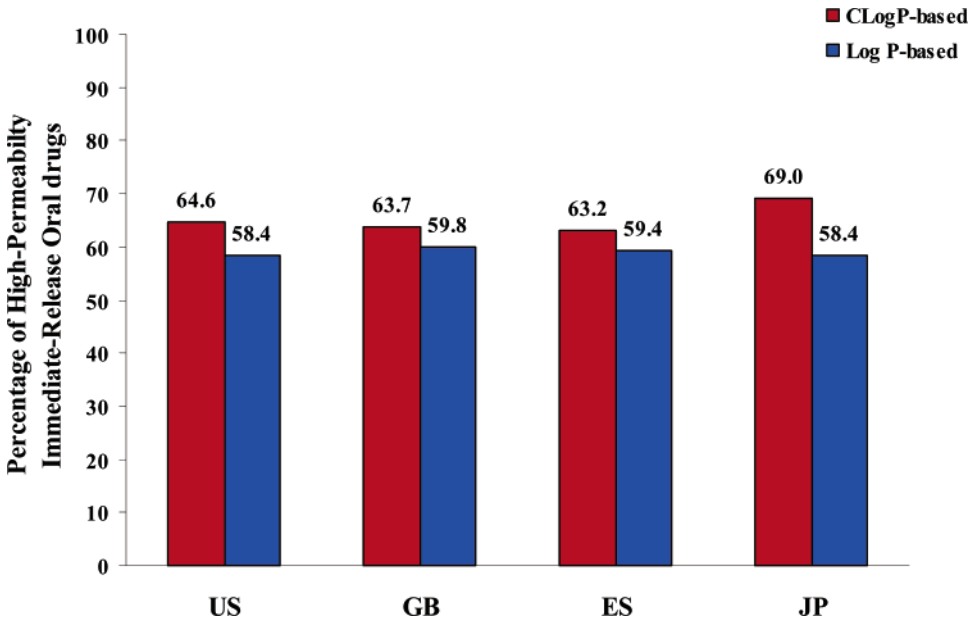

Figure 8. Comparison of the percentage of high-permeability drugs on the US, GB, ES, and JP lists.

were Class 1 in BDDCS but not in BCS of which 5 are actively transported (glucose, levodopa, phenylalanine, theophylline, and zidovudine), 2 are again listed as high-solubility drugs in BDDCS (ketoprofen and nifedipine), and 3 are borderline Class 1 in BCS (antipyrine, isosorbide dinitrate, and minocycline). Table SI7 (Supporting Information) shows the classification of all 164 drugs using BCS (CLogP cimetidine) and BDDCS.

The BCS classification using ranitidine indicates that 55 drugs are Class 1, 56 are Class 2, 44 are Class 3, and 9 are Class 4. A total of 41 drugs were Class 1 drugs in both BDDCS and BCS. The 18 additional drugs that were Class 1 in BDDCS but not in BCS included 5 that are actively transported (glucose, levodopa, phenylalanine, theophylline, and zidovudine), 2 that are listed as high-solubility drugs in BDDCS (ketoprofen and nifedipine), and 4 that are borderline

(36) Chau, N. P.; Zech, P. Y.; Pozet, N.; Hadj-Aissa, A. Ranitidine kinetics in normal subjects. *Clin. Pharmacol. Ther.* **1982**, *31*, 770−774.

(37) Garg, D. C.; Weidler, D. J.; Eshelman, F. N. Ranitidine bioavailability and kinetics in normal male subjects. *Clin. Pharmacol. Ther.* **1983**, *33*, 445−452.

(38) van Hecken, A. M.; Tjandramaga, T. B.; Mullie, A.; Verbesselt, R.; de Schepper, P. J. Ranitidine: single dose pharmacokinetics and absolute bioavailability in man. *Br. J. Clin. Pharmacol.* **1982**, *14*, 195−200.

(39) McNeil, J. J.; Mihaly, G. W.; Anderson, A.; Marshall, A. W.; Smallwood, R. A.; Louis, W. J. Pharmacokinetics of the H2-receptor antagonist ranitidine in man. *Br. J. Clin. Pharmacol.* **1981**, *12*, 411−415.

(40) Mason, W. D.; Winer, N.; Kochak, G.; Cohen, I.; Bell, R. Kinetics and absolute bioavailability of atenolol. *Clin. Pharmacol. Ther.* **1979**, *25*, 408−415.

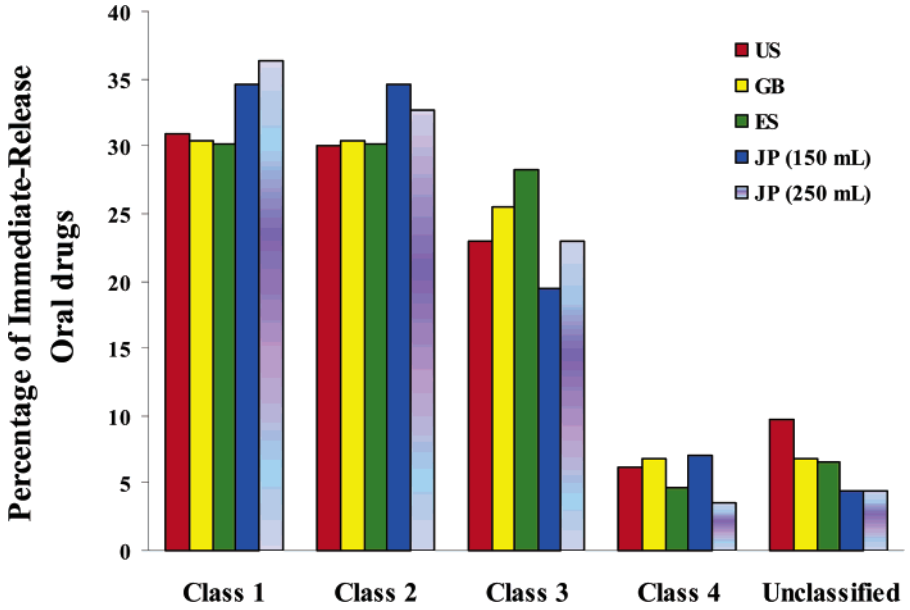

Figure 9. BCS classification of oral drugs in IR dosage forms on the US, GB, ES, and JP lists using Do and CLogP.

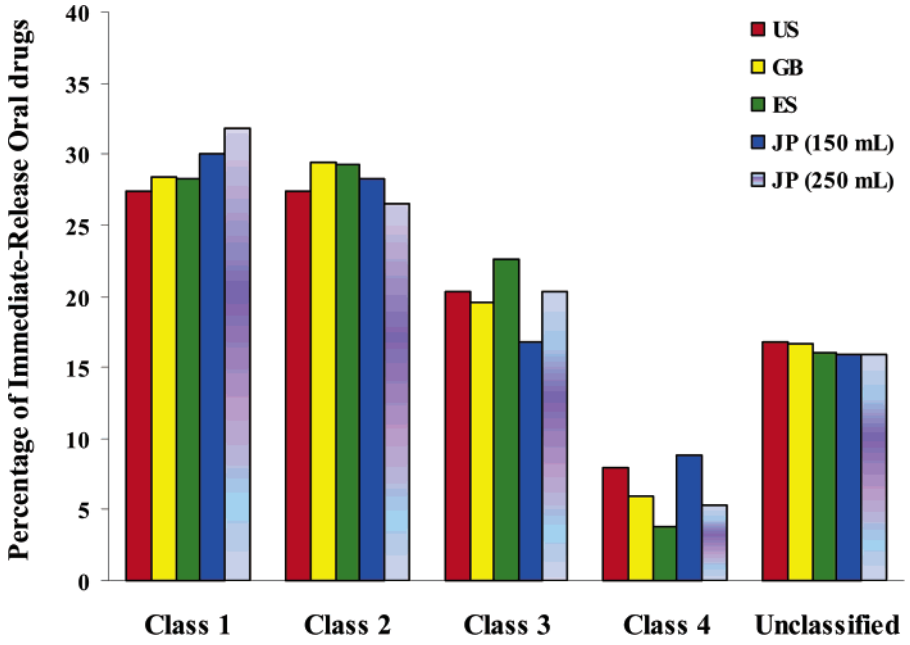

Figure 10. BCS classification of oral drugs in IR dosage forms on the US, GB, ES, and JP lists using Do and Log *P*.

Class 1 in BCS (abacavir, acetaminophen, isosorbide dinitrate, and morphine). Table SI8 (Supporting Information) shows the classification of all 164 drugs using BCS (CLogP ranitidine) and BDDCS.

The BCS classification using atenolol as the reference permeability drug shows that 72 drugs are Class 1, 58 are Class 2, 27 are Class 3, and 7 are Class 4 (Figure 11). The number of drugs that were Class 1 drugs in both BDDCS and BCS increased further to 51 when atenolol was used as the reference compound in the BCS classification. There were 8 additional drugs that were Class 1 in BDDCS but not in BCS and once again included ketoprofen and nifedipine that are listed as high-solubility drugs in BDDCS and 3 that are actively transported (glucose, levodopa, and phenylalanine). However, there were 21 additional drugs that were Class 1 in BCS but were classified otherwise in BDDCS (Table SI9, Supporting Information). A total of 15 of these drugs exhibited oral bioavailability[41,42] $\geq$50% (amiloride, atenolol, atropine, captopril, cetirizine, chloroquine, chlorthalidone, cimetidine, dicloxacillin, digoxin, ephedrine, ethambutol, lomefloxacin, metoclopramide, and ranitidine).

(41) Benet, L. Z.; Øie, S.; Schwarz, J. B. Design and optimization of dosage regimens: pharmacokinetic data. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Gilman, A. G., Eds.; McGraw-Hill: New York, 1996; pp 1707−1792.

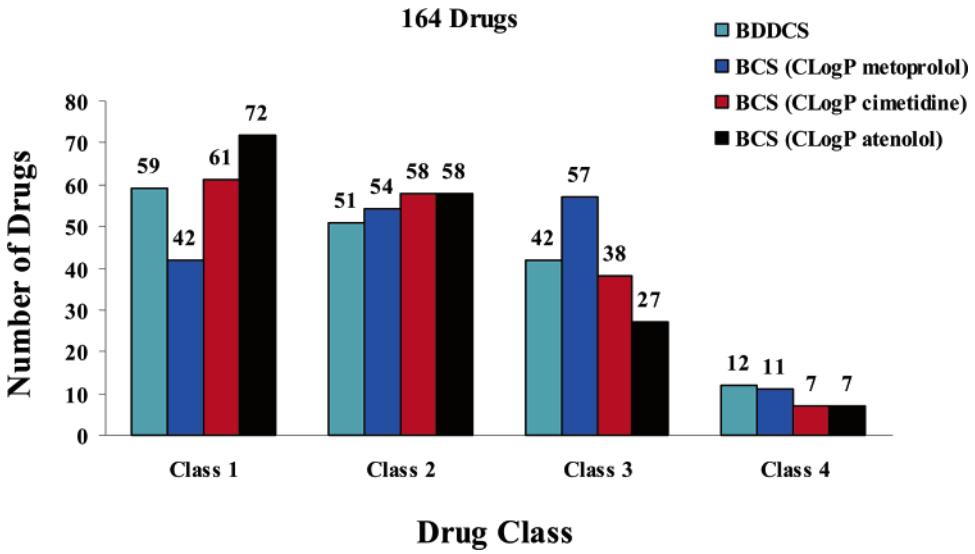

Figure 11. Comparison plots of the classification of 164 drugs by BDDCS and by BCS using three different reference permeability drugs.

A few drugs were consistently classified as high-permeability Class 1/Class 2 drugs in BCS regardless of the reference cutoff for permeability but were classified as Class 3 or Class 4 based on poor metabolism (bidisomide, cetirizine, chloroquine, cloxacillin, dicloxacillin, erythromycin, fexofenadine, metoclopramide, and pravastatin). A few of these, cetirizine, chloroquine, and metoclopramide, appear to be borderline BCS Class 1 drugs based on bioavailability alone.[41,42] It is also pertinent to note that chloroquine, colchicine, erythromycin, fexofenadine, and pravastatin are substrates of P-gp efflux transporters. With lower reference permeability cutoff classifications, additional drugs such as captopril (65−70% fraction dose absorbed[43]), digoxin (~80% fraction oral dose absorbed[44]), ephedrine (90% fraction oral dose absorbed[45]), and trimethoprim (100% oral bioavailability[41,46]), drugs with ≥70% oral bioavailability or ≥70% fraction oral dose absorbed are classified in BCS as Class 1 or Class 2 but are listed as Class 3 or Class 4 drugs in BDDCS.

Discussion

We previously reported the provisional biopharmaceutical classification of oral immediate-release drugs on the WHO Essential Drug List.[7] The results of the provisional classification suggested that a satisfactory BE test for 67% of the IR drug products on the WHO list may be based on an in vitro dissolution test (biowaivers). This finding suggested that the clinical performance of a majority of approved drugs essential for human health can be assured with an in vitro dissolution test. In this report, we extended our analysis of BCS classification to the top 200 drug products on the US, GB, ES, and JP markets and show that the distribution of these drugs into BCS classes is similar to the classification of drugs on the WHO list. The similarity is remarkable considering that only 5−20% of the drugs on the WHO list are found on the US, GB, ES, or JP lists.

The distribution of the top-selling drugs on the four lists (countries) in terms of solubility values was very similar (Figure 2) despite the observation that only 34−44 drugs on the JP list were in common with the US, GB, and ES lists. Interestingly, a predominant percentage of the drugs (~40%) on all four lists were categorized as practically insoluble drugs. The higher percentage of practically insoluble drugs on the US, GB, ES, and JP lists compared to that on the WHO list (27%) suggests a trend toward discovery and development of potent, highly lipophilic compounds in developed countries (Figure 2).

The average maximum and lowest dose strengths on the US, GB, and ES lists were similar, and this suggests a commonality with respect to use and clinical efficacy standards. Conversely, the dramatically lower dose strengths on the JP list compared to the US, GB, or ES lists (Figures 3 and 4) may reflect differences in therapeutic categories and a higher emphasis on safety issues.

The percentage of drugs categorized as high-solubility drugs, Do ≤ 1, calculated using maximum dose strength was

(42) Thummel, K. E.; Shen, D. D. Design and optimization of dosage regimens: pharmacokinetic data. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed.; Hardman, J. G., Limbird, L. E., Eds.; McGraw-Hill: New York, 2001; pp 1924−2023.

(43) Duchin, K. L.; Singhvi, S. M.; Willard, D. A.; Migdalof, B. H.; McKinstry, D. N. Captopril kinetics. *Clin. Pharmacol. Ther.* **1982**, *31*, 452−458.

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(45) Pade, V.; Stavchansky, S. Link between Drug Absorption Solubility and Permeability Measurements in Caco-2 Cells. *J. Pharm. Sci.* **1987**, *87*, 1604−1607.

(46) Klepser, M. E.; Zhu, Z.; Nicolau, D. P.; Banevicius, M. A.; Belliveau, P. P.; Ross, J. W.; Broisman, L.; Quintiliani, R.; Nightingale, C. H. Oral absorption of trimethoprim-sulfamethoxazole in patients with AIDS. *Pharmacotherapy* **1996**, *16*, 656−662.

~55% in the US, GB, and ES lists (Figure 5). The percentage of drugs with Do ≤ 1 calculated using lowest dose strength was also similar on the US, GB, and ES lists (~67%, Figure 5). Thus, roughly 12% of the IR drugs change BCS class over the recommended dose strength range. The percentage of high-solubility drugs (Do ≤ 1) on the JP list, calculated using maximum dose strength and 150 mL[26] (V_0), was similar to that on the US, GB, and ES lists (~55%, Figure 5). The similarity of the percentage of high-solubility drugs on the JP list despite a significantly lower average dose strength is due in part to the compensatory effect of the smaller V_0 of 150 mL compared to 250 mL used with drugs on the US, GB, and ES lists.

An examination of Figures 6 and 7 indicates that the permeability of drugs that are transported by carrier-mediated mechanisms, as expected, is predicted to be low on the basis of CLogP and Log *P* considerations. Further, as shown earlier,[7] the false-positive predictions for antipyrine and/or piroxicam in CLogP and Log *P* correlations would be absent if Log *D* correlations were used. However, due to the limited availability of pK_a values and experimental human jejunal permeability data or well-defined mass balance studies, permeability classification in this report was based on the estimated or calculated octanol−water partition coefficient of the uncharged form of the drug molecule. The percentage of drugs classified as high-permeability using CLogP was slightly higher than that using Log *P* (~5%) and may be a reflection of the greater number of drugs for which CLogP values could be calculated compared to Log *P*.

The oral drugs in IR dosage forms on the US, GB, ES, and JP lists were classified according to BCS on the basis of Do and CLogP or Log *P* criteria. The percentage of drugs that were classified as BCS Class 1 drugs on the US list was 31.0% with CLogP and 27.4% with Log *P* (Figures 9 and 10). The percentage with CLogP may be higher than that with Log *P* due to a greater number of drugs for which CLogP values were available (107) compared to Log *P* (100). The classification of Class 1 drugs in the other lists showed similar trends (GB, 30.4% with CLogP and 28.4% with Log *P*; ES, 30.2% with CLogP and 28.3% with Log *P*; JP, 34.5% with CLogP and 30.1% with Log *P* using 150 mL as V_0). Thus, according to the current FDA guideline, BE testing of around 30% of the top-selling drugs in these lists may be based on a suitable in vitro dissolution test procedure. On the basis of dose numbers alone (Figure 5), 55% of the drugs were high-solubility drugs (Class 1 plus Class 3) and may be eligible for biowaivers.

The suitability of biowaivers for high-solubility Class 3 drugs in immediate-release dosage forms has been recommended[3−6] although concerns of the effects of excipients on the oral bioavailability of the candidate drug have been expressed. Bioequivalence studies in humans conducted by the FDA on a large number of ranitidine IR formulations containing a wide variety and combinations of common excipients revealed no differences in oral bioavailability suggesting no excipient effects in vivo at levels normally used in immediate-release dosage forms on ranitidine permeation across the human intestine.[47] Recent publications on the effects of specified excipients on immediate-release atenolol,[48] ranitidine,[49] and cimetidine[50] products marketed in Germany, Finland, and The Netherlands suggest that IR products containing these three Class 3 drugs might be candidates for biowaivers, as excipient interactions appeared not to be critical with regard to their absorption in humans. The examples of atenolol, cimetidine, and ranitidine suggest that other Class 3 drugs that are passively (or actively) absorbed may be candidates for biowaivers.

The BDDCS is an innovative suggestion with many implications for metabolism and drug disposition. In general, a significant correlation between nonpolarity of an (uncharged) drug molecule, metabolism, and membrane permeability is expected. However, comparisons or correlations between the BDDCS and BCS will have some limitations since they are based on different processes at the molecular level, e.g., transport and enzyme binding vs (passive) membrane permeation transport in different cells (intestinal vs liver) with differences in membrane composition and transporter expression. However, some comparison with respect to the agreement as well as differences between the two approaches in the classification of the common set of 164 drug compounds is warranted. The agreement in classification of Class 2 and Class 4 drugs between BDDCS and BCS was excellent, ranging from 87% to 92% depending on the choice of the BCS permeability reference drug (metoprolol, cimetidine, or atenolol). The total number of Class 1 and Class 3 drugs in BDDCS and in BCS was almost the same (101/164 vs 100/164), with 64−72% being identically classified. The major differences in Class 1 vs 3 were due to the choice of permeability value (reference drug) for high-permeability classification in the BCS. The original choice for cutoff was purposely conservative. Altering the permeability cutoff for classification will definitely alter the agreement. In particular, the agreement between BCS and BDDCS in classification for Class 1 drugs increased from 56% (BCS/metoprolol) to 75% (BCS/cimetidine) to 86% (BCS/atenolol). The BCS classification using cimetidine as

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(48) Vogelpoel, H.; J. Welink, J.; Amidon, G. L.; Junginger, H. E.; Midha, K. K.; Möller, H.; Olling, M.; Shah, V. P.; Barends, D. M. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System (BCS) Literature Data: Verapamil Hydrochloride, Propranolol Hydrochloride, and Atenolol. *J. Pharm. Sci.* **2004**, *93*, 1945−1956.

(49) Kortejärvi, H.; Yliperttula, M.; Dressman, J. B.; Junginger, H. E.; Midha, K. K.; Shah, V. P.; Barends, D. M. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ranitidine Hydrochloride. *J. Pharm. Sci.* **2005**, *94*, 1617−1625.

(50) Jantratid, E.; Prakongpan, S.; Dressman, J. B.; Amidon, G. L.; Junginger, H. E.; Midha, K. K.; Shah, V. P.; Stavchansky, S. A.; Barends, D. M. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Cimetidine. *J. Pharm.* Sci. **2006**, *95*, 974−984.

the reference permeability drug appears to exhibit the best overall agreement with BDDCS for the 164 drugs (Figure 11); excluding 5 drugs that are actively transported and 3 that were borderline Class 1, the agreement in classification of high-permeability−extensive metabolism drugs was quite good (46/51 or ∼90%).

The requirement of extensive metabolism (in addition to being highly soluble) for a drug to be considered Class 1 in BDDCS excludes drugs that may be highly absorbed but are excreted unchanged into urine and bile. Drugs such as amoxicillin, chloroquine,[51] lomefloxacin, trimethoprim, and zalcitabine that exhibit ≥90% oral bioavailability are all listed as Class 3 drugs in BDDCS. Thus, classification of drugs based only on elimination (metabolism) may not be adequate. Lipophilicity considerations alone would not be expected to predict active carrier-mediated transport of drugs; however, a number of borderline BCS Class 3/Class 1 drugs would be reclassified as Class 1 drugs with a lower permeability criterion (70% fraction dose absorbed). Despite these differences, it is of utmost importance to note the substantial agreement of the two approaches in the classification of drugs for which a simplification in the bioequivalence test is highly merited. A more detailed examination of the importance and reliability of key parameters, particularly for drug compounds that are classified differently in the two approaches, might be beneficial.

It is recognized that exceptions to the general principle underlying the BDDCS are expected; nevertheless, we wish to stress that the institution of appropriate in vitro dissolution tests for high-solubility drugs would provide excellent low-risk alternatives to in vivo bioequivalence testing regardless of their permeability or metabolic characterization. We emphasize that, while membrane permeability is *the* parameter fundamentally controlling absorption as well as first-pass metabolism (by controlling the rate of presentation of drug to the metabolic site), it is dissolution in vivo that controls presentation of the drug to the intestinal membrane.

In conclusion, the provisional BCS classification of the top-selling drugs in US, GB, ES, and JP suggests that a minimum of 25−30% of the drug products on these markets are BCS Class 1 and candidates for waiver of in vivo BE testing based on the FDA guidance, and that an additional 20−25% are Class 3 drugs and are candidates for biowaiver. The impact of waivers of in vivo BE testing and its replacement with mechanistically based dissolution tests can not only accelerate new drug development but also significantly impact developing countries phasing in BE standards. The replacement of expensive in vivo testing with a simpler, more easily implemented, routinely monitored, and more reliable dissolution test would ensure clinical performance of approved drug products in a rapidly globalizing marketplace.

Acknowledgment. This work is supported in part by NIH Grant R01-GM37188.

Supporting Information Available: Maximum and lowest dose strengths, solubility, dose number, calculated Log *P* and CLogP, therapeutic categories, and provisional BCS classification of the oral drugs in immediate-release dosage forms on the top 200 US, GB, ES, and JP lists. Tabulation of revised BCS classification of oral drugs in immediate-release dosage forms on WHO essential medicines list. Comparison tables of BDDCS and BCS classification of 168 drugs. This material is available free of charge via the Internet at http://pubs.acs.org.

MP0600182

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