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Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification

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Abstract: The purpose of this study is to provisionally classify, based on the Biopharmaceutics Classification System (BCS), drugs in immediate-release dosage forms that appear on the World Health Organization (WHO) Essential Drug List. The classification in this report is based on the aqueous solubility of the drugs reported in commonly available reference literature and a correlation of human intestinal membrane permeability for a set of 29 reference drugs with their calculated partition coefficients. The WHO Essential Drug List consists of a total of 325 medicines and 260 drugs, of which 123 are oral drugs in immediate-release (IR) products. Drugs with dose numbers less than or equal to unity [Do = (maximum dose strength/250 mL)/solubility $\leq$ 1] are defined as high-solubility drugs. Drug solubility for the uncharged, lowest-solubility form reported in the Merck Index or USP was used. Of the 123 WHO oral drugs in immediate-release dosage forms, 67% (82) were determined to be high-solubility drugs. The classification of permeability is based on correlations of human intestinal permeability of 29 reference drugs with the estimated log *P* or CLogP lipophilicity values. Metoprolol was chosen as the reference compound for permeability and log *P* or CLogP. Log *P* and CLogP were linearly correlated (r^2 = 0.78) for 104 drugs. A total of 53 (43.1%) and 62 (50.4%) drugs on the WHO list exhibited log *P* and CLogP estimates, respectively, that were greater than or equal to the corresponding metoprolol value and are classified as high-permeability drugs. The percentages of the drugs in immediate-release dosage forms that were classified as BCS Class 1, Class 2, Class 3, and Class 4 drugs using dose number and log *P* were as follows: 23.6% in Class 1, 17.1% in Class 2, 31.7% in Class 3, and 10.6% in Class 4. The remaining 17.1% of the drugs could not be classified because of the inability to calculate log *P* values because of missing fragments. The corresponding percentages in the various BCS classes with dose number and CLogP criteria were similar: 28.5% in Class 1, 19.5% in Class 2, 35.0% in Class 3, and 9.8% in Class 4. The remaining 7.3% of the drugs could not be classified since CLogP could not be calculated. These results suggest that a satisfactory bioequivalence (BE) test for more than 55% of the high-solubility Class 1 and Class 3 drug products on the WHO Essential Drug List may be based on an *in vitro* dissolution test. The use of more easily implemented, routinely monitored, and reliable *in vitro* dissolution tests can ensure the clinical performance of drug products that appear on the WHO Essential Medicines List.

Keywords: BCS; solubility; dose number; permeability; partition coefficient; WHO essential drugs; pK_a

Introduction

Bioequivalence (BE) tests are accepted today as a pivotal standard upon which to base approval of major manufacturing changes and approval of generic drug product efficacy claims. For the past 25 years, this test has been based on measured plasma levels and equivalence of these levels to those of the drug product used in pivotal efficacy tests. While the *in vivo* BE test has been the accepted standard for the past 25 years, a new standard, applicable to a significant number of drug products, has been approved by the U.S. Food and Drug Administration (FDA).[1] This standard is based on ensuring that absorption is similar from the drug products being compared and is based on the fundamental processes controlling the absorption process. In this report, we provisionally classify the oral immediate-release drug products that appear on the World Health Organization (WHO) Essential Drug List.

For any orally administered drug product, the fundamental parameters controlling the drug absorption rate and extent are its aqueous solubility and gastrointestinal permeability.[2] The biopharmaceutic drug classification scheme (BCS) categorizes drugs into four classes according to their solubility and permeability.[2] BCS has been a useful guide for recognizing when and how dissolution tests can help in the design and evaluation of oral dosage forms,[3] and for defining which tests are most suitable for ensuring *in vivo* bioequivalence.[4] The FDA has recently implemented the BCS system to allow waiver of *in vivo* bioavailability and bioequivalence testing of immediate-release solid dosage forms for Class 1 high-solubility, high-permeability drugs.[1] Waivers for Class 3 (high-solubility, low-permeability) drugs are scientifically justified and have been recommended.[5,6] Such waivers have the potential to both decrease the cost and improve the quality of medicines.

Since 1977, the WHO has provided a "core list" of minimum medicines required for basic health care. Such essential medicines are selected on the basis of public health relevance, efficacy, safety, and cost-effectiveness. A total of 260 drugs are included in the 12th edition of the WHO list,[7] 123 of which are orally administered. For comparison, the annual list of the top 200 prescribed drugs in the United States (U.S.) includes 141 orally administered drugs,[8] 43 of which are also on the WHO list.

This report is focused on orally administered drugs included in the WHO Essential Drug List. Select comparisons to the immediate-release drug products in the top 200 U.S. drug list are also included. A comparison of the top U.S., European, and Japanese drug lists will be presented in a future publication. The classification of drug solubility is based on the dimensionless dose number, Do.[9] Do is the ratio of drug concentration in the administered volume (250 mL) to the saturation solubility of the drug in water [Do = (dose/250)/solubility]. Ideally, classification of drug permeability would be based on experimental human jejunal permeability data or well-defined mass balance studies, but since such information is readily available for only a small fraction of drugs, permeability classification in this report 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

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(1) Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2002. *FDA Guidance for Industry*; Federal Drug and Food Administration: Rockville, MD, 2002.
(2) Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of *In Vitro* Drug Product Dissolution and *In Vivo* Bioavailability. *Pharm. Res.* **1995**, *12*, 413−420.
(3) Dressman, J. B.; Amidon, G. L.; Reppas, C.; Shah, V. P. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. *Pharm. Res.* **1998**, *15*, 11−22.
(4) Galia, E.; Nicolaides, E.; Horter, D.; Lobenberg, R.; Reppas, C.; Dressman, J. B. Evaluation of Various Dissolution Media for Predicting *In Vivo* Performance of Class I and II Drugs. *Pharm. Res.* **1998**, *15*, 698−705.
(5) Yu, L. X.; Amidon, G. L.; Polli, J. E.; Zhao, H.; Mehta, M. U.; Conner, D. L.; Shah, V. P.; Lesko, L. J.; Chen, M.-L.; Lee, V. H. L.; Hussain, A. S. Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions. *Pharm. Res.* **2002**, *19*, 921−925.
(6) Blume, H. H.; Schug, B. S. The biopharmaceutics classification system (BCS): class III drugs—better candidates for BA/BE waiver? *Eur. J. Pharm. Sci.* **1999**, *9*, 117−121.
(7) WHO List of Essential Drugs, 12th ed., revised April 2002 (http://www.who.int/medicines/organization/par/edl/eml2002core.pdf).
(8) The Top 200 Prescriptions for 2002 by Number of U.S. prescriptions Dispensed (http://www.rxlist.com/top200.htm).
(9) Oh, D.-M.; Curl, R. L.; Amidon, G. L. Estimating the Fraction Dose Absorbed from Suspensions of Poorly Soluble Compounds in Humans: A Mathematical Model. *Pharm. Res.* **1993**, *10*, 264−270.
(10) Sun, D.; Lennernäs, H.; Welage, L. S.; Barnett, J. L.; Landowski, C. P.; Foster, D.; Fleisher, D.; Lee, K. D.; Amidon, G. L. Comparison of Human Duodenum and Caco-2 Gene Expression Profiles for 12,000 Gene Sequence Tags and Correlation with Permeability of 26 Drugs. *Pharm. Res.* **2002**, *19*, 1400−1416.
(11) Winiwarter, S.; Bonham, N. M.; Ax, F.; Hallberg, A.; Lennernäs, H.; Karlén, A. Correlation of Human Jejunal Permeability (in Vivo) of Drugs with Experimentally and Theoretically Derived Parameters. A Multivariate Data Analysis Approach. *J. Med. Chem.* **1998**, *41*, 4939−4949.

Table 1. Solubility Definitions

descriptive term (solubility definition)	parts of solvent required for one 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)	from 1000 to 10000	0.1−1	0.1
practically insoluble (pi)	≥10000	<0.1	0.01

of this analysis suggest that the majority of the drug products on the WHO list are candidates for biowaivers.

Methods

Solubility and pK_a. Values for drug solubility (milligrams per milliliter) were obtained from standard references.[13−15] For cases wherein specific values of solubility were not available, the lower limit of the range defined in the USP[13] (column 3, Table 1) was chosen as a conservative estimate. 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) was used in dose number calculations. Values of dissociation constants were obtained from the Merck Index[14] or USP DI[15] unless otherwise specified.

Maximum Dose Strength. For WHO oral drugs formulated in immediate-release dosage forms, values for maximum dose strength and lowest dose strength (milligrams) were obtained from the WHO Essential Medicines Core List.[7] For the oral drugs in immediate-release dosage forms in the top 200 U.S. list, this information was obtained from the Orange Book (online version updated June 2003).[16]

Dose Number Calculations. The following equation was used to calculate the dose number:[9]

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

where M_0 is the highest dose strength (milligrams), C_s is the solubility (milligrams per milliliter), and $V_0 = 250$ mL.

Partition Coefficients. Log *P* (*n*-octanol/water partition coefficient) values were calculated using three different fragmentation methods that are based on atomic contributions to lipophilicity.[17−19] CLogP values were calculated using the CLogP program (version 3.0) from BioByte Corp. (Claremont, CA) generated with algorithms based on theoretical treatments developed by Leo.[20] Estimates of log *P* as well as CLogP for the uncharged solute molecule were obtained using ChemDraw Ultra 6.0 (CambridgeSoft Corp., Cambridge, MA) and chemical structures of the drug as depicted in the Merck Index.[14]

Distribution Coefficients. Log *D*, the pH-dependent distribution coefficient for singly ionized species, was calculated from the estimated log *P* and the ionization constant (pK_a) using the following equations:[21]

$$\text{for acids, } \log D = \log P - \log(1 + 10^{\mathrm{pH}-\mathrm{p}K_a})$$

$$\text{for bases, } \log D = \log P - \log(1 + 10^{\mathrm{p}K_a-\mathrm{pH}})$$

Results

Characterization of Molecular Properties of Drugs. The maximum dose strength (milligrams), solubility (milligrams per milliliter), dose number, estimated log *P*, CLogP, and therapeutic class of the 123 oral drugs in immediate-release dosage forms on the WHO Essential Medicines List are shown in Table 2. Table 2 also shows pK_a values and, where possible, a provisional BCS classification based on dose number and log *P* or CLogP values (see below). A similar treatment for 141 oral drugs found in the top 200 medicines of the U.S. drug list is presented in Table 3.

Distribution of Drug Therapeutic Class. The percentage of anti-infective drugs on the WHO oral Essential Medicines List was significantly higher than that on the top 200 U.S. list (44.7% vs 17.7%), reflecting their greater need in developing nations. A breakdown comparison of the anti-infective drugs on the two lists is shown in Figure 1. Of the other major therapeutic classes, a significantly higher preponderance of antihypertensive, antidepressant, anxiolytic/antipsychotic, and antihyperlipoproteinemic drugs is found on the top 200 U.S. list than on the WHO list (Figure 2).

(12) Winiwarter, S.; Ax, F.; Lennernäs, H.; Hallberg, A.; Pettersson, C.; Karlén, A. Hydrogen bonding descriptors in the prediction of human in vivo intestinal permeability. *J. Mol. Graphics Modell.* **2003**, *21*, 273−287.

(13) *The United States Pharmacopeia*, 24th ed.; by authority of the United States Pharmacopeial Convention, Inc.; printed by National Publishing: Philadelphia, PA, 2000.

(14) *The Merck Index*, 13th ed.; Merck Research Laboratories: Rahway, NJ, 2001.

(15) *USP DI Volume III, Approved Drug Products and Legal Requirements*, 18th ed.; United States Pharmacopeial Convention, Inc.: Rockville, MD, 1998.

(16) Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, 23rd ed.; updated June 2003 (http://www.fda.gov/cder/ob/default.htm).

(17) Ghose, A. K.; Crippen, G. M. Atomic Physicochemical Parameters for Three-Dimensional-Structure-Directed Quantitative Structure−Activity Relationships. 2. Modeling Dispersive and Hydrophobic Interactions. *J. Chem. Inf. Comput. Sci.* **1987**, *27*, 21−35.

(18) Viswanadhan, V. N.; Ghose, A. K.; Reyankar, G. R.; Robins, R. K. Atomic Physicochemical Parameters for Three-Dimensional Structure Directed Quantitative Structure−Activity Relationships. 4. Additional Parameters for Hydrophobic and Dispersive Interactions and Their Application for an Automated Superposition of Certain Naturally Occurring Nucleoside Antibiotics. *J. Chem. Inf. Comput. Sci.* **1989**, *29*, 163−172.

(19) Broto, P.; Moreau, G.; Vandycke, C. Molecular Structure: perception, autocorrelation descriptor and SAR studies. *Eur. J. Med. Chem.* **1984**, *19*, 71−78.

(20) Leo, A. J. Calculating log P_{oct} from Structures. *Chem. Rev.* **1993**, *93*, 1281−1306. CLOGP and Masterfile from BioByte Corp., 201 W. Fourth St., Suite 204, Claremont, CA 91711.

(21) Hansch, C.; Leo, A. J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

Table 2. Oral Drugs in the Core WHO Essential Medicines List[a,b,c]

drug	maximum dose strength (mg)	solubility definition	solubility (mg/mL)	dose number (Do)	CLogP	log *P*	pK_a(s)	therapeutic class	BCS class: log *P*-based	BCS class: CLogP-based
abacavir sulfate	300		77	***0.016***	0.58	0.22	5.01	antiviral	3	3
acetazolamide	250	vss	0.1	10	−1.13	0.14	7.2	antiglaucoma, diuretic	4	4
acetylsalicylic acid	500	ss, 300	3.33	***0.601***	1.02	1.18	3.5	NSAIMs, antithrombolytic	3	3
acyclovir	200	sps	10	***0.08***	−2.42	−1.59		antiviral (anti-herpes)	3	3
albendazole	400	pi	**0.01**	160	3.46	2.55		anthelminthic (*Cestodes*)	2	2
allopurinol	100	vss	0.1	4	0.63	0.32	10.2	antiurolithic	4	4
amiloride hydrochloride	5	ss	1	***0.02***	−0.55	−0.73	8.7	diuretic	3	3
amitriptyline hydrochloride	25	fs	100	***0.001***	4.85	4.42	9.4	anxiolytic, antidepressant	1	1
amoxicillin	500	ss	4	***0.50***	−1.87	−0.58		antibacterial	3	3
artemether	20				2.92	3.51		antimalarial		
atenolol	100	sps	26.5	***0.015***	−0.11	0.50	9.6	antihypertensive, antianginal	3	3
atropine sulfate	1	vs, 0.5	2000	***0.000002***	1.30	1.53	4.35	antispasmodic	3	3
azathioprine	50	pi	**0.01**	20	0.51		8.2	antirheumatic		4
benznidazole	100		0.4	***1.0***	0.90			antiprotozoal (*Trypanosoma*)		3
biperiden hydrochloride	2	ss	1	***0.008***	4.42	3.56		antiparkinsonian	1	1
captopril	25	fs	100	***0.001***	0.89	0.24	3.7, 9.8	antihypertensive	3	3
carbamazepine	200	pi	**0.01**	80	1.98	2.93	7.0	anticonvulsant, antiepileptic	2	2
chloramphenicol	250	ss	2.5	***0.40***	1.28	−0.23		antibacterial	3	3
chloroquine phosphate	150	fs	100	***0.006***	5.06	3.73		antimalarial, antiamebic	1	1
chlorpheniramine maleate	4	fs	160	***0.0001***	3.15	3.62	9.2	antihistaminic	1	1
chlorpromazine hydrochloride	100	vs	1000	***0.000***	5.80	4.24		antiemetic, antipsychotic	1	1
cimetidine	200	ss	1	***0.80***	0.35	0.79	6.8	antiulcerative	3	3
ciprofloxacin hydrochloride	250	sps	10	***0.1***	−1.15	1.32		antibacterial	3	3
clofazimine	100	pi	**0.01**	40	7.50	5.39	8.37, 8.51	antibacterial (leprostatic)	2	2
clomiphene citrate	50	ss	1	***0.20***	7.15	6.7		gonad-stimulating principle	1	1
clomipramine hydrochloride	25	fs	100	***0.001***				antiobsessional agent		
cloxacillin sodium	1000	fs	100	***0.04***	2.52	2.06		antibacterial	1	1
codeine phosphate	30	fs	100	***0.0012***	0.98	1.45		narcotic analgesic, antitussive	3	3
colchicine	0.5	s	33	***0.0001***	1.20	0.05	12.35	gout suppressant	3	3
cyclophosphamide	25	s	40	***0.0025***	0.93			antineoplastic, DMARD		3
dapsone	100	vss	0.1	4	0.89	1.32	13.0 (pK_b)	antibacterial (leprostatic)	4	4
dexamethasone	0.5	vss	0.1	***0.02***	1.79	0.72		glucocorticoid, anti-inflammatory	3	1
diazepam	5	pi	**0.01**	2.00	3.17	2.98	3.4	anxiolytic, muscle relaxant	2	2
didanosine	200		27.3	***0.03***	−1.92	−1.1	9.12	antiviral	3	3
diethylcarbamazine citrate	100	vs	1000	***0.0004***	1.62	0.09		anthelminthic (nematodes)	3	1
digoxin	0.25	pi	**0.01**	***0.1***	1.27	1.95		cardiotonic (antiarrhythmic)	1	3
diloxanide furoate	500	vss	0.1	20	1.77	1.96		antiamebic	2	2
DL-methionine	250	s	33	***0.030***				specific antidote		
doxycycline	100	vss	0.1	4	−0.60	−3.66		antibacterial, antimalarial	4	4
efavirenz	200	pi	**0.01**	80	4.95	3.68	10.2	antiviral	2	2
ergometrine maleate	0.2	ss	10	***0.00008***	1.23	0.35	6.8	oxytocic	3	3
ergotamine tartrate	1	vss, 3200	0.3	***0.0133***	4.66	2.24		antimigraine	1	1
erythromycin ethyl succinate	250	vss, 1000	1	***1.0***	1.47		8.8	antibacterial		1
ethambutol hydrochloride	400	fs	100	***0.016***	0.12	0.06		antibacterial (tuberculostatic)	3	3
ethinyl estradiol	0.05	pi	**0.01**	***0.02***	3.86	4.0		estrogen (contraceptive)	1	1
ethosuximide	250	fs	100	***0.01***	0.40	0.88		anticonvulsant	3	3
ferrous sulfate	60	fs, 1.5	667	***0.0004***				hematopoietic (antianaemia)		
fluconazole	50	ss	1	***0.2***	0.53	0.99		antifungal	3	3

Table 2 Continued

drug	maximum dose strength (mg)	solubility definition	solubility (mg/mL)	dose number (Do)	CLogP	log *P*	pK_a(s)	therapeutic class	BCS class: log *P*-based	BCS class: CLogP-based
folic acid	5	vss	0.1	***0.2***	−2.31	−0.52		vitamin (hematopoietic)	3	3
furosemide	40	pi	**0.01**	16	1.9	0.74	3.9	diuretic, antihypertensive	4	2
glibenclamide	5	pi	**0.01**	2	4.24	3.53	5.3	antidiabetic	2	2
griseofulvin	250	vss	0.1	10	1.77	0.68		antifungal	4	2
haloperidol	5	pi	**0.01**	2	3.85	3.49	8.3	antipsychotic	2	2
hydralazine hydrochloride	50	s, 25	40	***0.005***	1.02	0.73	7.3	antihypertensive	3	3
hydrochlorothiazide	50	ss	1	***0.2***	−0.36	−0.15	7.9, 9.2	diuretic, antihypertensive	3	3
ibuprofen	400	pi	**0.01**	160	3.68	3.14	5.2	NSAIM, analgesic, antipyretic	2	2
indinavir sulfate	400	vs	1000	***0.0016***	3.68	2.49		antiviral	1	1
isoniazid	300	fs, 8	125	***0.01***	−0.67	0.64		antibacterial (tuberculostatic)	3	3
Ivermectin	6		0.004	6				anthelminthic (*Onchocerca*)		
lamivudine	150		70	***0.0086***	−1.46	0.06		antiviral	3	3
levamisole hydrochloride	150	fs	100	***0.006***	1.84	2.79		anthelminthic (nematodes)	1	1
levodopa	250	ss	1	***1.0***	−2.82			antiparkinsonian		3
levonorgestrel	0.75	pi	**0.01**	***0.3***	3.31	3.06		progestogen (contraceptive)	1	1
levothyroxine sodium	0.1	vss	0.15	***0.003***	3.51	7.36		thyroid hormone	1	1
lithium carbonate	300	sps	10	***0.12***				antimanic		
lopinavir (with ritonavir)	133.3		**0.01**	53.3	6.10	4.56		antiviral	2	2
lumefantrine (with artemether)	120		1	***0.48***	10.20	8.81		antimalarial	1	1
mebendazole (chewable)	500	pi	**0.01**	200	3.08	2.50		anthelminthic (nematodes)	2	2
mefloquine hydrochloride	250	ss	1	***1.00***	3.67	4.12		antimalarial	1	1
metformin hydrochloride	500	fs	100	***0.02***	−1.63	0.15	12.4	antidiabetic	3	3
methotrexate	2.5	pi	**0.01**	***1.0***	−0.53	0.94		antineoplastic, antirheumatic	3	3
methyldopa	250	sps	10	***0.1***	−2.73	0.39		antihypertensive	3	3
metoclopramide hydrochloride	10	vs	1000	***0.00004***	2.23	1.48	0.6, 9.3	antiemetic	3	1
metronidazole	500	sps	10	***0.2***	−0.46			antiprotozoal, antibacterial		3
nalidixic acid	500	vss	0.1	20	1.34	1.63		antibacterial	4	4
nelfinavir mesylate	250		4.5	***0.22***	5.84	4.62	−1.2	antiviral	1	1
neostigmine bromide	15	vs	1000	***0.00006***	2.23	2.39		cholinergic, muscle relaxant	1	1
nevirapine	200		0.1	8	2.42	2.05	2.8	antiviral	2	2
niclosamide (chewable)	500	pi	**0.01**	200	4.35	3.38		anthelminthic (*Cestodes*)	2	2
nicotinamide	50		100	***0.002***	−7.16			vitamin (enzyme cofactor)		3
nifedipine	10	pi	**0.01**	4	3.41	2.31		antianginal, antihypertensive	2	2
nifurtimox	250	s	33	***0.03***	0.02			antiprotozoal (*Trypanosoma*)		3
nitrofurantoin	100	vss	0.19	2.11	−0.47		7.2	antibacterial		4
norethindrone	1	pi	**0.01**	***0.40***	2.78	2.64		oral contraceptive	1	1
nystatin	100	pi	4	***0.1***	−3.20			antifungal		3
paracetamol	500		0.1	20	0.49	0.89		analgesic, antipyretic	4	4
penicillamine	250	fs	100	***0.01***	−1.73	−0.39		DMARD, antidote	3	3
penicillin V potassium	500		33	***0.06***	1.94	0.48		antibacterial	3	1
phenobarbital	100	vss, 1000	1	***0.4***	1.37	1.52	7.3, 11.8	anticonvulsant, hypnotic	3	1
phenytoin (chewable)	50	pi	**0.01**	20	2.09	2.14	8.06−8.33	anticonvulsant, antiepileptic	2	2
phenytoin sodium	100	fs	100	***0.004***	2.09	2.14		anticonvulsant, antiepileptic	1	1
praziquantel	600	vss	0.4	6	3.36	2.02		anthelminthic (*Schistosoma*)	2	2
prednisolone	5	vss	0.1	***0.2***	3.50	2.51		glucocorticoid, antiallergic	1	1
primaquine phosphate	15	s, 15	66.7	***0.0009***	2.60	1.47		antimalarial	3	1
proguanil hydrochloride	100	ss	1	***0.40***	2.53	3.17		antimalarial	1	1
promethazine hydrochloride	25	vs	1000	***0.0001***	4.90	3.90	9.1	antihistaminic, antiemetic	1	1
propranolol hydrochloride	40	s	33	***0.00***	2.75	2.65		migraine prophylaxis	1	1
propylthiouracil	50	ss	1	***0.20***	−0.03	0.57		antihyperthyroid	3	3
pyrantel embonate	250	pi	**0.01**	100	3.03	2.50		anthelminthic (nematodes)	2	2
pyrazinamide	400	ss	15	***0.107***	−0.68	−1.41	0.5	antibacterial (tuberculostatic)	3	3
pyridostigmine bromide	60	fs	100	***0.002***	−4.51			cholinergic, muscle relaxant		3
pyridoxine hydrochloride	25	fs	222.2	***0.0005***	−0.80	−0.49		vitamin (enzyme cofactor)	3	3

Table 2 Continued

drug	maximum dose strength (mg)	solubility definition	solubility (mg/mL)	dose number (Do)	CLogP	log *P*	pK_a(s)	therapeutic class	BCS class: log *P*-based	BCS class: CLogP-based
pyrimethamine	25	pi	**0.01**	10	3.00	1.5		antiprotozoal (*Toxoplasma*)	4	2
quinine sulfate	300	ss	1.2	***1***	2.79	2.48	5.07, 9.7	antimalarial, muscle relaxant	1	1
reserpine	0.25	pi	**0.01**	***0.1***	3.72	2.69	6.6	antihypertensive	1	1
retinol palmitate	110	pi	**0.01**	44	6.40	4.69		vitamin (antixerophthalmic)	2	2
rifampicin	300	vss	0.1	12			1.7, 7.9	antibacterial (tuberculostatic)		
ritonavir	100	pi	**0.01**	40	4.94	5.98		antiviral	2	2
salbutamol sulfate	4		33	***0.0005***	0.06	0.97		bronchodilator, tocolytic	3	3
saquinavir mesylate	200		2.22	***0.36***	4.73	2.73		antiviral	1	1
Senna (Sennoside A&B)	7.5	s, 35	28.6	***0.001***				cathartic		
spironolactone	25	pi	**0.01**	10	2.25	2.90		diuretic	2	2
stavudine	40		83	***0.002***	−0.73	−0.47		antiviral	3	3
sulfadiazine	500	pi, 13000	0.08	25	0.10	0.21		antibacterial	4	4
sulfamethoxazole	400	pi	**0.01**	160	0.56	0.86		antibacterial	4	4
sulfasalazine	500	pi	**0.01**	200	3.88	3.42		GI anti-inflammatory, DMARDs	2	2
theophylline	300	ss	1	1.2	−0.03	−1.03	8.77, 13.5, 11.5	bronchodilator	4	4
triclabendazole	250				6.44	5.44		anthelminthic (fasciola)		
trimethoprim	200	vss	0.4	2	0.98	1.43	6.6	antibacterial	4	4
valproic acid	500	ss	1.3	1.54	2.76	2.42	4.8	anticonvulsant, antimanic	3	3
verapamil hydrochloride	80	s	83	***0.004***	4.47	5.69	8.6	antianginal, antiarrhythmic	1	1
warfarin sodium	5	vs	1000	***0.00002***	2.90	2.97		anticoagulant	1	1
zidovudine	300		20.1	***0.06***	0.04			antiviral		3

[a] Drugs in italics common to both WHO and top 200 U.S. lists. [b] Practically insoluble (pi) drugs given in bold. [c] Values in bold italics indicate dose numbers of ≤1.0.

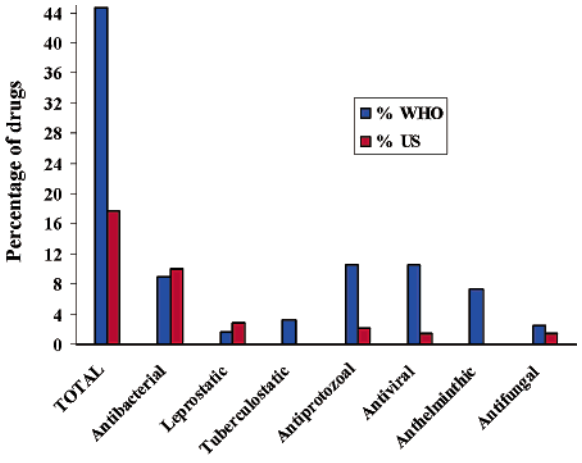

Figure 1. Comparison of the distribution of anti-infective drugs on the WHO and U.S. lists.

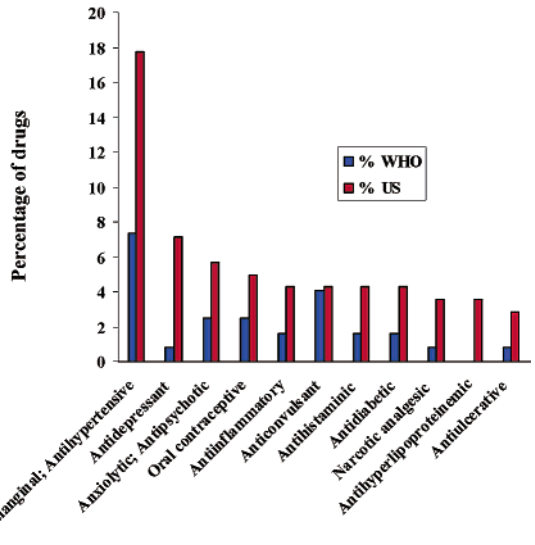

Figure 2. Comparison of the distribution of other therapeutic classes of drugs on the WHO and U.S. lists.

Classification of Drug Solubility. Figure 3 shows a comparison plot of the percentage of drugs on the two lists in various solubility categories. Drugs with dose numbers of ≤1 were classified as high-solubility drugs. Conversely, drugs with dose numbers of >1 were classified as low-solubility drugs. On the basis of these criteria, 82 of the 123 WHO oral drugs (67%) and 96 of the U.S. oral drugs (68%) were classified as high-solubility drugs. It is also evident from Figure 3 that the solubility distribution of the drugs on the WHO list is quite similar to that of the U.S. list. Dose number calculations using the lowest dose strength of the WHO oral drugs revealed that 89 of the 123 WHO drugs (72.4%) were classified as high-solubility drugs. Thus, seven drugs changed solubility classification (low to high solubility) when dose numbers were calculated using the drug's lowest dose strength.

Criteria for Classification of Permeability. The classification of permeability of the 123 oral drugs was based on correlations of experimentally determined human intestinal permeabilities of select compounds with estimated log *P*, CLogP, or log *D* values. Metoprolol was chosen as the reference compound for permeability and log *P*, CLogP, or log *D* since 95% of the drug is known to be absorbed from

Table 3. Oral Drugs in the Top 200 U.S. Drug Product List[a,b,c]

drug	maximum dose strength (mg)	solubility definition	solubility (mg/mL)	dose number (Do)	pK_a(s)	therapeutic class
acetylsalicylic acid	500	ss	3	***0.667***	3.5	NSAIMs, antithrombolytic
acyclovir	800	sps	10	***0.32***		antiviral (anti-herpes)
alendronate sodium	70	s	33	***0.008***		bone resorption inhibitor
allopurinol	300	vss	0.1	12	10.2	antiurolithic
alprazolam	2	pi	**0.01**	***0.8***		anxiolytic
amitriptyline hydrochloride	100	fs	100	***0.004***	9.4	anxiolytic, antidepressant
amlodipine besylate	10	ss	1	***0.04***		antianginal, antihypertensive
amoxicillin	875	ss	4	***0.88***		antibacterial
amphetamine (mixed salts)	30	fs	100	***0.0012***		CNS stimulant, anorexic
atenolol	100	sps	26.5	***0.015***	9.6	antihypertensive, antianginal
atorvastatin calcium	80		0.1	3.2		antihyperlipoproteinemic
azithromycin	600					antibacterial
benazepril hydrochloride	40	s	33	***0.005***		antihypertensive
bisoprolol fumarate	10	s	33	***0.001***		antihypertensive
bupropion hydrochloride	100		312	***0.001***	7.9	antidepressant
buspirone hydrochloride	30	vs	1000	***0.0001***	1.22, 7.32	anxiolytic
captopril	100	fs	100	***0.004***	3.7, 9.8	antihypertensive
carbamazepine	200	pi	**0.01**	80	7.0	anticonvulsant, antiepileptic
carbidopa	25	ss	1	***0.10***		antiparkinsonian
carisoprodol	350	vss, 2083	0.48	2.92		skeletal muscle relaxant
carvedilol	25	pi	**0.01**	10		antihypertensive and CHF
cefprozil	500					antibacterial
celecoxib	400					anti-inflammatory
cephalexin	500	ss	1	2	5.2, 7.3	antibacterial
cetirizine hydrochloride	10	fs	100	***0.0004***		antihistaminic
cimetidine	800	ss	1	3.20	6.8	antiulcerative
ciprofloxacin hydrochloride	750	sps	10	***0.3***		antibacterial
citalopram hydrobromide	40	sps	10	***0.016***		antidepressant
clarithromycin	500	pi	**0.01**	200		antibacterial
clindamycin hydrochloride	300	fs	100	***0.012***	7.6	antibacterial
clonazepam	2	pi	**0.01**	***0.8***	1.5, 10.5	anticonvulsant
clonidine hydrochloride	0.3	s	80	***0.000015***		antihypertensive, analgesic
clopidogrel bisulfate	75		100	***0.003***		antithrombotic
codeine phosphate	60	fs	100	***0.0024***		aarcotic analgesic, antitussive
cyclobenzaprine hydrochloride	10	fs	100	***0.0004***	8.47	skeletal muscle relaxant
desloratadine	5	ss	1	***0.02***		antihistaminic
desogestrel	0.15	pi	**0.01**	***0.06***		progestogen, contraceptive
diazepam	10	pi	**0.01**	4.00	3.4	anxiolytic, muscle relaxant
digoxin	0.25	pi	**0.01**	***0.1***		cardiotonic (antiarrhythmic)
diltiazem hydrochloride	120	fs	100	***0.005***		antianginal, antihypertensive
doxazosin mesylate	8	ss	8	***0.004***		antihypertensive
doxycycline	100	vss	0.1	4		antibacterial, antimalarial
enalapril maleate	20	sps	25	***0.0032***	3.0, 5.4	antihypertensive
estradiol	2	pi	**0.01**	***0.8***		estrogen
ethinyl estradiol	0.5	pi	**0.01**	***0.2***		estrogen (contraceptive)
famotidine	40	vss	0.1	1.6	7.1	antiulcerative
fenofibrate	200	pi	**0.01**	80		antihyperlipoproteinemic
fexofenadine hydrochloride	180	ss	1	***0.72***		antihistaminic
fluconazole	200	ss	1	***0.8***		antifungal
fluoxetine hydrochloride	40	s	33	***0.005***		antidepressant, antiobsessional
folic acid	1	vss	0.1	***0.04***		vitamin (hematopoietic)
fosinopril sodium	40	s	100	***0.002***		antihypertensive
furosemide	80	pi	**0.01**	32	3.9	diuretic, antihypertensive
gabapentin	800	fs	100	***0.032***	3.7, 10.7	anticonvulsant
gemfibrozil	600	pi	**0.01**	240		antihyperlipoproteinemic
glimepiride	4	pi	**0.01**	1.6		antidiabetic
glipizide	10	pi	**0.01**	4	5.9	antidiabetic
glyburide	6	pi	**0.01**	2.4	5.3	antidiabetic
hydrochlorothiazide	50	ss	1	***0.2***	7.9, 9.2	diuretic, antihypertensive
hydrocodone bitartrate	10	s	33	***0.001***		narcotic analgesic,antitussive
hydroxyzine hydrochloride	50	vs	1000	***0.0002***	2.6, 7	anxiolytic, antihistaminic
ibuprofen	800	pi	**0.01**	320	5.2	NSAIM, analgesic, antipyretic
irbesartan	300	pi	**0.01**	120		antihypertensive
isosorbide mononitrate	20	fs	100	***0.0008***		vasodilating agent
lansoprazole	30	pi	**0.01**	12		antiulcerative
levodopa	250	ss	1	***1.0***		antiparkinsonian
levofloxacin	750		50	***0.06***		antibacterial
levonorgestrel	0.75	pi	**0.01**	***0.3***		progestogen, contraceptive
levothyroxine sodium	0.3	vss	0.15	***0.008***		thyroid hormone
lisinopril	40	s	97	***0.002***	2.5, 4.0, 6.7, 10.1	antihypertensive
loratadine	10	pi	**0.01**	4		antihistaminic
lorazepam	2	pi	0.08	***0.1***	1.3, 11.5	anxiolytic, anticonvulsant
losartan potassium	100	fs	100	***0.004***	5−6	antihypertensive
meclizine hydrochloride	50	pi	**0.01**	20		antiemetic
medroxyprogesterone acetate	10	pi	**0.01**	4		progestogen
metaxalone	800	vss	0.1	32		analgesia (musculoskeletal)
metformin hydrochloride	1000	fs	100	***0.04***	12.4	antidiabetic
methylphenidate hydrochloride	20	fs	100	***0.0008***	8.9	CNS stimulant
methylprednisolone	32	pi	**0.01**	12.8		glucocorticoid
metoclopramide hydrochloride	10	vs	1000	***0.00004***	0.6, 9.3	antiemetic

Table 3 Continued

drug	maximum dose strength (mg)	solubility definition	solubility (mg/mL)	dose number (Do)	pK_a(s)	therapeutic class
metoprolol tartrate	100	vs	1000	***0.0004***	9.7	antihypertensive, antianginal
metronidazole	500	sps	10	***0.2***		antiprotozoal, antibacterial
minocycline hydrochloride	100	s	33	***0.01***		antibacterial
mirtazapine	45	ss	1	***0.18***		antidepressant
montelukast sodium	10		100	***0.0004***		antiasthmatic
naproxen sodium	500	s	33	***0.06***	4.15	anti-inflammatory
nifedipine	20	pi	**0.01**	8		antianginal, antihypertensive
nitrofurantoin	100	vss	0.19	2.11	7.2	antibacterial
norethindrone	1	pi	**0.01**	***0.4***		oral contraceptive
norgestimate	0.25	pi	**0.01**	***0.1***		oral contraceptive
nortriptyline hydrochloride	75	s	33	***0.009***	9.73	antidepressant
nystatin	100	pi	4	***0.1***		antifungal
olanzapine	20	pi	**0.01**	8		antipsychotic
oxybutynin chloride	5	fs	100	***0.0002***	6.96	antispasmodic
oxycodone hydrochloride	30	s	100	***0.0012***		analgesic (narcotic)
paracetamol	500		0.1	20		analgesic, antipyretic
paroxetine hydrochloride	40		5.4	***0.03***		antidepressant, antiobsessional
penicillin V potassium	500	s	33	***0.06***		antibacterial
phenytoin (chewable)	50	pi	**0.01**	20	8.06−8.33	anticonvulsant, antiepileptic
phenytoin sodium	100	fs	100	***0.004***		anticonvulsant, antiepileptic
pioglitazone hydrochloride	45	pi	**0.01**	18		antidiabetic
pravastatin sodium	80	s	33	***0.01***		antihyperlipoproteinemic
prednisolone	5	vss	0.1	***0.2***		glucocorticoid, antiallergic
promethazine hydrochloride	50	vs	1000	***0.0002***	9.1	antihistaminic, antiemetic
propoxyphene hydrochloride	65	fs	100	***0.0026***		narcotic analgesic
propranolol hydrochloride	90	s	33	***0.01***		antihypertensive, antianginal
pseudoephedrine hydrochloride	60	vs	2000	***0.00012***	9.22	decongestant (nasal)
quetiapine fumarate	300	ms	10	***0.12***		antipsychotic
quinapril hydrochloride	40	fs	100	***0.0016***		antihypertensive
raloxifene hydrochloride	60		0.1	2.4		antiosteoporotic
ramipril	10		33	***0.001***		antihypertensive
ranitidine hydrochloride	300	vs	1000	***0.0012***	8.2, 2.7	antiulcerative
risedronate sodium	35		33	***0.004***		antiosteoporotic
risperidone	4	pi	**0.01**	1.6		antipsychotic
rofecoxib	50	pi	**0.01**	20		anti-inflammatory
rosiglitazone maleate	8		33	***0.001***	6.8, 6.1	antidiabetic
sertraline hydrochloride	100	ss	3.8	***0.11***	9.48	antidepressant, antiobsessional
sildenafil citrate	100		3.5	***0.11***		erectile dysfunction
simvastatin	80	pi	0.03	10.7		antihyperlipidemic
spironolactone	100	pi	**0.01**	40		diuretic
sulfamethoxazole	800	pi	**0.01**	320		antibacterial
sumatriptan succinate	100	s	100	***0.004***		antimigraine
tamoxifen citrate	20	vss	0.1	***0.8***	8.85	antiestrogen, antineoplastic
tamsulosin hydrochloride	0.4		10	***0.0002***		benign prostatic hypertrophy
temazepam	30	vss	0.1	1.2		sedative, hypnotic
terazosin hydrochloride	10	fs	100	***0.0004***	7.04	antihypertensive
tetracycline hydrochloride	500	s	33	***0.06***		antibacterial
timolol maleate	20	s	33	***0.002***	9.0	antihypertensive
tolterodine tartrate	2		12	***0.001***	9.9	urinary incontinence
topiramate	200		9.8	***0.082***		anticonvulsant
tramadol hydrochloride	50	s	33	***0.006***	9.41	opiate analgesic
trazodone hydrochloride	300	sps	10	***0.12***		antidepressant
triamterene	100	pi	**0.01**	40	6.2	diuretic
trimethoprim	200	vss	0.4	2	6.6	antibacterial
valacyclovir hydrochloride	1000		174	***0.023***	1.9, 7.5, 9.4	antiviral
valdecoxib	20		**0.01**	8		NSAID, antirheumatic
valsartan	320		1	1.28		antihypertensive
venlafaxine hydrochloride	100		572	***0.001***	9.4	antidepressant
verapamil hydrochloride	120	s	83	***0.006***	8.6	antihypertensive, antianginal
warfarin sodium	10	vs	1000	***0.00004***		anticoagulant
zolpidem tartrate	10	sps	23	***0.002***	6.2	sedative, hypnotic

[a] Drugs in italics common to both WHO and top 200 U.S. lists. [b] Practically insoluble (pi) drugs given in bold. [c] Values in bold italics indicate dose numbers of ≤1.0.

the gastrointestinal tract. Thus, drugs with estimated log *P*, CLogP, and log *D* values greater than or equal to 1.72, 1.35, and −1.48, respectively, were classified as high-permeability drugs. Conversely, drugs with log *P*, CLogP, and log *D* values lower than 1.72, 1.35, and −1.48, respectively, were classified as low-permeability drugs.

Correlation of Human Intestinal Permeability with Log *P*. The experimentally determined human jejunal permeabilities for 29 drugs are listed in Table 4 along with the octanol/water partition coefficients, log *P*, calculated using ChemDraw Ultra 6.0. This set of drugs includes 14 compounds that are listed in the FDA Waiver Guidance as recommended drugs for permeability classification.[1] A plot of the experimentally determined human permeabilities against log *P* is shown in Figure 4. An examination of Figure 4 reveals that the classification of permeability based on metoprolol as the reference compound is correct for 18 of the 26 test drugs in Table 4 (69%) and for 11 of the 12 test drugs (92%) on the FDA reference list (log *P* values for ranitidine and losartan could not be calculated by the

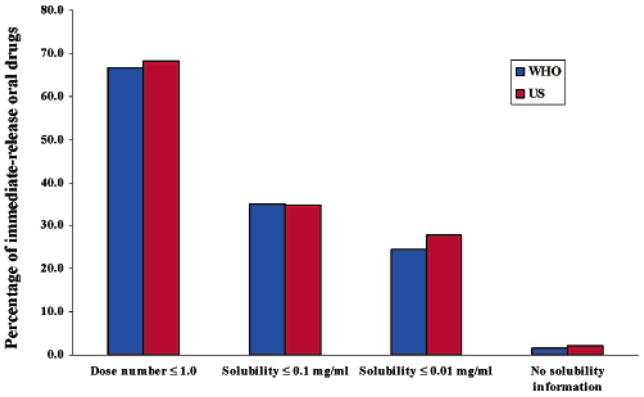

Figure 3. Comparison of the solubility classification of drugs on the WHO and U.S. lists.

Table 4. Estimated Log *P*, CLogP, and Human Jejunal Permeability of Reference Drugs

drug	log *P*	CLogP	human permeability ($\times 10^4$ cm/s)	permeability classification[a] log *P*-based	permeability classification[a] CLogP-based
α-methyldopa	0.39	−2.73	0.10	c	c
amoxicillin	−0.58	−1.87	0.30	c	c
antipyrine	1.01	0.20	5.60	fn	fn
atenolol	0.50	−0.11	0.20	c	c
carbamazepine	2.93	1.98	4.30	c	c
cephalexin	−0.67	−1.64	1.56	fn	fn
cimetidine	0.79	0.35	0.26	c	c
creatinine	−0.63	−1.77	0.29	c	c
desipramine	3.94	4.47	4.50	c	c
D-glucose	−3.52	−3.27	10.00	fn	fn
enalapril	1.77	0.67	1.57	c	fn
enalaprilat	1.17	0.88	0.20	c	c
fluvastatin	3.41	4.05	2.40	c	c
furosemide	0.74	1.90	0.05	c	fp
hydrochlorothiazide	−0.15	−0.36	0.04	c	c
ketoprofen	3.31	2.76	8.70	c	c
L-dopa	−2.39	−2.82	3.40	fn	fn
lisinopril	0.91	−1.69	0.33	c	c
L-leucine	−1.62	−1.67	6.20	fn	fn
losartan	na	4.11	1.15	na	fp
metoprolol	1.72	1.35	1.34	ref	ref
naproxen	2.86	2.82	8.50	c	c
phenylalanine	0.07	−1.56	4.08	fn	fn
piroxicam	0.29	1.98	6.65	fn	c
propranolol	2.65	2.75	2.91	c	c
ranitidine	na	0.63	0.27	na	c
terbutaline	1.16	0.56	0.30	c	c
valacyclovir	−1.06	−1.22	1.66	fn	fn
verapamil	5.69	4.47	6.80	c	c

[a] Abbreviations: c, correct; fn, false negative; fp, false positive; ref, reference; na, not available.

ChemDraw Ultra 6.0 algorithm due to missing fragments). Of the eight drugs that were classified as low-permeability drugs rather than high-permeability drugs as determined experimentally (false negatives), six are polar molecules transported by carrier-mediated mechanisms (D-glucose, L-leucine, L-Dopa, L-phenylalanine, cephalexin, and valacyclovir). The other two high-permeability drugs, classified as low-permeability drugs, were antipyrine and piroxicam.

Correlation of Human Intestinal Permeability with *C* Log *P*. Table 4 also lists CLogP values for the 29 drugs for which human jejunal permeabilities are available. A plot of the experimentally determined human permeabilities against CLogP is shown in Figure 5. An examination of Figure 5 reveals that the classification of permeability based on

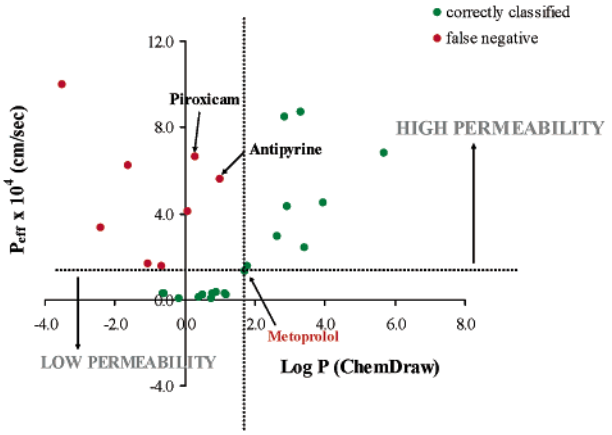

Figure 4. Correlation plot of the human jejunal permeability of 27 drugs with estimated log *P* values. Metoprolol was used as the reference drug.

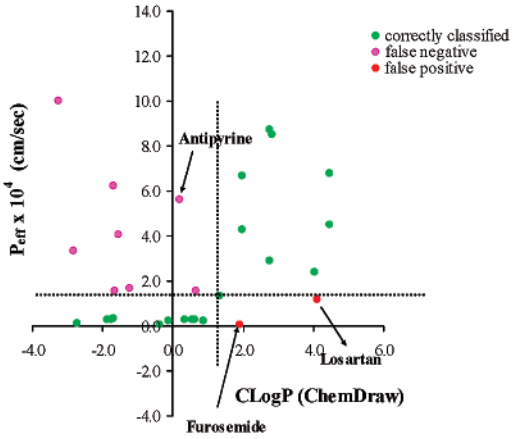

Figure 5. Correlation plot of the human jejunal permeability of 28 drugs with CLogP values.

metoprolol as the reference compound is correct for 18 of the 28 test drugs in Table 4 (64%) and for 11 of the 13 test drugs (85%) on the FDA reference list. In addition to the six polar compounds noted above, antipyrine and enalapril were classified as low-permeability drugs relative to metoprolol (false negatives). Furosemide and losartan, two low-permeability drugs, were classified as high-permeability drugs in the CLogP correlation plot (false positives).

Correlation of Human Intestinal Permeability with Log *D*. The octanol/water distribution coefficients, log *D*, obtained at pH 6.5 using log *P* estimates and pK_a values for 16 reference drugs are listed in Table 5. A correlation plot of human jejunal permeability against log *D* for the 16 drugs is shown in Figure 6. It is evident from the plot that the permeabilities of 13 of the 15 test drugs (87%) are correctly classified with respect to metoprolol. Cimetidine and losartan, two low-permeability drugs, however, were classified as high-permeability drugs in this plot (false positives).

BCS Classification of Essential WHO Immediate-Release Oral Drugs. The 123 oral drugs in immediate-release dosage forms on the WHO Essential Medicines List were provisionally classified into the BCS classes on the basis of dose number and log *P* or dose number and CLogP.

Table 5. pK_a, Log *D*, and Human Jejunal Permeability of Reference Drugs[a]

drug	pK_a	log *D* at pH 6.5	human permeability ($\times 10^4$ cm/s)	permeability classification
antipyrine	1.4	1.01	5.60	c
atenolol	9.6	−2.60	0.20	c
carbamazepine	NI	2.93	4.30	c
cimetidine	6.8	0.31	0.26	fp
creatinine	4.9[b]	−2.29	0.29	c
desipramine	10.2	0.24	4.50	c
fluvastatin	4.3[b]	1.22	2.40	c
furosemide	3.9	−1.86	0.05	c
hydrochlorothiazide	9.2	−2.85	0.04	c
ketoprofen	4.5	1.31	8.70	c
losartan	4.7[c]	1.69	1.15	fp
metoprolol	9.7	−1.48	1.34	ref
naproxen	4.2	0.51	8.50	c
piroxicam	5.1	−1.13	6.65	c
propranolol	9.5	−0.38	2.91	c
verapamil	8.6	3.59	6.80	c

[a] Abbreviations: c, correct; fp, false positive; ref, reference; NI, nonionizable; log *P* value used as log *D*. [b] From ref 11. [c] From ref 24.

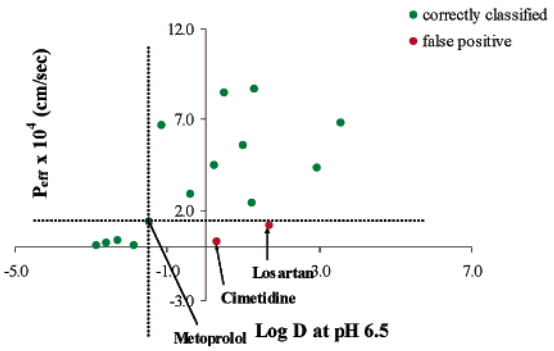

Figure 6. Correlation plot of the human jejunal permeability of 16 drugs with log *D* values at pH 6.5.

The BCS classification of the WHO drugs on the basis of dose number and log *D* was not attempted because of the limited availability of pK_a values from reference sources. Log *P* and CLogP estimates for 104 and 116 of the 123 drugs, respectively, were available and allowed a more comprehensive provisional BCS classification. Log *P* and CLogP values were fairly linearly related ($r^2 = 0.78$) for 104 drugs; however, doxycycline, levothyroxine sodium, and methyldopa appeared to be outliers on this plot (not shown). The linear correlation between log *P* and CLogP improved when these drugs were excluded ($r^2 = 0.85$). The percentages of the drugs in immediate-release dosage forms that were classified as BCS Class 1, Class 2, Class 3, and Class 4 drugs using dose number and log *P* were as follows: 23.6% in Class 1, 17.1% in Class 2, 31.7% in Class 3, and 10.6% in Class 4. The remaining 17.1% of the drugs could not be classified due to the inability to calculate log *P* values because of missing fragments or due to the unavailability of solubility data (two drugs). The corresponding percentages in the various BCS classes with dose number and CLogP criteria were as follows: 28.5% in Class 1, 19.5% in Class 2, 35.0% in Class 3, and 9.8% in Class 4. The remaining 7.3% of the drugs could not be classified since CLogP could not be calculated or due to the unavailability of solubility data (two drugs). Figure 7 shows a comparison plot of the BCS classification of the 123 WHO oral immediate-release drugs based on log *P* and CLogP.

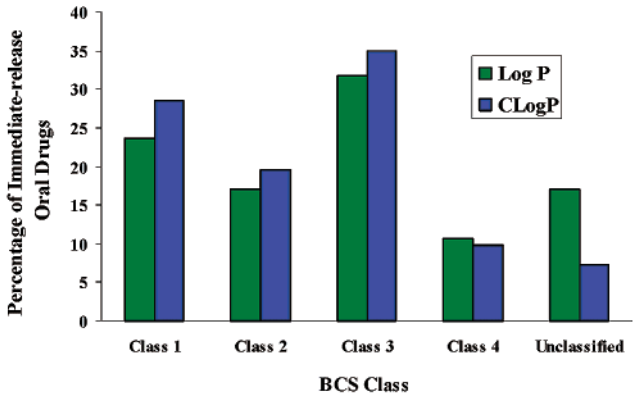

Figure 7. BCS classification of 123 oral drugs in immediate-release dosage forms on the WHO Essential Medicines List.

The 123 oral drugs in immediate-release dosage forms on the WHO list were also provisionally classified into BCS classes using dose numbers calculated using the lowest dose strength of the drug and log *P* or CLogP. The percentages of the drugs in immediate-release dosage forms that were classified as BCS Class 1, Class 2, Class 3, and Class 4 drugs using low dose strength-dose number and log *P* were as follows: 26.0% in Class 1, 14.6% in Class 2, 34.1% in Class 3, and 8.1% in Class 4. The corresponding percentages in the various BCS classes using low dose strength-dose number and CLogP criteria were as follows: 30.9% in Class 1, 17.1% in Class 2, 37.4% in Class 3, and 7.3% in Class 4. (17.1 and 7.3% of the drugs could not be classified due to the unavailability of solubility data or the inability to calculate log *P* and CLogP values, respectively).

Discussion

A compilation of simple molecular properties of 123 orally administered WHO essential drugs and of 141 U.S. top prescribed drugs, formulated as immediate-release dosage forms, is presented in Tables 2 and 3, respectively. Only 43 drugs were found on both lists. This is due to differences in treatment priorities, social acceptance, and awareness between the U.S. and the developing countries. Since the focus of this report is to provide a classification of oral drugs in immediate-release dosage forms contained on the WHO Essential Medicines List, the molecular descriptors listed in Tables 2 and 3 were obtained from reference data sources that are widely used and are easily accessible.

The BCS classification of the WHO medicines was conducted using two criteria. The first, a solubility classification, was based on the calculated dose number. Drugs were categorized as "soluble" if they had a dose number of ≤ 1. The finding that ~67% of the drugs on the WHO list and 68% on the top 200 U.S. list were classified as "high-solubility" drugs suggests that major differences in drug BCS

classification of the two lists are unlikely. The high-solubility classification is likely conservative, considering that conservative estimates of solubility were adopted in this report. A total of 43 drugs on the WHO list and 49 drugs on the U.S. list exhibited a solubility of <0.1 mg/mL. However, a few of these drugs were classified as "soluble" drugs on the basis of dose numbers and may reflect recent trends toward development of highly lipophilic, low-solubility drugs that are quite potent.

Interestingly, the number of drugs that were classified in the USP or Merck Index as practically insoluble was slightly higher on the U.S. list (39 drugs) than on the WHO list (30 drugs). According to the USP, for drugs defined as practically insoluble (pi), the solubility is less than 0.1 mg/mL. However, in this study, a more conservative solubility estimate of 0.01 mg/mL was applied to calculate the dose number of pi drugs. Further literature investigation into the solubility of practically insoluble drugs[22] provided a numerical value for only 19 of the 30 drugs on the WHO list, and only 16 of the 39 pi drugs on the U.S. list. Conflicting literature solubility data were found for drugs such as carbamazepine and nystatin that were on both lists, resulting in highly variable solubility and dose number estimation for these two drugs. A comparison of dose number classification based on literature estimates with those obtained using a conservative value of 0.01 mg/mL indicated agreement for 15 of the remaining 17 drugs on the WHO list and 12 of the 14 drugs on the U.S. list. The exceptions on the WHO list were diazepam and glibenclamide, which exhibited dose numbers greater than 1 when a solubility of 0.01 mg/mL was used as opposed to dose numbers that were less than 1 with literature solubility estimates. Estradiol was the only drug on the U.S. list that was classified as a soluble drug using a 0.01 mg/mL solubility estimate as opposed to one that was insoluble when literature solubility data were used. Thus, the incidence of classifying an "insoluble" drug as one that was "soluble" was exceedingly low (~3%) when dose numbers were calculated with a conservative estimate of 0.01 mg/mL for practically insoluble drugs. This suggests that the adoption of such a solubility value for this class of compounds is conservative.

The second criterion, a permeability classification, was based on correlations of human permeabilities of a set of 29 drugs with estimated log *P* or CLogP values. This set included 14 compounds that are recommended in the FDA Waiver Guidance[1] as reference compounds for permeability. Drugs exhibiting log *P* or CLogP values greater than or equal to the values for metoprolol (1.72 and 1.35, respectively) were categorized as "permeable" drugs. Metoprolol was chosen as the reference compound for permeability since 95% of the drug is known to be absorbed from the gastrointestinal tract.

An examination of Figure 4 indicates that the permeability of drugs such as glucose, L-leucine, phenylalanine, and L-Dopa, absorbed by carrier-mediated mechanisms, would be incorrectly predicted on the basis of log *P* considerations (false negatives). Indeed, these drugs would also be classified as low-permeability drugs on the basis of CLogP correlations as well (Figure 5). Also, in Figure 4, antipyrine and piroxicam would be classified as low-permeability drugs. Thus, although several carrier-mediated high-permeability drugs were classified in log *P* correlation plots as low-permeability drugs, it is noteworthy that predictions for low-permeability drugs were totally accurate.

In contrast, although correlation plots with either CLogP (Figure 5) or log *D* (Figure 6) were nearly as efficient as those with log *P*, they both classified two low-permeability drugs (furosemide and losartan in Figure 5 and cimetidine and losartan in Figure 6) as high-permeability drugs (false positives). It is interesting to note that cimetidine as well as furosemide and losartan[23,24] may be substrates for MDR1 and MRPs. Further, the total number of drugs for which log *D* values could be obtained was relatively low due to (a) the limited availability of pK_a values from reference sources such as the Merck Index and USP DI and (b) the complexity of calculations for drugs that would be multiply ionized or zwitterionic at pH 6.5. Thus, the BCS classification of the WHO drugs based on dose number and log *D* was not attempted since such a classification would have been quite limited. However, log *D*-based correlations could be useful if the pK_a of the test drug or log *D* values are experimentally determined.

Although log *P* correlations appear to be somewhat more reliable than those based on CLogP in classification of the permeability of the reference compounds, as evident from the absence of false positives, either parameter may be useful in permeability classification of oral drugs in immediate-release dosage forms on the WHO Essential Medicines List. Thus, a total of 53 (43.1%) and 62 (50.4%) drugs on the WHO list exhibited log *P* and CLogP estimates, respectively, that were greater than or equal to the corresponding metoprolol value and could be classified as high-permeability drugs on this basis.

Implications for Bioequivalence Regulatory Standards and Product Development. The 123 oral drugs in immediate-release dosage forms in the WHO Essential Medicines List were classified according to BCS on the basis of dose number and log *P* or CLogP criteria. The percentage of drugs that were classified as BCS Class 1 and Class 3 drugs were 23.6 and 31.7% with log *P* and 28.5 and 35.0% with CLogP, respectively (Figure 7). The estimates using CLogP are higher since a greater number of drugs could be classified (114 vs 102). Only 10 (9.8%) of the 102 drugs which were

(22) Yalkowsky, S.; He, Y. *Handbook of Aqueous Solubility Data*; CRC Press: Boca Raton, FL, 2003.

(23) Soldner, A.; Benet, L. Z.; Mutschler, E.; Christians, U. Active transport of the angiotensin-II antagonist losartan and its main metabolite EXP 3174 across MDCK-MDR1 and Caco-2 cell monolayers. *Br. J. Pharmacol.* **2000**, *129*, 1235−1243.

(24) Morsing, P.; Adler, G.; Brandt-Eliasson, U.; Karp, L.; Ohlson, K.; Renberg, L.; Sjöquist, P.-O.; Abrahamson, T. Mechanistic differences of various AT1-receptor blockers in isolated vessels of different origin. *Hypertension* **1999**, *33*, 1406−1413.

classified using both log *P* and CLogP changed classification. Thus, six drugs changed from Class 3 to Class 1, three from Class 4 to Class 2, and one drug from Class 1 to Class 3. It is noted that in the main, the change in classification was to a higher permeability class (with solubility class unchanged), indicating that in these cases log *P* values were underestimated compared to CLogP values. Thus, minimally, bioequivalence testing of more than 55% of the WHO drug products may be based on a suitable *in vitro* dissolution test procedure. On the basis of solubility alone, 67% of the drugs were high-solubility drugs, representing the potential number of drugs that may be eligible for *in vitro* BE testing and biowaivers. The difference between the two percentages (55 vs 67%) can be attributed to the inability to obtain permeability estimates.

In summary, provisional BCS classification of the drugs contained on the WHO Essential Medicines List suggests that the majority of the drug products contained on the WHO list are candidates for waiver of *in vivo* bioequivalence testing based on an *in vitro* dissolution test "biowaiver". According to the FDA Guidance[1] for biowaivers, the test product should dissolve ≥85% in ≤30 min by the USP I (basket) dissolution test at 100 rpm or the USP II (paddle) dissolution test at 50 rpm in ≤900 mL of 0.1 N HCl, pH 4.5, and pH 6.8 buffers and should meet the f2 criteria of ≥50. For very rapid dissolution, 85% in ≤15 min, f2 criteria are not required. The impact of waiver of *in vivo* bioequivalence (BE) testing and its replacement with rapid and affordable dissolution standards in developing countries is expected to be profoundly significant. The replacement of expensive *in vivo* testing standards with a simpler, more easily implemented, routinely monitored, and more reliable dissolution test would ensure clinical performance of marketed products worldwide.

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