Pharmaceutical Research, Vol. 23, No. 10, October 2006 (© 2006)
DOI: 10.1007/s11095-006-9000-y

Research Paper

A 'Rule of Unity' for Human Intestinal Absorption

S. H. Yalkowsky,[1,2] J. L. H. Johnson,[1] T. Sanghvi,[1] and S. G. Machatha[1]

Received October 31, 2005; accepted March 6, 2006; published online August 24, 2006

Abstract. The ability to predict the passive intestinal absorption of organic compounds can be a valuable tool in drug design. Although Lipinski's 'rule of 5' is commonly used for this purpose, it does not routinely give reliable results. An alternative 'rule of unity' is proposed to predict the absorption efficiency of orally administered drugs that are passively transported. The rule of unity based upon the theoretical principals that govern passive transport. The 'rule of 5' and the 'rule of unity' are compared using experimentally determined passive human intestinal absorption data for 155 drugs. Absorption values which are >50% of the dose are classified as well absorbed and absorption values which are ≤50% of the dose are classified as classified as poorly absorbed. Comparison of the two models using a receiver operating characteristic (ROC) plot and McNemar's test reveal striking differences in absorption predictability. The 'rule of 5' gives twice as many false predictions than the 'rule of unity.'

KEY WORDS: absorption; passive transportation; "rule of 5"; "rule of unity"; solubility.

INTRODUCTION

It is generally recognized that poor passive transport across the membranes of the gastrointestinal tract is a major determinant of the low oral bioavailability. Numerous models have been proposed to estimate oral absorption; including those of Dressman *et al.* (1) and Balon *et al.* (2). Johnson and Swindell (3) introduced the concept of maximum absorbable dose (MAD), which is the quantity of drug that could be absorbed if the small intestine could be saturated for 4.5 h. They showed that the sensitivity of absorption to particle size decreased with increasing dose or solubility. Curatolo (4), addressed the different approaches that have been employed to estimate drug absorption and the different stages a drug goes through before clinical development.

Recently, Sanghvi *et al.* (5) developed a new absorption parameter Π which can predict whether or not a drug will be well absorbed (i.e., at least half of the administered drug is absorbed). Using the absorption model described by Stehle and Higuchi (6), Flynn and Yalkowsky (7) and Yalkowsky and Flynn (8), they defined the absorption parameter as the drug's octanol–water partition coefficient, K_{ow}, divided by its luminal over-saturation number, i.e.,

$$\Pi = \frac{K_{ow}}{O_{Lumen}} \tag{1}$$

The luminal over-saturation number is defined as the maximum of either unity or the dose in grams per 0.250 l of water divided by the aqueous solubility, S_w, of the drug in grams per liter, i.e.,

$$O_{Lumen} = \max\left(1, \frac{Dose/0.250}{S_w}\right) = \max\left(1, \frac{4Dose}{S_w}\right) \tag{2}$$

The luminal over-saturation number is a dimensionless number which cannot be less than unity and which distinguishes between drugs that are soluble in the gastrointestinal contents from drugs that are not. The former will dissolve readily whereas the latter will exist as suspensions that will maintain a saturated solution in the gut until sufficient absorption has taken place so that no suspended particles remain.

If the solubility of a drug is not known it is calculated from its melting point, MP, and its partition coefficient by the General Solubility Equation of Yalkowsky (9) which was modified by Jain and Yalkowsky (10) to be

$$\log S_w = 0.5 - \log K_{ow} - 0.01(MP - 25) \tag{3}$$

Combining Eqs. (1), (2), and (3) gives

$$\Pi = \frac{K_{ow}}{\max\left(1, \frac{4Dose}{MW^* 10^{[0.5-0.01(MP-25)-\log K_{ow}]}}\right)} \tag{4}$$

which expresses the absorption parameter as a function of the melting point and partition coefficient of the drug.

If the drug is a weak electrolyte the partition coefficient and melting point of the unionized form should be used. It is not necessary to know either the pK_a of the drug or the pH of the GI tract. Ni *et al.* (11) has shown that the product of solubility and distribution coefficient at any pH is identical to

[1] Pharmaceutical Science, University of Arizona, 1703 E. Mabel St., Tucson, Arizona 85721, USA.
[2] To whom correspondence should be addressed. (e-mail: yalkowsky@pharmacy.arizona.edu)

Table I. Physical Properties, Dose and Fraction Absorbed

Name	MP (°C)	log K_{ow}	Dose (mg)	FA	log S_w	log O_{Lumen}	Rule of 5	log Π
Acebutolol	121	1.70	300	0.8	−2.16	0.00	0.00	1.70
Acetaminophen	170	0.49	700	0.8	−1.44	0.00	0.00	0.49
Acrivastine	222	1.48	6	0.88	−2.95	0.00	0.00	1.48
Acyclovir	257	−2.07	200	0.23	0.25	0.00	0.00	−2.07
Adefovir	283	−1.99	210	0.16	−0.09	0.00	1.00	−1.99
Alendronate	234	−5.64	5	0.01	4.05	0.00	1.00	−5.64
Alprazolam	228	2.19	1	0.9	−3.72	0.00	0.00	2.19
Alprenolol	58	2.65	100	0.93	−2.48	0.00	0.00	2.65
Amikacin	201	−4.12	400	0	2.86	0.00	3.00	−4.12
Amiloride	241	−0.69	20	0.5	−0.97	0.00	1.00	−0.69
Aminopyrine	135	0.57	250	1	−1.17	0.00	0.00	0.57
Amphetamine	25	1.74	20	0.9	−1.24	0.00	0.00	1.74
Amphotericin B	170	−3.65	3500	0.03	2.7	0.00	3.00	−3.65
Antipyrine	112	0.2	700	0.97	−0.57	0.00	0.00	0.20
Atropine	115	1.32	2	0.98	−1.72	0.00	0.00	1.32
Betaxolol	71	2.32	8.93	0.9	−2.28	0.00	0.00	2.32
Bromazepam	238	1.69	3	0.84	−3.32	0.00	0.00	1.69
Bumetanide	231	3.35	1.5	0.96	−4.91	0.13	0.00	3.22
Bupropion	25	3.43	86.9	0.87	−2.93	0.09	0.00	3.34
Camazepam	174	3.64	20	1	−4.63	0.96	0.00	2.68
Capreomycin	254	−5.11	100	0.5	3.32	0.00	3.00	−5.11
Carbamazepine	190	1.98	200	0.7	−3.13	0.66	0.00	1.32
Cefamandole nafate	[a]	0.31	2000	0	−3.43	1.67	1.00	−1.36
Ceforanide	150	−3.15	1000	0	2.4	0.00	3.00	−3.15
Ceftizoxime	227	0.95	500	0.72	−2.47	0.19	1.00	0.76
Chloramphenicol	151	1.28	250	0.9	−2.04	0.00	0.00	1.28
Chlorothiazide	342	−0.31	125	0.49	−2.36	0.00	0.00	−0.31
Cidofovir	260	−2.43	700	0.03	0.58	0.00	1.00	−2.43
Cimetidine	142	0.35	200	0.64	−1.02	0.00	0.00	0.35
Cisapride	109	3.65	12.5	1	−3.99	0.02	0.00	3.63
Clofibrate	25	4.12	1500	0.97	−3.62	2.01	0.00	2.11
Clonidine	130	1.41	0.3	0.95	−1.96	0.00	0.00	1.41
Codeine	158	0.98	70	0.95	−1.81	0.00	0.00	0.98
Cymarin	148	0.72	3	0.47	−1.45	0.00	1.00	0.72
Cyproterone acetate	203	3.54	25	1	−4.82	1.20	0.00	2.34
Cytarabine	213	−2.24	50	0.2	0.86	0.00	1.00	−2.24
Desipramine	212	4.47	150	1	−5.84	3.19	0.00	1.28
Dexamethasone	262	1.75	1.5	0.8	−3.62	0.00	0.00	1.75
Diazepam	132	3.16	15	1	−3.73	0.05	0.00	3.11
Diclofenac	157	4.32	50	1	−5.14	1.97	0.00	2.35
Dihydrocodeine	112	1.26	60	0.89	−1.63	0.00	0.00	1.26
Diltiazem	188	3.65	60	0.92	−4.78	1.54	0.00	2.11
Disulfiram	71	3.88	250	0.97	−3.84	1.37	0.00	2.51
Doxorubicin	230	−0.5	55	0.12	−1.05	0.00	3.00	−0.50
Ethambutol	88	0.12	1400	0.8	−0.25	0.00	0.00	0.12
Ethinylestradiol	181	3.86	30	1	−4.92	1.53	0.00	2.33
Famciclovir	103	−0.03	312.5	0.77	−0.25	0.00	0.00	−0.03
Famotidine	164	0.26	20	0.38	−1.15	0.00	1.00	0.26
Felbamate	152	0.5	650	0.9	−1.27	0.00	0.00	0.50
Felodipine	145	5.58	27.5	0.88	−6.28	2.74	1.00	2.84
Fenclofenac	135	4.71	400	1	−5.31	3.04	0.00	1.67
Flecainide	104	4.64	100	0.81	−4.93	1.92	0.00	2.72
Fluconazole	139	0.47	100	0.95	−1.11	0.00	0.00	0.47
Flumazenil	202	1.08	200	0.95	−2.35	0.00	0.00	1.08
Fluoxetine	158	4.57	30	0.8	−5.4	1.99	0.00	2.58
Fluvastatin	111	4.05	6	1	−4.41	0.18	0.00	3.87
Furosemide	265	1.87	40	0.61	−3.77	0.46	0.00	1.41
Gallopamil	25	4.1	25	1	−3.6	0.00	0.00	4.10
Ganciclovir	250	−2.65	75	0.03	0.9	0.00	1.00	−2.65
Gentamicin	97	−3.77	420	0	3.55	0.00	2.00	−3.77
Glyburide	170	4.23	3.13	1	−5.18	0.72	0.00	3.51
Guanabenz	228	2.96	24	0.8	−4.49	1.11	0.00	1.85
Guanoxan	165	0.55	7.5	0.5	−1.45	0.00	0.00	0.55

Table I. (continued)

Name	MP (°C)	log K_{ow}	Dose (mg)	FA	log S_w	log O_{Lumen}	Rule of 5	log Π
Hydrocortisone	213	1.7	200	0.91	−3.08	0.42	0.00	1.28
Ibuprofen	76	3.68	400	0.95	−3.69	1.58	0.00	2.10
Imipramine	172	5.04	50	1	−6.01	2.86	1.00	2.18
Indomethacin	155	4.18	50	1	−4.98	1.73	0.00	2.45
Iothalamate sodium	285	1.42	800	0.02	−3.52	1.24	1.00	0.18
Isoxicam	260	1.59	200	1	−3.44	0.82	0.00	0.77
Isradipine	169	4.2	12.5	0.92	−5.14	1.27	1.00	2.93
Kanamycin	180	−3.88	4000	0.01	2.83	0.00	2.00	−3.88
Ketoprofen	94	2.76	112.5	0.92	−2.95	0.20	0.00	2.56
Ketorolac	161	1.62	10	0.9	−2.48	0.00	0.00	1.62
Labetalol	188	2.5	600	0.95	−3.63	1.49	1.00	1.01
Lactulose	169	−3.59	4685.4	0.01	2.65	0.00	2.00	−3.59
Lamotrigine	179	2.19	127.5	0.98	−3.23	0.53	0.00	1.66
Lansoprazole	169	3.07	30	0.85	−4.01	0.52	0.00	2.55
Levonorgestrel	240	3.31	0.15	1	−4.96	0.00	0.00	3.31
Lormetazepam	206	2.6	2	1	−3.91	0.00	0.00	2.60
Lornoxicam	228	2.33	4	1	−3.86	0.00	0.00	2.33
Meloxicam	255	2.28	30	0.9	−4.08	0.61	0.00	1.67
Metaproterenol	100	0.09	1.6	0.44	−0.34	0.00	0.00	0.09
Methadone	101	4.17	20	0.8	−4.43	0.84	0.00	3.33
Methylprednisolone	233	1.7	42	0.82	−3.28	0.00	0.00	1.70
Metolazone	253	2.42	2.5	0.64	−4.2	0.00	0.00	2.42
Metoprolol	35	1.35	300	0.95	−0.95	0.00	0.00	1.35
Mifobate	82	0.69	500	0.82	−0.76	0.00	0.00	0.69
Minoxidil	248	0.48	20	0.98	−2.21	0.00	0.00	0.48
Moxonidine	218	1.42	0.2	0.88	−2.85	0.00	0.00	1.42
Nadolol	130	0.38	80	0.57	−0.93	0.00	0.00	0.38
Naltrexone	169	0.36	100	0.96	−1.3	0.00	0.00	0.36
Naproxen	153	2.82	250	0.99	−3.6	1.24	0.00	1.58
Nefazodone	84	5.56	100	1	−5.65	2.58	1.00	2.98
Netivudine	243	−1.42	200	0.28	−0.26	0.00	0.00	−1.42
Nicotine	25	0.9	15	1	−0.4	0.00	0.00	0.90
Nisoldipine	153	4.86	15	0.9	−5.64	1.83	0.00	3.03
Nitrendipine	158	4.02	20	0.88	−4.85	1.20	0.00	2.82
Nordiazepam	216	3.01	10	0.99	−4.42	0.59	0.00	2.42
Norfloxacin	221	−0.99	400	0.35	−0.47	0.00	0.00	−0.99
Olanzapine	195	4.02	10	0.75	−5.22	1.33	0.00	2.69
Olsalazine	300	4.5	2500	0.24	−6.75	5.27	0.00	−0.77
Omeprazole	156	2.53	20	0.8	−3.34	0.00	0.00	2.53
Ondansetron	232	2.72	8	1	−4.29	0.33	0.00	2.39
Ouabain	200	−0.35	8	0.01	−0.9	0.00	3.00	−0.35
Oxatomide	154	5.64	60	1	−6.43	3.18	1.00	2.46
Oxazepam	198	2.29	15	0.89	−3.52	0.00	0.00	2.29
Oxprenolol	79	2.09	160	0.95	−2.13	0.00	0.00	2.09
Phenoxymethylpenicillin	124	1.94	22	0.59	−2.43	0.00	0.00	1.94
Phenytoin	286	2.08	400	0.9	−4.19	1.99	1.00	0.09
Pindolol	172	1.67	5	0.87	−2.64	0.00	0.00	1.67
Piroxicam	199	1.89	20	1	−3.13	0.00	0.00	1.89
Piroximone	265	0.96	56	0.81	−2.86	0.00	0.00	0.96
Practolol	135	0.75	312.5	0.95	−1.35	0.00	0.00	0.75
Praziquantel	134	3.36	1960	1	−3.95	2.35	0.00	1.01
Prazosin	279	1.1	1	0.86	−3.14	0.00	0.00	1.10
Prednisolone	235	1.38	30	0.99	−2.98	0.00	0.00	1.38
Progesterone	129	3.77	1.7	1	−4.31	0.00	0.00	3.77
Propranolol	95	2.75	300	0.99	−2.95	0.62	0.00	2.13
Quinidine	174	2.79	330	0.81	−3.78	1.39	0.00	1.40
Raffinose	80	−7.96	8000	0	7.91	0.00	3.00	−7.96
Ranitidine	70	0.63	60	0.64	−0.58	0.00	0.00	0.63
Rimiterol	204	0.57	10	0.48	−1.86	0.00	0.00	0.57
Saccharin	228	0.72	2000	0.88	−2.25	0.89	0.00	−0.17
Scopolamine	59	0.3	0.5	0.95	−0.14	0.00	0.00	0.30
Sotalol	207	0.23	240	0.95	−1.55	0.00	0.00	0.23
Spironolactone	135	2.25	125	0.73	−2.85	0.00	0.00	2.25

Table I. (continued)

Name	MP (°C)	log K_{ow}	Dose (mg)	FA	log S_w	log O_{Lumen}	Rule of 5	log Π
Sulindac	185	3.16	200	0.9	−4.26	1.61	0.00	1.55
Sulpiride	179	1.11	200	0.44	−2.15	0.00	0.00	1.11
Sultopride	185	1.93	75	0.89	−3.03	0.00	0.00	1.93
Sumatriptan	170	0.74	200	0.57	−1.69	0.00	0.00	0.74
Telmisartan	262	7.46	40	0.9	−9.33	5.82	2.00	1.64
Tenidap	230	1.94	120	0.89	−3.49	0.66	0.00	1.28
Tenoxicam	211	1.61	55	1	−2.97	0.00	0.00	1.61
Terazosin	273	1.02	7.5	0.9	−3	0.00	0.00	1.02
Terbutaline	121	0.48	5	0.62	−0.94	0.00	0.00	0.48
Timolol	72	1.53	30	0.95	−1.5	0.00	0.00	1.53
Tobramycin	173	−3.44	70	0	2.46	0.00	2.00	−3.44
Tolbutamide	129	2.5	500	0.85	−3.04	0.91	0.00	1.59
Tolmesoxide	93	1.09	300	0.98	−1.27	0.00	0.00	1.09
Topiramate	126	0.04	650	0.86	−0.55	0.00	0.00	0.04
Torasemide	163	2.34	10	0.96	−3.22	0.00	0.00	2.34
Toremifene	109	6.53	120	1	−6.87	3.94	1.00	2.59
Tramadol	25	3.1	75	0.9	−2.6	0.00	0.00	3.10
Trapidil	103	2.21	200	0.96	−2.49	0.08	0.00	2.13
Trimethoprim	201	0.88	2	0.97	−2.14	0.00	0.00	0.88
Urapidil	157	1.76	60	0.78	−2.58	0.00	0.00	1.76
Valproicacid	25	2.98	600	1	−2.48	0.70	0.00	2.28
Valsartan	117	5.04	200	0.55	−5.46	2.72	1.00	2.32
Venlafaxine	103	3.27	50	0.97	−3.55	0.41	0.00	2.86
Verapamil	25	4.47	120	1	−3.97	0.99	0.00	3.48
Viloxazine	185	1.76	200	0.98	−2.86	0.39	0.00	1.37
Warfarin	161	2.89	5	0.98	−3.75	0.00	0.00	2.89
Ximoprofen	178	2.33	30	0.98	−3.36	0.02	0.00	2.31
Xipamide	256	1.89	20	0.7	−3.7	0.05	0.00	1.84
Zopiclone	*178*	*1.17*	*8*	*0.8*	−2.2	0.00	0.00	1.17

[a] Experimental solubility value is used as melting point is not available.

the product of the intrinsic solubility and partition coefficient. For example

$$S_w\text{pH7.4} \times K_D\text{pH7.4} = S_w\text{int} \times K_{ow} \quad (5)$$

Therefore, the pK_a of the drug and the pH of the GI tract do not need to be known for suspensions. Furthermore, it is not necessary to distinguish/know the pH in the gut lumen, the gut wall, or the microenvironment of the drug particles. Equation (5) is applicable only when the dose divided by the lumen volume is significantly greater than the intrinsic solubility. This relationship assumes that ion pair partitioning and common ion effects are not significant in the GI tract.

In order to validate the above parameter Sanghvi *et al.* (5) collected literature data for human intestinal absorption for 132 compounds. From these they eliminated drugs which are known to be subject to first pass metabolism and drugs known to be subject to gastrointestinal metabolism, degra-

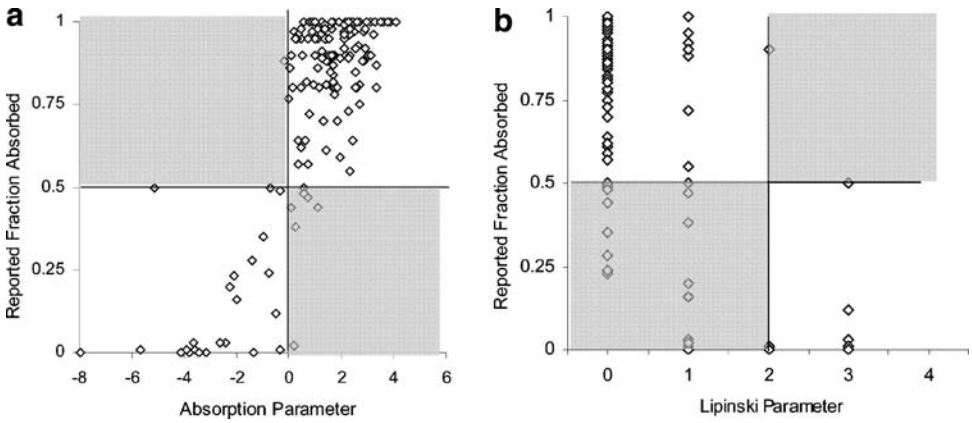

Fig. 1. Relationship of the reported fraction absorbed in humans to (a) the absorption parameter, Π, (b) the Lipinski parameter based on the 'rule of 5.' The *shaded areas* in both plots represent false overpredictions and underpredictions.

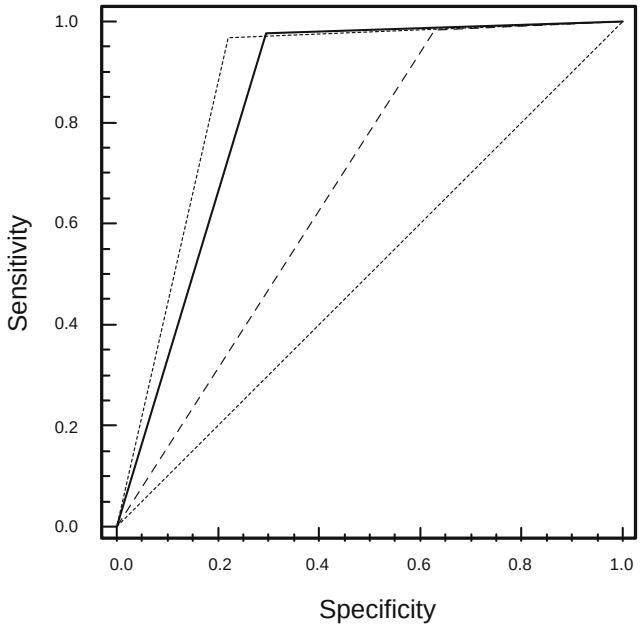

Fig. 2. Comparison of models using ROC curves. Using Log K_{ow} (——). 'rule of unity'(----) and 'the rule of 5' model (– –).

dation, active transport, or paracellular transport. In doing this they created a dataset of 97 drugs which are passively absorbed from the human intestinal tract.

Using this dataset they showed that drugs with an absorption parameter of greater than unity tend to be well absorbed (i.e., fraction absorbed, FA > 0.5) and that drugs with Π values of less than or equal to one are poorly absorbed (FA ≤ 0.5). Thus, absorption is most efficient when the absorption parameter, Π, is greater than unity. This most often occurs when the partition coefficient is greater than unity and/or the over-saturation number is equal to unity. Hence, the 'rule of unity.'

Recently, Waterbeemd *et al.* (12) and Zmuidinavicius *et al.* (13) showed that since its introduction by Lipinski (14) the 'rule of 5' has become accepted by medicinal chemists as a useful guideline for the design of drugs that will be efficiently transported from the gastrointestinal tract to the blood. The 'rule of 5' states that if two or more of the following criteria are met the drug will likely be poorly absorbed:

1. Molecular weight >500
2. log K_{ow} >5
3. Number of hydrogen bond donors per molecule >5
4. Number of hydrogen bond acceptors per molecule >10

The 'rule of 5' is named for the fact that each of the four limiting values is a multiple of 5. The rule is based upon inspection of the properties of compounds that have survived to enter phase II efficacy studies. In this note, the abilities of the 'rule of 5' and the 'rule of unity' to predict passive human intestinal absorption efficiency will be compared. No consideration is given to intrinsic biological activity.

EXPERIMENTAL

Data

Experimental melting point, dose and fraction absorbed data were taken from the literature as described by Sanghvi *et al.* (5) and Zhao *et al.* (15) From these they eliminated drugs which are known to be subject to first pass metabolism and drugs known to be subject to gastrointestinal metabolism, degradation, active transport, or paracellular transport.

Partition coefficients were calculated with the aid of CLOGP software.

Solubilities, oversaturation numbers, and Π values were calculated from Eqs. (3), (2), and (4), respectively.

Analysis

In order to compare the 'rule of 5' and the 'rule of unity' on equal ground, both predictive methods were tested for their ability to predict whether each of the 155 drugs would be well absorbed on a qualitative, "yes or no," basis. Experimental data were qualitatively separated according to the cut-off value of FA = 0.5.

The receiver operating characteristic (ROC) curve is a plot of all possible sensitivity (fraction of true positive predictions) *versus* specificity (fraction of true negative predictions) combinations for the model in question. MedCalc (16) software was used to create a ROC plot for each predictive model to obtain measures of overall model accuracy. McNemar's tests (17) were used to determine the significance of the differences between the experimental outcomes and the predictions of the 'rule of unity' and the 'rule of 5' methods.

RESULTS

The values of the properties of the 155 drugs considered are given in Table I.

Figure 1a and b show plots of the reported fraction absorbed following oral administration of the 155 drugs against the absorption parameter and the Lipinski parameters, respectively. They are essentially graphical representations of

Table II. Statistical Evaluation of the Models (14)

Model	ROC AUC	Sensitivity	Specificity	*p* values[a] of differences from experimental data
Perfect model	1.0	1.0	1.0	
'Rule of 5'	0.68	0.98	0.37	0.005 (Significant)[b]
'Rule of unity'	0.87	0.97	0.78	0.289 (Not significant)[b]
Log K_{ow}	0.84	0.98	0.70	0.039 (Significant)[b]
No relationship	0.5	0.5	0.50	

[a] *p* values calculated using McNemar's tests.
[b] Level of significance <0.05.

contingency tables. They show the accuracy of each model's dichotomous prediction against that of the reported fraction absorbed. In both cases the shaded areas represent false predictions.

From Fig. 1, it is clear that absorption parameter is a more accurate predictor of absorption efficiency than the Lipinski parameter. The absorption parameter is equal to K_{ow} when there is no significant positive difference between the dose/lumenal volume ratio and the intrinsic solubility. Thus, would not warrant the use of the oversaturation term described in Eq. (3).

Figure 2 shows the ROC curves for both methods of predicting absorption and also using just the log K_{ow}. The solid line represents the 'rule of unity' model and the dotted lines represent the 'rule of 5' model and log K_{ow}. For comparison, the diagonal line from lower left to upper right represents no relationship between the model and its intended measurement and has an AUC of 0.5.

An AUC of 1.0 (sensitivity = 1.0 and specificity = 1.0) indicates perfect prediction. All statistical comparisons are summarized in Table II. The AUC obtained using either the, 'rule of unity' or log K_{ow} is significantly greater than that obtained with the 'rule of 5.' Although the sensitivities are comparable the specificity is much greater with the 'Rule of unity' and log K_{ow} is much greater than with that of the 'rule of 5.'

Furthermore, McNemar's tests show that the predictions with both the 'rule of 5' and log K_{ow} are significantly different from the experimental results, while the predictions with the 'rule of unity' are not.

The total number of false positive and false negative predictions obtained by both rules using a cut off value of FA = 0.5 to distinguish well absorbed from poorly absorbed drugs are 16 for the 'rule of 5' and 8 for the 'rule of unity,' respectively. Using, the 'rule of 5' gives twice as many false predictions than the 'rule of unity.'

DISCUSSION

The ROC curve is the standard tool for evaluating models which predict dichotomous or "yes/no" outcomes (17). In general, the AUC of a ROC curve is a measure of the overall model accuracy and comparison of ROC AUCs is commonly used in selecting the best model (18,19). The ROC curve provides an overview of the model by plotting the specificity (x-axis) and sensitivity (y-axis) combination for each possible cut-off value in the model. The greater ROC plot AUC obtained with the 'rule of unity' indicates that it is more accurate than the 'rule of 5.' Because sensitivity measurements are similar for the two models, the strength of using the 'rule of unity' lies in its specificity of 0.79 which is significantly greater than that of the 'rule of 5.'

McNemar's test was chosen because all predictions and experimental determinations for whether or not a compound will be well absorbed are binomial (20). In addition, the three data sets (reported fraction absorbed, the 'rule of unity' and the 'rule of 5') are matched in that they each contain observations of the same set of compounds. The fact that using the 'rule of unity' does not give significantly different observations from the experimentally determined outcomes ($p = 0.29$) but the 'rule of 5' does ($p = 0.005$) indicates that the former predictive method is more accurate.

Both the 'rule of 5' and the 'rule of unity' are largely dependent on the octanol–water partition coefficient of the drug. For efficient absorption the 'rule of 5' requires that log K_{ow} be less than 5.0, whereas the 'rule of unity' suggests that it be greater than 1.0.

The remaining parameters of the 'rule of 5' are molecular weight and two simple atom counts. Thus it has the advantage of not requiring any physical measurement of the drug. This makes it ideal for drug design. However, because it is empirical and because it is based on data that may not always reflect passive absorption, its applicability to human intestinal absorption is uncertain.

The 'rule of unity' has the advantage of being based on well accepted diffusion theory and a recently demonstrated relationship between partition coefficient and distribution coefficient (8). This applies to drugs that do not exist as suspensions in the GI tract. In addition, it is validated on passive human intestinal absorption data. However, either the melting point of the drug or its water solubility is required to calculate Π for drugs that are not completely soluble in the GI lumen.

Another reason for the discrepancy between the two models is the fact that they are based on different types of data. The 'rule of unity' is based on human intestinal absorption data whereas the 'rule of 5' is based on compounds that have cleared phase I clinical studies and have entered into phase II efficacy studies. Clearing phase I studies is not entirely due to satisfactory intestinal transport. Drugs that are poorly absorbed but effective and not toxic at very low blood levels are likely to be selected for further study. Similarly well absorbed drugs that are toxic will likely be discarded early.

CONCLUSION

The superiority of the 'rule of unity' in predicting absorption efficiency is the result of several differences between the approaches. The 'rule of 5' is an empirical relationship designed on the history of acceptance of drugs into phase II efficacy studies whereas the 'rule of unity' is a theoretically based semi-empirical relationship applied to passive human absorption data. While the former has proven to be a useful predictor of the ability of a drug to clear phase I, the latter is shown to be a better indicator of the absorption of orally administered drugs.

REFERENCES

1. J. B. Dressman, G. L. Amidon, and D. Fleisher. Absorption potential: estimating the fraction absorbed for orally administered compounds. *J. Pharm. Sci.* **4**(5):588–589 (1985).
2. K. Balon, B. U. Riebesehl, and B. W. Muller. Drug liposome partitioning as a tool for the prediction of human passive intestinal absorption. *Pharm. Res.* 882–888 (1999).
3. K. C. Johnson and A. C. Swindell. Guidance in the setting of drug particle size specifications to minimize variability in absorption. *Pharm. Res.* **13**:1795–1798 (1996).
4. W. Curatolo. Physical chemical properties of oral drug candidates in the discovery and exploratory development settings. *Pharm. Sci. Tech. Today* **1**:387–393 (1998).

5. T. Sanghvi, N. Ni, M. Mayersohn, and S. H. Yalkowsky. Predicting passive intestinal absorption using a single absorption parameter. *QSAR* **22**:247–257 (2003).
6. R. G. Stehle and W. I. Higuchi. Diffusional model for transport rate studies across membranes. *J. Pharm. Sci.* **56**:1367–1368 (1967).
7. G. L. Flynn and S. H. Yalkowsky. Correlation and prediction of mass transport across membranes. I. Influence of alkyl chain length on flux determining properties of barrier and diffusant. *J. Pharm. Sci.* **61**:838–852 (1972).
8. S. H. Yalkowsky, G. L. Flynn, and T. G. Slunick. Importance of chain length on physicochemical and crystalline properties of organic homologs. *J. Pharm. Sci.* **61**:852–857 (1972).
9. S. H. Yalkowsky. *Solubility and Solubilization in Aqueous Media*, Oxford University Press, New York, New York, p. 67 1999.
10. N. Jain and S. H. Yalkowsky. Estimation of the aqueous solubility. I. Application to organic nonelectrolytes. *J. Pharm. Sci.* **90**:234–252 (2001).
11. N. Ni, T. Sanghvi, and S. H. Yalkowsky. Independence of the product of solubility and distribution coefficient on pH. *Pharm. Res.* **19**:1864–1868 (2002).
12. H. Van de Waterbeemd, D. A. Smith, K. Beaumont, and D. K. Walker. Property-based design: optimization of drug absorption and pharmacokinetics. *J. Med. Chem.* **44**:1313–1333 (2001).
13. D. Zmuidinavicius, R. Didziapetris, P. Japertas, A. Avdeef, and A. Petrauskas. Classification structure-activity relations (C-SAR) in prediction of human intestinal absorption. *J. Pharm. Sci.* **92**:621–633 (2003).
14. C. A. Lipinski, L. Franco, B. W. Dominy, and P. J. Feeney. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **23**:3–25 (1997).
15. Zhao, J. Le, M. H. Abraham, A. Hersey, P. J. Eddershaw, C. N. Luscombe, D. Boutina, G. Beck, B. Bherborne, I. Cooper, and J. A. Platts. Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure activity relationship (QSAR) with the Abraham descriptors. *J. Pharm. Sci.* **90**:749–784 (2001).
16. MedCalc Statistical Software, version 6.16, Broekstraat 52, 9030 Mariakerke, Belgium. www.medcalc.com.
17. P. F. Griner, R. J. Mayewski, A. I. Mushlin, and P. Greenland. Selection and interpretation of diagnostic tests and procedures. *Ann. Inter. Med.* **94**:553–600 (1981).
18. J. A. Hanley and B. J. McNeil. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Diagn. Radiol.* **143**:29–36 (1982).
19. M. H. Zweig and G. Campbell. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin. Chem.* **39**:561–577 (1993).
20. M. Pagano and K. Gauvreau. *Principles of Biostatistics*, Duxbury, Belmont, California, 1993. pp. 349–352.