

# Evaluation of Human Intestinal Absorption Data and Subsequent Derivation of a Quantitative Structure–Activity Relationship (QSAR) with the Abraham Descriptors

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Received 19 July 2000; revised 8 November 2000; accepted 16 November 2000

**ABSTRACT:** The human intestinal absorption of 241 drugs was evaluated. Three main methods were used to determine the human intestinal absorption: bioavailability, percentage of urinary excretion of drug-related material following oral administration, and the ratio of cumulative urinary excretion of drug-related material following oral and intravenous administration. The general solvation equation developed by Abraham's group was used to model the human intestinal absorption data of 169 drugs we considered to have reliable data. The model contains five Abraham descriptors calculated by the ABSOLV program. The results show that Abraham descriptors can successfully predict human intestinal absorption if the human absorption data is carefully classified based on solubility and administration dose to humans. © 2001 Wiley-Liss, Inc. and the American Pharmaceutical Association *J Pharm Sci* 90:749–784, 2001

**Keywords:** intestinal absorption; QSAR; solvation equation; solubility

## INTRODUCTION

The prediction of human intestinal absorption is a major goal in the design, optimization, and selection of candidates for the development of oral drugs. The focus of modern drug discovery is now not simply on the pharmacological activity, but also on seeking favorable absorption, distribution, metabolism, and excretion properties.<sup>1–4</sup> The growth in drug discovery of combinatorial chemistry methods, where large numbers of candidate compounds are synthesized and screened in parallel for *in vitro* pharmacological activity, has

dramatically increased the demand for rapid and efficient models for estimating human intestinal absorption. Although cell membrane methods<sup>5–7</sup> and *in vivo* animal studies<sup>8</sup> have been used instead of human intestinal absorption methods, these techniques are still costly and labor intensive.

Quantitative structure–activity relationships (QSARs) are mathematical models that statistically relate the biological activity of a compound to its physicochemical properties. Several recent studies have shown their importance to the prediction of human intestinal absorption.<sup>9–14</sup> The so-called “rule of 5” has proved very popular as a rapid screen for compounds that are likely to be poorly absorbed.<sup>9,15</sup> This rule states that if a compound satisfies any two of the following rules, it is likely to exhibit poor intestinal absorption: (1) molecular weight > 500, (2) number of hydrogen

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*Journal of Pharmaceutical Sciences*, Vol. 90, 749–784 (2001)  
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bond donors  $> 5$  (a donor being any O-H or N-H group), (3) number of hydrogen acceptors  $> 10$  (an acceptor being any O or N including those in donor groups), and (4)  $C \log P > 5.0$  or  $M \log P > 4.15$ .

Palm and Clark<sup>9,11,16</sup> recently developed a theoretical method, based on the determination of dynamic surface properties—polar molecular surface area (PSA), to predict the human intestinal absorption. An excellent sigmoidal relationship was established between the absorbed fraction after oral administration to humans and PSA for 20 drugs ( $r^2 = 0.94$ ). Drugs that are completely absorbed ( $> 90\%$ ) had a  $PSA \leq 60 \text{ \AA}^2$ , whereas drugs that are  $< 10\%$  absorbed had a  $PSA \geq 104 \text{ \AA}^2$ . However, the prediction for a large set (74 drugs) was not as good.<sup>9</sup> Wessel et al.<sup>10</sup> used a neural network to find the six independent calculated molecular structure descriptors that best described human absorption for a training set consisting of 67 structurally different drug and drug-like compounds. The network was fed with  $> 100$  topological, electronic, and geometric descriptors and binary strings indicating the presence or absence of substructure features or fragments. In addition to percent absorption data, other human absorption data in the form of permeability coefficients is available from the Lennernas group using his LOC-1-GUT technique.<sup>17</sup>

The largest data set of compounds yet analyzed is that of Wessel et al.<sup>10</sup> who constructed a set of 86 compounds. However, there was potentially much more data available. The first aim of the present work was to collect data from the literature and, unlike previous work,<sup>9,10</sup> to assess the data to obtain a much larger data set that could be analyzed with some confidence. The second aim was to construct a QSAR for human intestinal absorption that could be used as a rapid screening method for candidate drugs.

## MATERIALS AND METHODS

### Human Intestinal Absorption Data

The names of drug and drug-like compounds and related data are listed in Table 1 and 2. The absorption data was collected and evaluated from 244 papers.<sup>1-5,8-12,18-251</sup> The following information concerning human drug absorption was recorded from the literature:

- absorption data given from the literature;
- oral bioavailability or absolute bioavailability;

- percentage of cumulative urinary excretion of unchanged drug and its metabolites following oral and intravenous administration;
- percentage of metabolites in urine or first-pass effect following oral and intravenous administration;
- percentage of unchanged drug in urine following oral and intravenous administration;
- percentage of excretion of drug in bile following oral and intravenous administration;
- percentage of cumulative excretion of drug in feces following oral and intravenous administration;
- total recovery of drug in urine and feces following oral and intravenous administration;
- single dose level in mg or mg/kg and daily oral dose in mg.

### Physicochemical Descriptors

The water solubility (WS) at 25°C listed in Table 1 was estimated by WS-KOW for Windows (William Meylan 1994–1996),<sup>252</sup> and experimental values were obtained from a data base of Syracuse Corporation. Melting points were not used to correct solubility because most of them were unavailable.

The logarithm of the octanol–water partition coefficient ( $C \log P$ ) was calculated by use of the  $C \log P$  for Windows software (Biobyte version 2.0.0b, Claremont, CA).

The QSAR that we use is of the form of our general solvation equation,<sup>253</sup>

$$SP = c + eE + sS + aA + bB + vV \quad (1)$$

Here, the dependent variable, SP, is a property of a series of compounds in a given system. Specifically, in this work, SP will be the percent drug absorbed *in vivo*. We use a simplified notation for the independent variables, or solute descriptors as follows: **E** is an excess molar refraction in units of  $(\text{cm}^3 \text{ mol}^{-1})/10$ , **S** is the dipolarity/polarizability, **A** and **B** are the hydrogen bond acidity and basicity, respectively, and **V** is the McGowan characteristic volume in units of  $(\text{cm}^3 \text{ mol}^{-1})/100$  that can simply be calculated from structure. The equation coefficients, *c*, *e*, *s*, *a*, *b*, and *v*, are obtained by multiple linear regression. Equation 1 has been applied to numerous physicochemical and biochemical processes, mostly using experimentally derived descriptors.<sup>254-260</sup> More recently, Platts et al.<sup>261</sup> have calculated the descriptors using a fragment based scheme, ABSOLV, and have shown<sup>262</sup> how partition coefficients can then

**Table 1.** Molecular Weight (MW), Water Solubility (WS), and Octanol–Water Partition Coefficient ( $C \log P$ )

No.	Name	MW	WS(Calc) <sup>a</sup> (mg/L)	$M \log P^c$	$C \log P^d$
Training set 1 <sup>f</sup>					
1	Cisapride	466	2.71		3.43
2	Valproicacid	144	895	2.75	2.76
3	Salicylicacid	138	3808 <sup>b</sup> /2059	2.26	2.19
4	Diazepam	285	59 <sup>b</sup> /50	2.99	3.29
5	Sudoxicam	337	3015	1.64	2.60
6	Glyburide	358	35		4.08
7	Gallopamil	485	0.52		3.14
8	Mexiletine	179	8248	2.15	2.57
9	Nefazodone	470	0.060		5.00 <sup>e</sup>
10	Naproxen	230	145	3.34	2.82
11	Lamotrigine	256	3127		3.24
12	Tolmesoxide	214	10850		0.89
13	Disulfiram	296	64 <sup>b</sup> /4.09	3.88	3.88
14	Torasemide	348	137		3.34
15	Metoprolol	267	4777	1.88	1.20
16	Naloxone	327	1415	2.09	−0.04
17	Terazosin	387	205		2.71
18	Sulindac	356	17	3.05	2.81
19	Sultopride	354	724		1.93
20	Topiramate	339	13640		−0.07
21	Tolbutamide	270	183 <sup>b</sup> /109	2.34	2.50
22	Propiverine	367	8.85		4.06
23	Digoxin	781	3.78 <sup>b</sup> /64	1.26	1.32
24	Mercaptoethanesulfonicacid	142	1000000		−0.52
25	Cimetidine	252	10460	0.40	0.35
26	Furosemide	330	149	2.03	1.87
27	Metformin	129	1000000		−2.64 <sup>e</sup>
28	Rimiterol	223	399500		0.36
29	Cymarine	548	99		−0.15
30	Ascorbic acid	176	1000000	−1.64	−2.21
31	Fosfomycin	138	960700		−0.48
32	Fosmidomycin	183	1000000		−3.11
33	k-strophanthoside	873	20510		−5.42
34	Adefovir	273	42380		−2.08
35	Acarbose	646	1000000		−10.62
36	Ouabain	584	10340	−1.70	−4.58
37	Kanamycin	484	1000000		−7.77
38	Lactulose	342	1000000		−5.56
Test set					
39	Camazepam	372	24		3.64
40	Indomethacin	358	3.11 <sup>b</sup> /0.94	4.27	4.18
41	Levonorgestrel	312	36		3.31
42	Tenoxicam	337	442		2.42
43	Theophylline	180	2800 <sup>b</sup> /7356	−0.02	−0.06
44	Oxatamide	426	0.60		5.41
45	Desipramine	266	0.99 <sup>b</sup> /59	4.90	4.09
46	Fenclofenac	297	2.52	4.80	4.96
47	Imipramine	280	1.00 <sup>b</sup> /18	4.80	4.41
48	Lormetazepam	335	94		2.60
49	Diclofenac	296	5.61	4.40	3.03
50	Granisetron	312	28		1.79
51	Testosterone	288	68	3.32	3.22

**Table 1.** (Continued)

No.	Name	MW	WS(Calc) <sup>a</sup> (mg/L)	<i>M</i> log <i>P</i> <sup>c</sup>	<i>C</i> log <i>P</i> <sup>d</sup>
52	Caffeine	194	2632 <sup>b</sup> /21000	-0.07	-0.06
53	Corticosterone	346	143	1.94	2.32
54	Ethinylestradiol	296	116	3.67	3.66
55	Isoxicam	335	1046	2.83	2.40
56	Lornoxicam	372	1572		3.15
57	Nicotine	162	1000000	1.17	1.32
58	Ondansetron	293	5.70		2.64
59	Piroxicam	331	521 <sup>b</sup> /23	1.98	2.70
60	Verapamil	455	4.47	3.79	3.71
61	Progesterone	314	5.00	3.87	3.78
62	Stavudine	224	6595	-0.81	-0.48
63	Toremifene	406	0.072		6.35
64	Cyproterone acetate	417	0.65		3.39
65	Praziquantel	312	88		3.43
66	Cicaprost	374	21		2.01
67	Aminopyrine	231	4227		1.00
68	Nordiazepam	270	57	2.93	3.01
69	Carfecillin	454	2.91	2.96	3.12
70	Prednisolone	360	221 <sup>b</sup> /223	1.62	1.64
71	Propranolol	259	609	2.98	2.75
72	Viloxazine	237	29210		1.34
73	Warfarin	308	17	2.70	2.44
74	Atropine	289	3944	1.83	1.32
75	Minoxidil	209	3423	1.24	1.09
76	Clofibrate	243	21		3.68
77	Trimethoprim	290	2334 <sup>b</sup> /400	0.91	0.95
78	Venlafaxine	277	267		2.11
79	Antipyrine	188	23760 <sup>b</sup> /51900	0.38	0.41
80	Bumetanide	364	32		3.90
81	Trapidil	205	1696		1.94
82	Fluconazole	306	1086		-0.11
83	Sotalol	272	136800	-0.44	0.23
84	Codeine	299	13400	1.14	0.82
85	Flumazenil	303	128		1.06
86	Ibuprofen	206	2440	3.50	3.68
87	Labetalol	328	73		2.50
88	Oxprenolol	265	3182	2.10	1.69
89	Practolol	266	4472	0.79	0.75
90	Timolol	316	2741	1.83	1.61
91	Alprenolol	249	547	2.89	2.65
92	Amrinone	189	8067		-0.59
93	Ketoprofen	254	120	3.12	2.76
94	Hydrocortisone	362	219 <sup>b</sup> /320	1.61	1.70
95	Betaxolol	307	451	2.81	2.17
96	Ketorolac	255	572		1.62
97	Meloxicam	351	3.60	3.01	3.10
98	Phenytoin	252	1267	2.47	2.08
99	Amphetamine	135	28000	1.76	1.59
100	Chloramphenicol	323	389 <sup>b</sup> /3750	1.14	0.69
101	Felbamate	238	6116		-0.29
102	Nizatidine	331	77690		0.50
103	Alprazolam	309	13	2.12	2.30
104	Tramadol	263	1151	2.63	2.31
105	Nisoldipine	388	25	4.53	4.24
106	Oxazepam	287	179	2.24	2.29

**Table 1.** (Continued)

107	Tenidap	321	2676		0.63 <sup>e</sup>
108	Dihydrocodeine	301	6866		1.30
109	Felodipine	384	20	4.80	4.96
110	Nitrendipine	360	77	4.15	3.39
111	Saccharin	183	789	0.91	0.52
112	Moxonidine	242	16450		1.02
113	Bupropion	240	140		3.21
114	Pindolol	248	7883	1.75	1.67
115	Lamivudine	229	1000000	-0.93	-1.54
116	Morphine	285	13810 <sup>b</sup> /40000	0.76	0.24
117	Lansoprazole	369	3.43		3.07
118	Oxyfedrine	313	3.43		2.84
119	Captopril	217	6857		1.19
120	Bromazepam	316	1394	1.69	1.69
121	Acetylsalicylic acid	180	4600	1.19	1.02
122	Sorivudine	349	1207		-1.66
123	Methylprednisolone	374	123		1.96
124	Mifobate	359	3298		0.69
125	Flecainide	414	1.48		4.43
126	Quinidine	324	104 <sup>b</sup> /140	2.64	2.93
127	Piroximone	217	11890		0.96
128	Acebutolol	336	259	1.71	1.63
129	Ethambutol	204	948800		0.12
130	Acetaminophen	151	30350	0.51	0.49
131	Dexamethasone	392	93 <sup>b</sup> /89	2.01	2.01
132	Guanabenz	231	1055		2.96
133	Isoniazid	137	16700	-0.70	-0.71
134	Omeprazole	345	82	2.23	2.53
135	Methadone	309	48	3.93	3.13
136	Famciclovir	321	2609		-0.36
137	Metolazone	366	133		2.42
138	Fenoterol	303	41370		0.83
139	Nadolol	309	22400	0.71	0.23
140	Atenolol	266	685	0.16	-0.11
141	Sulpiride	341	2275		1.11
142	Metaproterenol	211	973500		0.08
143	Famotidine	337	1271	-0.57	-0.56
144	Foscarnet	126	1000000		-1.93 <sup>c</sup>
145	Cidofovir	279	1000000		-3.56
146	Isradipine	371	49	4.18	3.57
147	Terbutaline	225	212800	0.08	0.48
148	Reproterol	389	1424		-0.98
149	Lincomycin	406	927	0.20	-0.12
150	Streptomycin	582	1000000		-7.17
151	Fluvastatin	411	0.47		3.19
152	Urapidil	387	157		2.56
153	Propylthiouracil	170	514		2.80
154	Recainam	263	2158		1.13
155	Cycloserine	102	166000		-1.72 <sup>e</sup>
156	Hydrochlorothiazide	298	1292 <sup>b</sup> /722	-0.07	-0.40
157	Pirbuterol	240	521000		-0.93
158	Sumatriptan	295	21360	0.93	0.58
159	Amiloride	230	1256		-0.26
160	Mannitol	182	1000000 <sup>b</sup> /216300	-3.10	-4.67
161	Ganciclovir	255	28340	-2.07	-2.99
162	Neomycin	615	1000000		-9.03

**Table 1.** (Continued)

No.	Name	MW	WS(Calc) <sup>a</sup> (mg/L)	<i>M</i> log <i>P</i> <sup>c</sup>	<i>C</i> log <i>P</i> <sup>d</sup>
163	Raffinose	504	1000000 <sup>b</sup> /202600		-7.96
164	Phenglutarimide	288	325		1.54
165	Bornaprine	329	2.16		4.30
166	DphenylalanineLproline				
167	Scopolamine	303	17400 <sup>b</sup> /100000		0.26
168	Noloxone				
169	Ziprasidone	413	2.13		4.42
170	Guanoxan	207	16120		0.33
171	Netivudine	282	5918		-2.03
172	Gentamicin-C1	484	1000000		-3.77
Zwitterionic drugs					
173	Cefadroxil	363	1110	-2.06	-2.57
174	Ofloxacin	361	28260	-0.28	-0.24
175	Prefloxacin	333	11390	0.27	0.08
176	Cephalexin	347	1789	-1.74	-1.90
177	Loracarbef	349	2785		-0.47
178	Glycine	75	625600 <sup>b</sup> /249000	-3.21	-3.21
179	Amoxicillin	365	3433	-1.99	-1.92
180	Tiagabine	376	0.66		2.79
181	Telmisartan	514	0.0000029		7.26
182	Trovoflaxacin (CP99219)	416	285		-1.19
183	Acrivastine	348	262		1.13
184	Nicotinic acid	123	48000		0.80
185	Levodopa	197	320100	-2.74	-2.82
186	Cefatrizine	463	2505		-2.96
187	Ampicillin	349	3574 <sup>b</sup> /10100	-1.13	-1.25
188	Vigabatrin	129	55140		-2.94
189	Tranexamicacid	157	25000		-1.80
190	Eflornithine	182	256000		-3.00
191	Methyldopa	211	41810		-2.11
192	Ceftriaxone	554	958		-2.09 <sup>e</sup>
Drugs with missing fragments from ABSOLV program					
193	Distigminebromide	578			
194	Zidovudine	267	311	0.05	-0.20
195	Ximoprofen	261	453		2.18
196	Clonidine	230	13580	1.57	1.37
197	Viomycin	685	1000000		-8.03
198	Ceftizoxime	382	910000		-4.30 <sup>e</sup>
199	Capreomycin	653	1000000		-7.25
200	AAFC	243	1000000		-3.91 <sup>e</sup>
201	Bretvliumtosylate	244	4280		-1.25
Dose-limited, dose-dependent, and formulation-dependent drugs					
202	Spironolactone	417	28 <sup>b</sup> /22	2.26	2.25
203	Etoposide	588	59	0.60	-1.89
204	Cefetamet pivoxil	511	19		2.33
205	Cefuroximeaxetil	510	29	0.89	0.25
206	Azithromycin	749	7.09		1.83
207	Fosinopril	564	0.000033		7.74
208	Pravastatin	425	12		0.57
209	Cyclosporin	1202	0.0000076		3.80 <sup>e</sup>
210	Bromocriptine	654	0.0020		6.69
211	Doxorubicin	543	93	0.10	-1.45
212	Cefuroxime	424	145	-0.16	-0.17

**Table 1.** (Continued)

213	Iothalamatesodium	613	7.24		1.42
214	Sulfasalazine	398	2.44		3.83
215	Benazepril	425	2.23		1.82
216	Lisinopril	405	13		-1.71
217	Enalaprilat	348	11		0.86
218	Amphotericin B	924	1.16		-2.46 <sup>e</sup>
219	Aztreonam	435	810		-3.46 <sup>e</sup>
220	Mibefradil	516	0.041		4.41
221	Ranitidine	314	24660	0.27	1.33
222	Chlorothiazide	296	1854 <sup>b</sup> /283	-0.24	-0.31
223	Acyclovir	225	33990	-1.56	-2.07
224	Norfloxacin	319	177900	-1.03	1.57
225	Methotrexate	454	2600		-0.30
226	Gabapentin	171	4491		-1.18
227	Prazosin	383	310		2.45
228	Olsalazine	302	1.92		4.50
Drugs expected to have higher absorption					
229	Ciprofloxacin	331	11480	-1.08	1.40
230	Ribavirin	244	67180	-1.85	-3.23
231	Pafenolol	337	172		1.67
232	Azosemide	371	201		1.35
233	Xamoterol	339	11810	0.61	0.39
234	Enalapril	376	35		0.79
235	Phenoxymethylpenicillin	350	101	2.09	1.90
236	Gliclazide	323	138		1.09
237	Benzylpenicillin	334	210	1.83	1.70
238	Thiacetazone	236	3302		0.88
239	Lovastatin	405	2.14	4.26	4.08
240	Cromolynsodium	468	210	1.92	1.85
241	Erythromycin	734	1.43	2.54	0.65

<sup>a</sup>Calculated WS values (Calc) from Meylan method.<sup>b</sup>Experimental WS Values from a data base of Syracuse Corporation.<sup>c</sup>Experimental log *P* (*M* log *P*) from *C* log *P* program.<sup>d</sup>Calculated log *P* (*C* log *P*)<sup>e</sup>Calculated log *P* from Meylan method.<sup>f</sup>Training set 2: Drugs 7-8, 11, 15, 18-19, 21-22, 24-38, 136-141, and 143-145.

be calculated from these solute descriptors. We have used the ABSOLV program to calculate all the descriptors used in this work, other than **V**. The program was written to read molecular structures as SMILES strings. After calculation of the solvation descriptors, an error code was given by the program for each drug as an indication of the quality of the parameter calculations.

Although the basis of calculation of descriptors by Platts' method is that of group contributions, the method incorporates provision for intramolecular interactions. For example, phenol has **A** = 0.60 and **B** = 0.30, but the calculated values for catechol (1,2-dihydroxybenzene) are **A** = 0.84 and **B** = 0.68; intramolecular hydrogen bonding between the ortho-hydroxyl groups considerably reduces overall hydrogen bond acidity. Platts

et al.<sup>261</sup> list several examples of ortho-substituted phenols in which the overall hydrogen bond acidity is less than the sum of the **A** values for the individual monofunctional compounds.

### Statistical Analysis

The data set was analysed using Excel 97. Stepwise regression analysis was used to determine the most significant descriptors. The regression coefficients were obtained by least-squares regression analysis. For each regression, the following descriptive information is provided: number of observations used in the analysis (*n*), square of the correlation coefficient (*r*<sup>2</sup>), cross-validated *r*<sup>2</sup> (*r*<sup>2</sup> cv), standard error of the estimate (*S*), and Fisher's criterion (*F*).

**Table 2.** Absorption, Dose and Percentage of Excretion in Urine, Bile, and Feces of Drugs From Literature

No.	% Abs. <sup>a</sup>	% Abs. <sup>b</sup>	% Bio. <sup>c</sup>	Excretion <sup>d</sup> in Urine (% Dose)	Metab. <sup>e</sup> in Urine (% Dose)	Parent <sup>f</sup> Drug in Urine (% Dose)	Excretion <sup>g</sup> in Bile (% Dose)	Excretion <sup>h</sup> in Feces (% Dose)	Excretion <sup>i</sup> in Urine & Feces (% Dose)	Oral Dose <sup>j</sup> (mg)	% Insoluble <sup>k</sup> Drug (IS) in 250 ml of Water	Ratio <sup>l</sup> Between Insoluble Drug and Dose After Absorption	% Abs. <sup>m</sup> Chosen	Method <sup>n</sup> for Obt- aining %Abs. <sup>m</sup>	Quality <sup>o</sup> of the % Abs. <sup>m</sup> Data	Ref. <sup>p</sup>
Training set 1																
1	100		100	53		< 1		5	100	5-20	96	0	100	BIO	Good	1,18-20
2	100	~100	90(68-100)	26/17		0				600	63	0	100	BIO + RA	Good	21
3	100	100		100								0	100	EU	Good	22-23
4	97-100	100		71		small	/5.4			10-20	17	0	100	REV	Good	24
5		100											100	REV	Good	25
6				~50			~50			1.25-5	0	0	100	REV + EUB	Good	4
7		~100	15							25	99	0	100	REV	Good	26
8		100	88					< 10		100-400	0	0	100	REV	Good	27
9		100	15-23							100	100	0	100	REV	Good	28
10	94-99	100	99							250	86	0	99	BIO	Good	2,29
11	70		98	70	63/0	7-30				15-240	0	0	98	BIO	Good	3,30
12	100		85	98						200-400	0	0	98	EU	Good	31
13		91		97	~91			0	97	250	100	3	97	EU	Good	32
14			96							10	0	0	96	BIO	Good	26
15	95-100	> 90	50		95(50F)	3			> 95	300 mg/d	0	0	95	EU	Good	33,34
16				59/65						0.1	0	0	91	RA	Good	35
17	91	~100	90	38.8		> 10.4		55.6	94.4	7.5	0	0	90	BIO	Good	36
18		90		40-60			25	20~30		200	98	8	90	REV	Good	37
19	100	~100		89						50-100	0	0	89	EU	OK	38
20			81-95	> 80		59				100-1200	0	0	86	BIO	OK	39
21				85									85	EU	OK	40
22		84		54/75						15	85	1	84	RA	Good	41
23			67	66/81		52/76		32/17		1.2	21	0	81	RA	Good	42
24				49/65		17/32				800	0	0	77	RA	Good	43
25	62-98		60			48/75	< 2			200	0	0	64	RAP	OK	1
26	61	61	61	30-50 /50-95				> 2/6-9	32-52 /59-100	40	7	0	61	BIO + RA	Good	44
27			50-60A			35-50/80		27		500-1500	0	0	53	RAP + BIO	OK	45-46
28				44/92				40/1.4	76/94	10	0	0	48	RA	Good	47
29		47		21/46						3	0	0	47	RA	Good	48
30				30/85						1000	0	0	35	RA	Good	49
31						25/80				20-40 mg/kg	0	0	31	RAP	OK	50-51
32		30				26/86				500	0	0	30	RAP	OK	52
33		16		11.3/73						4.77	0	0	16	RA	Good	48
34	12		12			16/98				3 mg/kg	0	0	16	RAP	OK	53
35		1-2			35	1.7/94		51/ < 1		200	0	0	2	RA	Good	54
36		1.4		0.5/33						8	0	0	1.4	RA	Good	48
37				0.7/94					/94	4000	0	0	1	RA	Good	55-56
38	0.6	0.6		0.53/93						10000	0	0	0.6	RA	Good	57-59

**Table 2.** (Continued)

Test set															
39	99		100A						20	70	0	100	BIO	Good	60
40	100		100A						50	100	0	100	BIO	Good	61
41			100A	40-68			16-48	56-100			0	100	BIO	Good	4
42			100		66	traces	33	99	10-100	0	0	100	BIO	Good	25
43	96		100A								0	100	BIO	Good	62
44	100			> 80		0.1	0.5	> 80	60	100	0	100	EF	Good	63
45	95-100	> 95	40		> 95	< 5			50	71	0	100	EU	Good	64
46	100			99.5					200-600	100	0	100	EU	Good	65-66
47	95-100	> 95	22-77		> 95	< 5			40-60	91	0	100	EU	Good	64
48	100	100	80	/75	(20F)				1-3	0	0	100		Good	67
49	100		90A	60-70/61			/30	/91	50	97	0	100	RA	Good	68
50	100	100		60/60		5-25	36/36	97/95	0.1 mg/kg	0	0	100	RA	Good	69
51	100	100		100/100	> 30	small			20	15	0	100	RA	Good	70
52	100	100				1			1-300	0	0	100	REV	Good	71
53	100	100										100	REV	Good	72
54	100	~100	59						30	3	0	100	REV	Good	4,73
55		100				2			200	0	0	100	REV	Good	25
56		100							4	0	0	100	REV	Good	25
57	100	100		17-50							0	100	REV	Good	71
58	100	100	60	44-53		/5			8	82	0	100	REV	Good	74
59	100	100				5-10			20	71	0	100	REV	Good	25
60	100	> 90	10-52	70		3	15	85	80-160	99	0	100	REV	Good	75
61	91-100	91							1-2.5	38	0	100		Good	76
62			100			40			40	0	0	100	BIO	Good	26
63			100						120	100	0	100	BIO	Good	26
64		100	100						25	99	0	100	BIO	Good	77
65		100		80-90					6-50 mg/kg	89	0	100	REV	Good	78
66		100		60/60			35/35	95/95	0.008	0	0	100	RA	Good	79
67	100			100		0.2			250	0	0	100	EU	Good	80
68	99		99A						10	0	0	99	BIO	Good	81
69	100			99			< 1	100	650	100	1	99	EU	Good	82
70	99		70-100	99	60			98	10-50	0	0	99	EU	Good	83-85
71	90-100	> 90	30		99(60F)	< 1			300	49	0	99	EU	Good	34,86
72	100	~100	61-98A				< 2		200	0	0	98	EF	Good	87-88
73	98	~100	93-98		~100	traces		100	5	15	0	98	EU	Good	89
74		90		65/66			5/1.5	69-86/67	2	0	0	98	RA	Good	90
75		95										98	REV	Good	91
76	96		95-99	78-122	43-73	11	< 1		1000-2000	100	3	97	BIO	Good	92-93
77	97		92-102						2	0	0	97	BIO	Good	94
78	92			97					50	0	0	97	EU	Good	95
79	100	~100	97A	67/69.5		2.5/3.7	0.5-1	68/70	10 mg/kg	0	0	97	RA	Good	96
80	100	~100		78/81	33		16/8.7	94/90	0.5	0	0	96	RA	Good	97
81			96									96	BIO	Good	98
82	95-100		> 90		11	64-90			50-150	0	0	95	BIO	Good	99
83	95	~100	90-100A		< 20(0F)	75			240 mg/d	0	0	95	BIO	Good	34, 100-101
84	95		91			0.18			1 mg/kg	0	0	95	EU	Good	102-103
85	95	> 95	16	90-95		0.2	5-10	95-100	200	84	0	95	EU	Good	104

**Table 2.** (Continued)

No.	% Abs. <sup>a</sup>	% Abs. <sup>b</sup>	% Bio. <sup>c</sup>	Excretion <sup>d</sup> in Urine (% Dose)	Metab. <sup>e</sup> in Urine (% Dose)	Parent <sup>f</sup> Drug in Urine (% Dose)	Excretion <sup>g</sup> in Bile (% Dose)	Excretion <sup>h</sup> in Feces (% Dose)	Excretion <sup>i</sup> in Urine & Feces (% Dose)	Oral Dose <sup>j</sup> (mg)	% Insoluble <sup>k</sup> Drug (IS) in 250 ml of Water	Ratio <sup>l</sup> Between Insoluble Drug and Dose After Absorption	% Abs. <sup>m</sup> Chosen	Method <sup>n</sup> for Obt- aining %Abs. <sup>m</sup>	Quality <sup>o</sup> of the % Abs. <sup>m</sup> Data	Ref. <sup>p</sup>
86	100			95	80					400	0	0	95	EU	Good	105
87	90-95	> 90	33		95(~60F)	< 4				600 mg/d	91	0	95	EU	Good	34
88	97	90	50		95(40F)	3				160 mg/d	0	0	95	EU	Good	34
89	95	~100		95	0	95				25-600	0	0	95	EU	Good	106
90	72	> 90	75		(25F)	5		6	81	30 mg/d	0	0	95	REV	Good	34,107
91	93-96	> 93		93		0.4				100	0	0	93	EU	Good	108-109
92		93								75-150	0	0	93	REV	Good	98
93	100	~100	> 92A	80	80	0-50	1			25-200	73	0	92	BIO	Good	110
94	89-95	84-95		84/90		~4	/4			200	60	0	91	RA	Good	111-112
95	90	90	80-89	> 80		15			> 80	20 mg/d	0	0	90	BIO	Good	33
96	100	well	80-100A	92	75	5-10				10	0	0	90	BIO	Good	113
97	90		90A	43	> 43	0.25		47	90	30	97	7	90	BIO	Good	114
98	90	90	90A							400	21	0	90	BIO	Good	85,115
99				90		30				15-25	0	0	90	EU	Good	71
100	90		80	90		5-15	2.7			250	0	0	90	EU	Good	116-117
101		90-95		90		43-63				100-1200	0	0	90	EU	Good	3,118
102	99		> 90	> 90		60		< 6	~100	150 mg/d	0	0	90	EU	Good	1
103			80-100							1	0	0	90	BIO	good	26
104			65-75	90		~15		10					90	EU	Good	119
105				74/82		~0		12.0/14		10-20	58	0	90	RA	Good	120
106	97	~100	92.8	71/80		71.9				15	0	0	89	RA	Good	121
107	90		89A							120	0	0	89	BIO	OK	122
108			20	> 89	> 59	~30				60	0	0	89	EU	OK	119
109	100	100	16	62/70		0		9.8/11	72/81	27.5	82	0	88	RA	Good	123
110			23	88(80-113)		0.5/0.5				20	3	0	88	EU	OK	124-125
111	97	88				89/101				2000	90	2	88	RAP	OK	126
112			88										88	BIO	OK	98
113	87		87			< 1				50-200	72	0	87	EU	OK	4,127
114	92-95	> 90			60(13F)	35				15 mg/kg	0	0	87	EU	OK	34
115			86-88A							100	0	0	87	BIO	OK	128
116	100	~100	20-30	85		2				20	0	0	85	EU	OK	129
117			85							30	97	12	85	BIO	OK	26
118			85										85	BIO	OK	98
119	67	71	62A	67-76/93	45-50	38/40		16/0.3	91	100	0	0	84	RA + EF	Good	130-131
120	84		84	/63-76						6	0	0	84	BIO	OK	132-133
121				84						1200	4	0	84	EU	OK	22-134
122	82	82	61	70/84		47/71		7.0/2	77/86	20	0	0	82	RA	Good	135
123	82		82							0.6 mg/kg	0	0	82	BIO	OK	2,136
124				74-88						400-600	0	0	82	EU	OK	93
125			81							100	100	19	81	BIO	OK	137
126	80	81	81							330	89	8	81	BIO	OK	138-139

**Table 2.** (Continued)

127			81						0.6–1 mg/kg	0	0	81	BIO	OK	98
128	90	90	50	65(30F)	18		> 90	300mg/d	35	0	0	80	REV	Good	33–34,140
129		75–80			40–80		79–94/82	15–25 mg/kg	0	0	0	80	REV	Good	55,141
130	80–100	80	68–95	85–95	4			500–1000	0	0	0	80	BIO	OK	142–143
131	92–100		80A					1.5				80	BIO	OK	144
132	75			77–80	1.4		8–32	87–98	16–32	0	0	80	EU	OK	145
133				75–95	75–95				300	0	0	80	EU	OK	55
134					75–80	~0.1	20–25	95–100				80	EU	OK	1
135			80									80	BIO	OK	119
136			77		50–60/94				125–500	0	0	77	BIO +	OK	146
													RAP		
137	64	62–64		56/90					2.5 mg/d	0	0	64	RA	Good	147
138		60		35/60	2.0/27		40/15	75/75	5–20	0	0	60	RA	Good	148–149
139	20–35	34	34		0	34/60	/15	/75	80 mg/d	0	0	57	RA	DP?	34,150, 151, 271
140	50–54	50	50	10(< 10F)	40/90–95			> 95	200 mg/d	0	0	50	BIO +	OK	34–150
													RAP		
141	36		30		40/91				200	0	0	44	RAP	OK	152
142		44	10	36/82					1.6	0	0	44	RA	Good	153
143			37–45		25–30							38	BIO + RAP	OK	1
					/65–80										
144	17	17			/73–94		/73–94		16000 mg/d	0	0	17	RA	Good	154
		(12–22)													
145			< 5		2.7/90				10 mg/kg	0	0	3	RAP	OK	53
146	92	90–95	17	60–67	0		26~32	86–99	5–20	7	0	92	EF		155
147	60–73	50–73	16		(78F)	8.7/56			5	0	0	62			156
148		60										60	REV		157
149		20–35										28	REV		158
150		poor					small					1	REV		55
151	100	> 90	19–29	4.9/3.4	< 1		92/89	100	2–10	98	0	100	RA	IVL	159–160
152			78									78	BIO	OK?	98
153	75		76						400	68	0	76	BIO	OK?	161–162
			(53–88)A												
154				71	60		18		500	98	27	71	EU	OK?	163
155				64–81					250	0	0	73	EU	OK?	55
156	67–90	65–72			65–72				12.5–75	0	0	69(65–72)	EU	OK?	164
157				60	10				10	0	0	60	EU	OK?	165
158	55–75	> 57	14	57			36/< 15	94	200	0	0	57	EU	OK?	166–168
159				50				88	20	0	0	50	EU	OK?	169
160	16–26				15.6				500	0	0	16	EU	OK?	57–58
161	3–3.8	3	3	0	3				50–100	0	0	3	EU	OK?	170
									mg/d						
162				0.6					2800	0	0	1	EU	OK?	56
163	0.3			0.26					8000	0	0	0.3	EU	OK?	171
164	100											100		Check	8
165	100											100		Check	8
166	100											100		Check	5
167	90–100											95		Check	9–10,12

**Table 2.** (Continued)

No.	% Abs. <sup>a</sup>	% Abs. <sup>b</sup>	% Bio. <sup>c</sup>	Excretion <sup>d</sup> in Urine (% Dose)	Metab. <sup>e</sup> in Urine (% Dose)	Parent <sup>f</sup> Drug in Urine (% Dose)	Excretion <sup>g</sup> in Bile (% Dose)	Excretion <sup>h</sup> in Feces (% Dose)	Excretion <sup>i</sup> in Urine & Feces (% Dose)	Oral Dose <sup>j</sup> (mg)	% Insoluble <sup>k</sup> Drug (IS) in 250 ml of Water	Ratio <sup>l</sup> Between Insoluble Drug and Dose After Absorption	% Abs. <sup>m</sup> Chosen	Method <sup>n</sup> for Obt- aining %Abs. <sup>m</sup>	Quality <sup>o</sup> of the % Abs. <sup>m</sup> Data	Ref. <sup>p</sup>
168	91												91		Check	5
169	60												60		Check	5,9-10
170		50											50		Check	172
171		28											28		Check	7
172	0	Poor											Poor		Check	9,158
Zwitterionic drugs																
173			100			70				500	45	0	100	BIO	Good	173
174			100										100	BIO	Good	174
175			100							400	0	0	100	BIO	Good	26
176	98	100				85-100				500	11	0	100	EU	Good	173
177	100	100				100				100-500	0	0	100	EU	Good	175
178	100												100		Check	5
179	94		93			71/82				375-1000	0	0	93	BIO + RAP	Good	176-180
180			90A										90	BIO	Good	26
181	90	Rapid	43	< 2				> 98	> 98 / > 90	40	100	10	90		Check	5
182	88		88A	23		6		63	86	200	64	0	88	BIO	OK	4,181
183	88			88		59		12	100	4-8	0	0	88	EU	OK	182
184				88									88	EU	OK	93
185	100	80-90	86A							250	0	0	86	BIO	OK	183
186			75A			42-60/80				250	0	0	75	BIO + RAP	OK	184
187						46/73				500	0	0	62	RAP	OK	185
188				50-65						1000-3000	0	0	58	EU	OK?	30
189	55			53 / > 95	< 10					500-2000	0	0	55	RA	Good	186
190						44/80				10-20 mg/kg	0	0	55	RAP	OK	187
191		41		/57						250	0	0	41		Good	188-189
192	1	1											1		Check	190
Drugs with missing fragments from the ABSOLV program																
193			4.7	6.5/85				88/4		5	0	0	8	RA	Good	191
194	100	100	63		60-75 /60-75	14-20/19				10 mg/kg	89	0	100	RA	Good	192-193
195	100		98							30	0	0	98	BIO	Good	194
196	95-100	100	75-95		50	30-33				0.3	0	0	95	BIO	Good	195-197
197						85							85	EU	OK	50
198				58/81						500	0	0	72	RA	Good	198
199						50				100 mg/d	0	0	50	EU	OK?	55
200		32		24/74				19-35		2-20 mg/kg	0	0	32	RA	Good	199

**Table 2. (Continued)**

201	23		23 (12-37)A	/100		13/71			5-200	0	0	23	BIO + RAP	OK	200		
Dose-limited, dose-dependent, and formulation-dependent drugs																	
202		> 73		53		0	20	37	40-95	50-200	96	23	73	EUB	DL	201	
203	50		50 (25-75)			6-25 /30-50			/0-16 /30-66	100-600	96	46	50 (25-75)	BIO	DL	202-203	
204			47			38/80				500	99	52	47	RAP	DL	204	
205	36		36-52			36				500	99	63	44 (36-52)	RA	DL	205	
206	35-37		37			4.5/12				500	100	63	37	RAP + BIO	DL	206	
207		36	25-29	8.6/29					63-81 /42-61	72-90	10	100	64	36	RA	DL	207-208
208	34	34	18	20/60					71/34	91/94	20	85	51	34	RA	DL?	159,209
209	35		10-60								8 mg/kg	100	65	28(10-65)	BIO	DL	210-211
210	28	28	6	2.5-5.5		> 5			85		0.5-2.5 mg/d	100	72	28	REV	DL	4,212
211	5	trace	5	5(0.7-23)					25-45		50-60	58	53	12 (0.7-23)	BIO + EU	DL	213-214
212						1.0/95					1000	96	95	1	RAP	DL?	215
213	1.9	1.9				1.4/75					800	100	98	1.9	RAP	DL	216
214	12-13			56-61							2000	100	35	59(56-61)	EU	DL?	217
215	37	> 37		37		0.4			97		20	97	60	≥ 37	EU	DL?	218-219
216	25	25	25-50A	/100		29			56	97	10-20	78	40	28 (25-50)	BIO + EF	DL?	220-221
217	9-10	10-40				29			69	98	10	72	43	25(10-40)	EU	DL?	222-224
218	5	poor		2-5	0						2000-5000	100	95	3(2-5)	EU	DL	225
219		< 1	< 1	0.7/68							500	60	59	1	RA	DL?	226-227
220			37-109								10-320	100	31	69 (37-100)	BIO	DP	228
221	50-61		50 (39-88)			30/70					40-80	0	0	64(39-88)	BIO	DP	1
222	13-56				0	33-56/92					50-250	0	0	49(36-61)	RA	DP	229
223	20-30		15-30	/98	8-14	14/75	/2				100-600	0	0	23(15-30)	BIO	DP	230
224	35	30-40	~70			30	small	29	69		400	0	0	71	EF	DP	231-232
225	20-100	100		48-70/84	35/10			0-7	78/88		0.1-10 mg/kg	0	0	70(57-83)	RA	DP	233-235
226	50	well	60A (36-74)		0	74-43					100-900	0	0	59(43-74)	BIO + EU	DP	3,30,143
227	100		44-69			< 4	77-95				1	0	0	86(77-95)	EUB	FD	236
228	2.3		2.3A	17-31		0.25-1.1 /22					1000-4000	100	76	24(17-31)	EU	DL?-M	237
Drugs expected to have higher absorption																	
229	69-100		69			42/60					200	0	0	≥ 69	RAP		238-239
230			33			4.4/17	6.2/29				800	0	0	≥ 33	BIO + RAP		240
231			28		1.9/4.8	16/56		74/28			40	0	0	≥ 29	RAP		241

**Table 2.** (Continued)

No.	% Abs. <sup>a</sup>	% Abs. <sup>b</sup>	% Bio. <sup>c</sup>	Excretion <sup>d</sup> in Urine (% Dose)	Metab. <sup>e</sup> in Urine (% Dose)	Parent <sup>f</sup> Drug in Urine (% Dose)	Excretion <sup>g</sup> in Bile (% Dose)	Excretion <sup>h</sup> in Feces (% Dose)	Excretion <sup>i</sup> in Urine & Feces (% Dose)	Oral Dose <sup>j</sup> (mg)	% Insoluble <sup>k</sup> Drug (IS) in 250 ml of Water	Ratio <sup>l</sup> Between Insoluble Drug and Dose After Absorption	% Abs. <sup>m</sup> Chosen	Method <sup>n</sup> for Obt- aining %Abs. <sup>m</sup>	Quality <sup>o</sup> of the % Abs. <sup>m</sup> Data	Ref. <sup>p</sup>
232			10			2.0/20				20–80	0	0	≤ 10	RAP		242
233			5	/90		3.1/62				50–200	0	0	≥ 5	RAP		243
234	66	60–70	29–50			61		29	90	10	13	0	66 (61–71)	EU + EF		223–224 244–246
235	45	45 (31–60)		49		30	0	32 (22–52)	71–100	22	0	0	59(49–68)	EU~ EF		247
236				60–70				10–20	70–90				≥ 65	EU		40
237	30	15–30				15–30				500	90	60	≥ 30	EU	DL?	248
238						20				150	0	0	≥ 20	EU		55
239	30	31		9.6				83	93	20–100	99	68	≥ 10	EU	DL	159,249
240					0	0.4		82		20	0	0	≥ 0.4	EU		250
241	35		35	> 4.5									≥ 35	BIO		2,251

<sup>a</sup>The data used for **QSAR** studies was taken from Clark (1999) and Wessel (1998), Palm (1997), Yazdani (1998), Yee (1997), and Chiou (1998).

<sup>b</sup>Absorption data obtained from the original and review literature.

<sup>c</sup>Bioavailability or absolute bioavailability of oral administration.

<sup>d</sup>Percentage of cumulative drug and its metabolites in urine following oral/intravenous administration.

<sup>e</sup>Percentage of metabolites in urine by oral/intravenous administration or first pass effect (F).

<sup>f</sup>Percentage of unchanged drug in urine by oral/intravenous administration.

<sup>g</sup>Percentage of excretion in bile by oral/intravenous administration.

<sup>h</sup>Percentage of excretion in feces by oral/intravenous administration.

<sup>i</sup>Percentage of cumulative recovery in urine and feces by oral/intravenous administration.

<sup>j</sup>Single dose (mg or mg/kg) and daily dose (mg/d).

<sup>k</sup>Percentage of insoluble oral dosed drugs in 250 ml water (IS).

<sup>l</sup>Ratio between insoluble drug and dose administered after absorption  $100 \times [\text{Dose} \times (1 - \text{fraction absorbed}) - 0.25 \times \text{WS}] / \text{Dose}$ .

<sup>m</sup>Absorption data (or averaged values) chosen here based on the analysis of literature.

<sup>n</sup>Method for obtaining absorption data (%Abs.<sup>m</sup>).

<sup>o</sup>Quality of the data based on the analysis of literature.

<sup>p</sup>Notes for some of the drugs from literature:

1. Drug 35: Additionally, up to 35% of radioactivity of acarbose was absorbed after degradation by digestive enzymes and/or intestinal microorganisms.
2. Drug 59: 100% oral absorption in humans was obtained from studies in rabbits.
3. Drug 61: Absorption data were obtained from the small intestinal zone 100–200 cm.
4. Drugs 144, 191, and 205: Absorption was evaluated from the urinary excretion ratio of oral and intravenous administration based on literature, although the authors did not give the urinary excretion in detail.
5. Drug 146: Assuming all intact PN200-100 found in feces to represent unabsorbed drug, the extent of absorption could be as high as 90–95% of the dose. Although the possibility of drug metabolism by intestinal epithelium or microbial flora cannot be predicted, rapid urinary excretion of the administered dose also supported efficient oral absorption.
6. Drug 147: The absorbed amount was calculated as the sum of unchanged drug, systemically and presystemically conjugated terbutaline plus deficit.
7. Drug 202: The extent of absorption must be at least ~73% because 53% and 20% of an orally administered radioactive dose of spironolactone in an alcoholic solution were excreted in urine and bile, respectively.
8. Drug 206: Azithromycin gains entry into cells by both passive and active transport.
9. Drug 215: If biliary excretion occurred, the extent of absorption may well have been greater. In animal studies, significant biliary excretion has been found (> 50% of intravenous dose or of absorbed fraction of oral dose).
10. Drug 224: Recovery of the drug in feces from 12 healthy volunteers given single oral 400-mg doses averaged 28% over the ensuing 48 h. Because the drug is excreted in the bile to only a small extent, these results imply an oral bioavailability of ~70%.
11. Drug 227: the data of 77–95 is the percentage of excretion in urine and bile.
12. Drug 239: Estimate for absorption in humans based upon hydroxyacid form as intravenous reference.

## RESULTS AND DISCUSSION

### Evaluation of Human Intestinal Absorption Data

Drug absorption is a complex process that is dependent on numerous biochemical, physiological, and physicochemical factors. In a thorough review of the subject, Sietsema<sup>263</sup> accurately points out that the terms absorption and bioavailability are often incorrectly and interchangeably used. Sietsema defined absorption as "the drug passing from the lumen of the gastrointestinal (GI) tract into the tissue of the GI tract. Once in the tissue, the drug is considered absorbed".

Surveying the papers, it was found that the absorption data were obtained by different methods. Most of the absorption data from the literature were based on one of the three main methods outlined next. These data form the basis by which all methods of predicting absorption are judged and from which all are devised.

#### Method 1: Bioavailability

Bioavailability measurements are one method of obtaining absorption data (Drugs 1–2, 10, 39–40, 64, 76–77, and 96–98). If bioavailability is high (>80%), it can be assumed that the bioavailability of the drug can reflect absorption because the effect of first-pass metabolism is minimal and almost all the absorbed drug can reach the systemic circulation. However, it may underestimate absorption if the bioavailability of the drug is low (Drug 241) because a fraction of the absorbed drug may not reach the systemic circulation. Following absorption from the gastrointestinal tract, the drug passes directly to the liver via the hepatic portal vein where it may be extensively metabolized before reaching the systemic circulation.

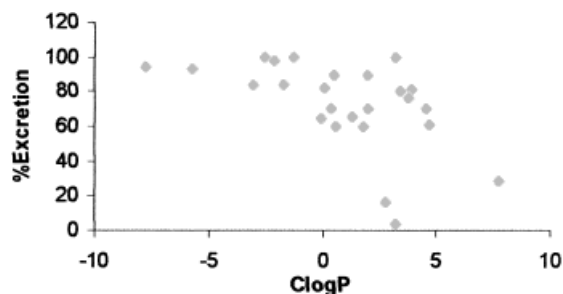
#### Methods 2: Excretion in Urine and Feces Following Oral Administration

The percentage of cumulative excretion of drug in urine or feces following oral administration is another common method used to derive absorption data. For example, absorption data were derived from the percentage of cumulative urinary excretion of unchanged drug and its metabolites (Drugs 3, 12, 15, 45–47, 69–71, and 84–89), percentage of cumulative fecal excretion of unchanged drug (Drug 146) or drug-related material (Drugs 44, 72, and 224), and the range between the percentage of parent drug in urine and 100% of metabolites excreted in the feces (Drug 234).

There were fewer excretion data in feces available in comparison with urinary excretion data.

If the drug could be completely recovered from the urine and feces, and urinary excretion was the main elimination route for the absorbed drug, use of this method is correct. However, this method would result in significant mis-estimation if one of following cases occurred. (1) The drug cannot be completely recovered in urine and feces. A deficit fraction of the drug may still be in the human intestinal tract or the absorbed drug may not have fully been excreted in urine because of the time limit (Drugs 147 and 224).<sup>156</sup> This situation can be seen on the total recovery of drugs 28, 44, 60, 74, 79, 109, and 122 following oral administration and drugs 74, 79, 109, 138, 139, and 203 following intravenous administration. (2) If the urinary data are used when the absorbed drug is also excreted by a route other than the urine. For example, after intravenous administration, <50% of certain drugs (Drugs 2, 151, and 207) were shown to be excreted in the urine. Thus a fraction of the absorbed drug could also be excreted in the feces. In this respect, if it cannot be proved that urinary excretion is the main route for excretion of absorbed drug (i.e., by intravenous administration), it is difficult to say whether absorption obtained by this method is reliable (Drugs 236–240).

To investigate the excretion route of absorbed drug, regression analysis was carried out by use of percentage of excretion in urine and feces (Table 2) following intravenous administration. The results showed that the percentage of urinary excretion decreased or fecal excretion increased with increasing octanol–water partition coefficient, especially for the drugs with  $C \log P > 0$  (Figure 1). This result suggests that the more hydrophobic a drug, the more likely it is to be excreted in the feces. Figure 1 may suggest that if the  $C \log P$  was larger than zero, the absorbed drug would not be



**Figure 1.** Dependence of urinary excretion of drug-related material following intravenous administration on  $C \log P$ .

completely excreted in urine; it would be excreted in feces as well. This would result in mis-estimation with use of the urinary excretion method for highly hydrophobic drugs.

### **Method 3: The Ratio of Cumulative Urinary Excretion of Drug-Related Material Following Oral and Intravenous Administration**

The ratio of cumulative urinary excretion of drug-related material (parent drug and its metabolites) following oral and intravenous administration was used to evaluate the absorption of drug; for example, drugs 22, 29, 32–36, 38, 50–51, 66, and 79–80. This method is better than the urinary excretion method because the absorption data can be estimated more accurately even if the urinary excretion of absorbed drug is not the main route or the drug is not completely recovered from urine and feces. The greater the extent of urinary excretion of drugs from intravenous administration, the greater the validity of the absorption data. This relationship would result in greater mistakes for drugs in which both urinary excretion fractions from oral and intravenous administrations were very low.

Although this method is better than the urinary recovery method, the intravenous administration of some drugs has not been determined in humans,<sup>141,167–232</sup> sometimes because of the low aqueous solubility of the drugs.<sup>201</sup> If the drug undergoes extensive hepatic metabolism, the absorption cannot be accurately evaluated by the ratio of urinary excretion of parent drug; this method will under-estimate the absorption. For example, the absorptions evaluated by the ratio of cumulative urinary excretion of mercaptoethane and fenoterol are 75% and 60%, respectively. However the absorptions evaluated by the ratio of urinary excretion of the parent drugs are 25% and 7%, respectively. There are 25% and 53% estimation errors between the two approaches for the two drugs, respectively. Absorption evaluated by the ratio of cumulative urinary excretion of parent drug (Drugs 229–233) is not reliable.

### **Difficulties in Evaluation of Absorption**

*(1) Low Solubility and Dose-Limited Absorption.* Water solubility is an important factor in drug absorption. Phenytoin is well known for its poor solubility in water; its absorption varies considerably among different preparations and dosages.<sup>264</sup> For dose-limited drugs with poor solubility, incomplete dissolution and hence incomplete absorp-

tion may occur. Absorption is highly variable for these drugs (Drugs 202–219).<sup>159,210,214</sup> For instance, the excretion in feces of fosinopril varies from 63 to 81%, and total cumulative excretion in urine and feces of spironolactone varies from 40 to 95%, following oral administration. One reason for this variability may be their hydrophobic properties, which would prevent complete dissolution in the intestinal fluid. The lack of dispersion of the drug is one cause of incomplete absorption.<sup>210</sup> For instance, the volume of water required to dissolve 20 mg of lovastatin is >15 L (the solubility is 0.0013 g/L at pH 5.0 and 23°C).<sup>159</sup> Some of the drugs were completely insoluble in the intestinal fluid (Drugs 181, 207, 209, and 210). Oily and alcoholic solution were used to dissolve drugs 202 and 209.

To correct for low solubility, Dressman<sup>85</sup> introduced the absorption potential (AP). With this approach,  $\log P$  is corrected for molar fraction of un-ionized species at pH 6.5 ( $F_{\text{non}}$ ), the solubility of the un-ionized species in water (WS), the volume of the luminal contents ( $V_L$ ), and the dose administered ( $X_O$ ):

$$\text{AP} = \log(P \times F_{\text{non}} \times \text{WS} \times V_L / X_O) \quad (2)$$

Doses received by subjects listed in Table 2 showed that 20 drugs were dosed singly at >1 g (Drugs 20, 27, 30, 37, 38, 76, 101, 111, 121, 130, 144, 162, 163, 179, 188, 189, 212, 214, 218, and 228); the highest single dosage being 10 g (Drug 38). However, when a large dose was given orally, urinary excretion and bioavailability decreased greatly.<sup>184, 234, 235</sup> This result could be understood on the basis of an “absorption window” effect.<sup>184</sup> The question then arises as to whether these drugs were completely dissolved in the intestinal fluid.

Generally, the average weight of subjects was taken to be 70 kg for pharmacokinetic studies. The subjects either received single dosed drugs with 200 mL of water (usually 100–250 mL), or subjects received the drugs three times a day. Because small intestinal volume is assumed to be 250 mL,<sup>265</sup> the percentage of undissolved drugs for a single dose in 250 mL of water [ $100 \times (1 - 0.25 \times \text{WS}/\text{Dose})$ ] was calculated and listed in Table 2. The results showed (Table 2) that there were 37 drugs for which the insoluble percentage was >90% in 250 mL of water. However, absorption is not a partition process and water is not the same as intestinal fluid. Also, large estimation errors in the Meylan solubility calculations may arise for the larger drug molecules.

The ratios between the amount of insoluble drug and dose in 250 mL of water after absorption  $\{100 \times \text{Dose} \times (1 - \text{fraction absorbed}) - 0.25 \times \text{WS}\} / \text{Dose}$  are also listed in Table 1. The results show that there were 22 drugs for which the ratio was still  $>20\%$  after absorption. These drugs were dose limited because of their low solubility and absorption. However, for a drug that has low solubility but a high absorption of 80%, the absorption of drug will still be reliably estimated because, after absorption, the insoluble drug would represent  $<20\%$  of the administered dose (Drugs 1, 2, 7, 9, 13, 18, 40, 44, 46, 60, and 63).

(2) *Formulation and Salt Dependent Absorption.* Many drugs were not administered orally as the free base or acids because of their poor water solubility, stability, hygroscopicity, crystallinity, or purity. These drugs were usually combined with acids or bases to form a salt or formulated with a lipophilic solvent, a hydrophilic solvent, and a surfactant that interact to aid in dispersion and emulsification. Therefore, the absorption of some drugs was formulation or salt dependent.<sup>236</sup>

(3) *Dose-Dependent Absorption.* Dose-dependent absorption of the drug is based on the observation that the percentage of the oral dose absorbed, bioavailability, and excretion in urine declined with increasing dose (Drugs 220–226). Variable urinary recovery or bioavailability with dose may reflect a variation in absorption.<sup>232</sup>

(4) *Drugs Metabolized in Intestinal Tract.* Certain drugs may be metabolized by enzymes or microflora that reside in the gut or gut wall and it is difficult to quantify this intestinal metabolism. Absorption can be unreliable if metabolism occurs in the intestine. Within the gastrointestinal tract, metabolic reactions (namely, conjugation, enzymatic hydrolysis of esters, and reduction processes) occur primarily via microflora. Phase-I biotransformation occurs predominantly via cytochromes P450, the major enzyme being CYP3A. More than 50% of drugs may be substrates for CYP3A, thus resulting in poor oral bioavailability due to extensive metabolism in the intestine<sup>266–267</sup> (for example, drugs 35 and 228).

#### **Classification of Absorption Data**

Because the absorption data obtained from the literature was from different methods, it seems unrealistic to expect to find a single model that

will accurately predict all classes of compounds if the absorption data is not classified carefully.<sup>9,268</sup> Therefore, it is very necessary to sort out the data based on the original papers before embarking on QSAR studies.

The absorption data chosen for modeling in Table 2 (%Abs.<sup>m</sup>) were based on one of the following methods:

1. BIO: Absorption was obtained from bioavailability values after oral administration. If the bioavailability was low, the absorption should be equal to or higher than the values of bioavailability (Drug 241).
2. RA: Absorption was evaluated from the ratio of urinary excretion of drug-related material following oral and intravenous administration.
3. RAP: Absorption was evaluated from the ratio of urinary excretion of parent drug following oral and intravenous administration.
4. EU: Absorption was obtained from cumulative urinary excretion of drug-related material following oral administration. If the urinary excretion was low ( $<80\%$ ) and it could not be proved that urinary excretion of absorbed drug was the main route or nearly all the drug was recovered in urine and feces, the absorption should be equal to or higher than the percentage of urinary excretion of the drug (Drugs 236–240).
5. EF: Absorption was obtained from excretion in feces ( $100 - \% \text{ excreted in feces}$ ).
6. EUB: Absorption was obtained from the cumulative excretion of drug in urine and bile.
7. REV: Absorption was obtained from review papers.
8. EU~EF: Intravenous administration showed that nearly all of the drug was excreted in urine or that excretion in bile was small; however, the drug was not completely recovered in urine and feces. Thus, the absorption should be between the percentage of excretion in urine and feces ( $100 - \% \text{ excreted in feces}$ ).

The following key was used as an indication of the quality of the data based on the analysis just presented;

Good:

1. The absorption data are evaluated based on the ratio of cumulative urinary excretion of

drug-related material following oral and intravenous administration, and intravenous administration results showed that percentage of urinary excretion was  $> 20\%$ , or

2. Drugs with bioavailability  $\geq 90\%$  (absorption would be 90–100%, estimation error would be  $< 10\%$ ), or
3. Cumulative urinary excretion following oral administration is  $> 90\%$  (absorption would be 90–100%, estimation error would be  $< 10\%$ ) or cumulative fecal excretion is  $< 10\%$ , or
4. Values from review papers, provided that the quoted absorption was  $> 80\%$ .

OK:

1. The bioavailability is 80–90% (absorption would be 80–100%; estimation error would be  $< 20\%$ ), or
2. The percentage of cumulative drug-related material in urine is 80–90% (absorption would be 80–100%; estimation error would be  $< 20\%$ ) or the cumulative fecal excretion is 10–20%, or
3. The absorption data are evaluated based on the ratio of urinary excretion of parent drug following oral and intravenous administration and percentage of urinary excretion of parent drug following intravenous administration is  $> 70\%$ . The absorption may be underestimated by this approach. For example, the absorption evaluated by the ratios of cumulative urinary excretion of sorivudine-related material and parent drug are 82% and 66%, respectively. There is 16% estimation error between the two approaches. The approach may (or partly) reflect the absorption if the drug has a higher intravenous administration.

OK? (Uncertain):

1. Based on the analysis of the excretion in urine following intravenous administration (Figure 1), the  $C \log P$  of these drugs is  $< 0$ ; therefore, the urinary excretion may be the main route for the absorbed drug. If the drug could be completely recovered in urine and feces, the percentage of excretion in urine would reflect the absorption of the drug, or
2. Bioavailability or the urinary excretion of drug-related material is 70–80% (estimation would be  $< 30\%$ ).

DP:

1. The absorption of the drugs is dose-dependent based on the literature.

DL:

1. The drugs are dose-limited and  $> 20\%$  of the drug is still insoluble in 250 mL of water after absorption. Absorption is highly variable and incomplete for these drugs.

DL?:

1. The drugs may not be dose-limited after the correction of solubility by  $pK_a$  at  $pH = 6.5$ .

FD:

1. The absorption is variable depending on the formulation of the drug (formulation dependent).

M:

1. The drugs were metabolized in the intestine before passing through the membrane.

IVL:

1. The excretion in urine is so low following intravenous administration ( $\leq 20\%$ ) that the absorption data may not be reliable based on the method of the ratio of urinary excretion following oral and intravenous administration.

In summary, it is difficult to be absolutely sure that some of these data refer to true absorption figures. If metabolism could occur during passage across the gastrointestinal tract, absorption data would be not reliable from the ratio of urinary excretion of drug-related material following oral and intravenous administration.<sup>54</sup> Bioavailability and urinary excretion data  $> 70\%$  may also reflect the absorption (Drugs 152–154). Although there is no doubt that some drugs are dose-limited, it is difficult to give a definition of a dose-limited drug because many factors can affect the solubility in the intestinal fluid and absorption in humans, such as the absorption mechanisms,<sup>268</sup> drug formulation, food composition, chemical composition, pH of the intestinal secretions, gastric emptying time, intestinal motility, and blood flow.<sup>269</sup> The pharmacokinetics of some drugs were

extremely complex, and our knowledge of their *in vivo* behavior is still far from complete.<sup>225</sup> Nadolol seems to be a dose-dependent drug.<sup>271</sup> Some absorption data have not been checked because these original papers have not been found (Drugs 164–172 and 241). The absorption information contained in each of the original references were extracted and recorded in the hope that this would be of value of investigators interested in QSAR studies on oral drug absorption.

### Relationship between Human Intestinal Absorption and Abraham Descriptors

To apply eq.1 to the absorption data, we take % absorption as the dependent variable, SP. Although this approach is contrary to the idea of eq. 1 as a linear free energy relationship, it is the only practical way of including all the relevant data. It is possible to convert percent absorption into a rate constant, or the logarithm of a rate constant, but only by omitting all drugs with 0% absorption and 100% absorption. Thus, all our correlation equations are couched in terms of eq.1, with percent absorption as SP.

To model human intestinal absorption using the Abraham descriptors, two training sets were selected from drugs 1–145 because these absorption data are considered to be comparatively reli-

able (Good and OK). Training set 1 is chosen by an alternative space-filling design technique developed by Kennard and Stone.<sup>270</sup> The principle of the method is based on the distribution of chosen descriptors. The descriptors of a training set should cover the whole descriptor space of the total set, and the histogram of the training set should relate to that of the total set, as shown in Figure 2 for training set 1. However, the histogram of the total set, and of course training set 1, is completely biased towards drugs with 100% absorption and it might be suggested that any mathematical analysis will also be biased in this way. We therefore chose another training set, based on histogram analysis, that is not biased towards 100% absorption. Although this second training set enables us to test for bias in the dependent variable, it is not statistically as sound as training set 1, because it does not take into account the distribution of descriptors. Therefore, we use training set 2 only as a test for the aforementioned bias. Figure 2 shows the histograms for the two separate training sets, the total data set and also the histogram of the data set from Wessel et al.<sup>10</sup>

Results of the two training set regression analyses using the Abraham descriptors in eq. 1 are given in Table 3 (Models 1 and 3). Step-wise regression was carried out to find the significant

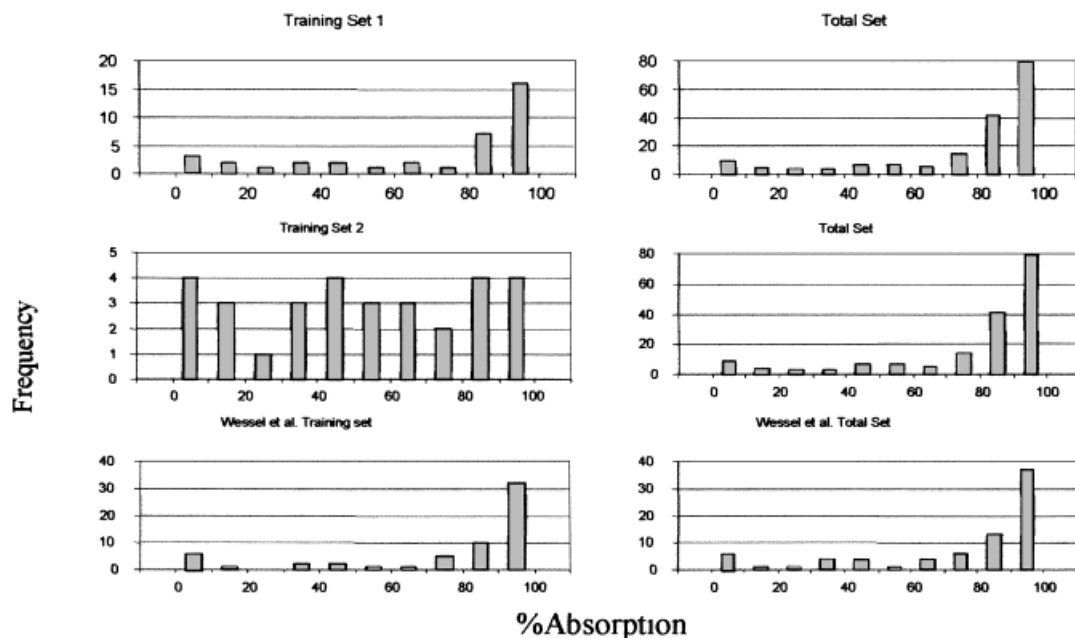


Figure 2. Histograms of training set and total set.

**Table 3.** Regression Results of Different Training Sets by Abraham Descriptors<sup>a</sup>

No.	Data Set	Model	Training Set						Test Set			
			$r^2$	$r^2_{cv}$	$n$	$S$	$F$	RMSE	$n$	RMSE	AAE	AE
1	Training 1	%Abs. = 90 + 2.11E + 1.70S - 20.7A - 22.3B + 15.0V	0.83	0.75	38	16	31	14	131	14	11	-1
2	Training 1	% Abs. = 92 - 20.0A - 21.9B + 17.2V	0.82	0.77	38	15	53	14	131	14	11	-1
3	Training 2	% Abs. = 82 + 3.97E - 3.58S - 19.5A - 18.0B + 14.0V	0.85	0.73	31	14	28	12	138	19	16	-13
4	Training 2	% Abs. = 83 - 19.9A - 18.6B + 13.6V	0.85	0.78	31	13	50	12	138	19	17	-14
5	Total data	% Abs. = 92 + 2.94E + 4.10S - 21.7A - 21.1B + 10.6V	0.74	0.72	169	14	93	14	—	—	—	—
6	Total data	% Abs. = 96 - 20.0A - 19.8B + 13.9V	0.72	0.71	169	15	144	14	—	—	—	—
7	Training 1 + DL	% Abs. = 89 - 24.0A - 18.9B + 16.8V - 0.421IS	0.80	0.75	49	17	43	16	—	—	—	—
8	Total data + DL	% Abs. = 93 - 21.3A - 19.0B + 14.6V - 0.386IS	0.74	0.72	180	15	124	15	—	—	—	—

<sup>a</sup> Training Set 1: see Table 1. Training set 2: drugs 7–8, 11, 15, 18–19, 21–22, 24–38, 136–141, and 143–145. Total data: drugs 1–172. RMSE: root mean square error,  $RMSE = [\sum (\text{Calc} - \text{Obs})^2 / n]^{0.5}$ . AAE: average absolute error,  $AAE = \sum |\text{Calc} - \text{Obs}| / n$ . AE: average error,  $AE = \sum (\text{Calc} - \text{Obs}) / n$ . IS: % insoluble oral dosed drug in 250 mL of water.

descriptors. The result showed that the significant descriptors were **A**, **B**, and **V** (Models 2 and 4 in Table 3) and the two dominant descriptors were **A** and **B**. This is in agreement with previous work that suggests hydrogen-bond donors and hydrogen-bond acceptors or polar molecular surface are good descriptors with which to model human intestinal absorption.<sup>9–11</sup> The coefficient standard errors of the variables are  $\sim 5$  for the two training sets (Models 1–4) and 2.5 for the whole data set (Models 5–6). The results indicate that models 1, 2, 3, and 4 are relatively similar. The two different ways of obtaining a training set result in very similar absorption models. However, Models 1 and 2 are statistically superior to Models 3 and 4. Use of Kennard and Stone selection results in training and test sets that have less bias (bias is defined as the average difference between the predicted and actual values in the test set). Models 1–4 show that increasing the volume (hydrophobic part) and decreasing the polarity of a compound can increase human intestinal absorption. Introducing solubility, octanol–water partition coefficient, molecular weight, and pKa terms did not improve the regression results. The details of drugs used for analysis are listed in Table 4.

For the full equation (Model 5), we have calculated the  $t$ -statistic as follows: **E** (1.05), **S** (1.71), **A** (8.20), **B** (-12.6), and **V** (5.11). These results show, as already indicated by our step-wise regression, that the descriptors **E** and **S** are

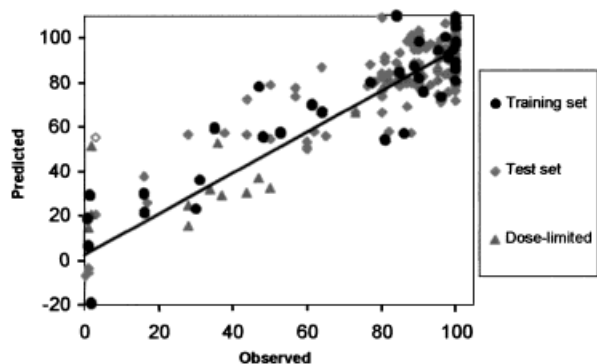
**Table 4.** Details of drugs used for analysis

Parameter	Number of Drugs	Drug No. in Tables 1,2, and 5
Total number investigated	241	1–241
Training set 1	38	1–38
Test set	131	39–165, 167, 169–171
Dose-limited drugs added for analysis in Models 7 and 8	11	202–212

statistically not very significant. We have also checked the inter-correlation of descriptors, and for the full data set of 169 compounds used in Models 5 and 6 we find cross-correlations in  $r^2$  to be as follows:

	S	A	B	V
E	0.617	0.053	0.312	0.373
S		0.197	0.426	0.460
A			0.272	0.037
B				0.404

The only cross-correlation that is rather high is that between **E** and **S**. Fortunately, neither **E** nor **S** is very significant and so the **E/S** cross-correlation presents no real problem. Thus for the truncated equation (Model 6) the largest cross-correlation in  $r^2$  is only 0.404, between **B** and **V**.



**Figure 3.** Relationship of the observed and predicted absorption.

Figure 3 shows the prediction result for the test set by Model 1 (Drugs 39–172). The predicted absorption is in agreement with observed absorption for 131 compounds. Only drug 161 ( $\diamond$  in Figure 3) is an obvious outlier according to the Abraham model. A possible reason for this outlier is that the drug may not be completely recovered in the urine and feces, even if the urinary excretion is the main route. Absorption may be underestimated by use of the percentage of excretion in urine. Absorption correction for dose-limited drugs was applied both to Model 2 and to the total data set by using additional descriptors (viz.: solubility, octanol–water partition coefficient, molecular weight, and administered dose). The result (Models 7 and 8; Figure 3) shows that the best additional descriptors were the solubility and dose. The latter was expressed by the percentage of insoluble drug (IS) administered in 250 mL of water (Table 2) for dose-limited drugs, with the percentage taken as zero for drugs 1–172. The regression result suggests that the more insoluble a dose-limited drug, the lower the absorption will be.

Table 5 lists the predicted absorption and also the residuals (Observed – Predicted) for dose-dependent, dose-limited drugs before the dose and solubility correction and drugs 229–241 obtained by Model 1 in Table 3. Results (Figure 4) show that almost all the absorption predicted for dose-dependent drugs (Drugs 220–226) is in the range of observed absorption. Absorption prediction for some of the dose-limited drugs (Drugs 203, 205, 206, and 209) is in agreement with or is in the range of the observed absorption, and for some of the dose-limited drugs (202, 204, 207, 208, and 210–212), the predicted values are higher than the observed absorption. This result is in agree-

ment with the point that absorption is highly variable and incomplete for the dose-limited drugs.<sup>163, 218, 223</sup> Platts method cannot accurately calculate the descriptors for drugs 193–201 because of missing fragments. The absorption prediction for some of these drugs does not agree well with the observed absorption, possibly because of the inaccurate calculation of descriptors.

The prediction of absorption for drugs 229–241 is higher than the observed absorption; which is in agreement with what we would expect for these drugs based on the method from which the absorption was derived. For example, absorption evaluated by the percentage of urinary excretion of drugs 236–240 is lower than the predicted absorption because excretion in urine for the absorbed drug may not be the only route for excretion. These drugs have  $C \log P$  values above zero; fecal excretion may be another route for the absorbed drug. Hence, absorption would be underestimated by the urinary excretion method.

All the descriptors used in our calculation refer to the neutral form of drugs, and we have included no correction for ionization of strong Brønsted acids and bases. Inspection of the calculated and observed % absorption reveals no particular trend of ionizable drugs. However, to assess more rigorously any effects, we carried out an analysis of 169 drugs used in Model 5 with inclusion of an indicator variable (**I**) for strong acids with  $pK_a < 4.5$  and bases with  $pK_a > 8.5$ ; **I** is taken as unity for the strong acids and strong bases, and zero for all other compounds. The resulting equation is:

$$\begin{aligned} \% \text{ Abs.} &= 94 + 2.90\mathbf{E} + 2.71\mathbf{S} - 20.7\mathbf{A} - 20.9\mathbf{B} \\ &\quad + 11.2\mathbf{V} - 3.14\mathbf{I} \\ n &= 169 \quad S = 14\% \quad r^2 = 0.74 \quad F = 78 \quad (3) \end{aligned}$$

It can be seen that the additional indicator variable (**I**) is hardly significant ( $\rho = 0.25$ ,  $t = -1.16$ ), and so we conclude that any ionization of Brønsted acids and bases has a very small effect indeed (3%) on the percent absorption. It is noteworthy that previous workers<sup>9–11</sup> have made no ionization correction either.

It is useful to compare the statistics of the various equations put forward for the correlation of percent absorption. Clark<sup>9</sup> carried out only a qualitative analysis, but Wessel et al.<sup>10</sup> and Palm et al.<sup>11</sup> both listed statistics as shown in Table 6. In their analysis, Palm et al.<sup>11</sup> gave standard deviations in the percent absorption observed

**Table 5.** Observed and predicted absorption from Model 1

No	Method for obtaining %Abs.	Quality of the %Abs. Data	Observed %Abs.	Predicted %Abs.	Obs. – Pred.	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	Error Code <sup>a</sup>
1	BIO	Good	100	97	3	2.30	3.40	0.46	2.04	3.40	–0P
2	BIO + RA	Good	100	89	11	0.24	0.47	0.59	0.44	1.31	–0P
3	EU	Good	100	85	14	1.05	0.89	0.72	0.38	0.99	–0P
4	REV	Good	100	104	–4	2.38	2.11	0.00	1.15	2.07	–0P
5	REV	Good	100	80	19	2.87	3.60	0.58	1.91	2.17	–0P
6	REV + EUB	Good	100	87	13	2.60	3.89	1.30	1.88	3.56	–0P
7	REV	Good	100	107	–7	1.72	2.56	0.00	2.28	3.99	–0P
8	REV	Good	100	98	2	0.97	0.81	0.03	0.84	1.58	–0P
9	REV	Good	100	109	–9	3.07	2.83	0.00	2.08	3.59	–0P
10	BIO	Good	99	94	5	1.62	1.40	0.59	0.75	1.78	–0P
11	BIO	Good	98	91	7	2.79	2.81	0.50	1.09	1.65	–0P
12	EU	Good	98	92	6	1.19	2.21	0.00	1.28	1.62	–0P
13	EU	Good	97	100	–3	2.12	1.25	0.00	1.39	2.29	–0P
14	BIO	Good	96	73	23	2.14	2.95	1.12	1.90	2.58	–0P
15	EU	Good	95	94	1	1.13	1.18	0.10	1.44	2.26	–0P
16	RA	Good	91	75	15	2.24	2.09	0.55	2.11	2.36	–0P
17	BIO	Good	90	82	8	3.25	3.78	0.25	2.64	2.83	–0P
18	REV	Good	90	98	–8	2.28	3.09	0.59	1.28	2.57	–0P
19	EU	OK	89	87	2	1.77	3.25	0.22	2.18	2.71	–0P
20	BIO	OK	86	57	29	1.20	2.40	0.54	2.78	2.21	–0P
21	EU	OK	85	84	1	1.35	2.15	0.93	1.09	2.06	–0P
22	RA	Good	84	109	–26	1.73	1.88	0.00	1.45	3.00	–0P
23	RA	Good	81	53	27	3.20	5.34	1.72	4.62	5.75	–0P
24	RA	Good	77	79	–3	1.13	1.60	0.35	0.99	0.89	–0P
25	RAP	OK	64	66	–3	1.53	2.11	0.59	2.14	1.96	–0P
26	BIO + RA	Good	61	69	–9	2.05	2.55	1.36	1.47	2.10	–0P
27	RAP + BIO	OK	53	57	–5	1.18	1.35	0.27	2.17	1.09	–0P
28	RA	Good	48	55	–7	1.55	1.45	1.41	1.68	1.73	–0P
29	RA	Good	47	78	–31	2.50	4.41	0.86	3.08	4.08	–0P
30	RA	Good	35	59	–24	1.39	2.18	0.78	1.71	1.11	–0P
31	RAP	OK	31	36	–5	0.67	1.42	1.52	1.78	0.86	–0P
32	RAP	OK	30	23	7	0.83	2.44	1.88	2.37	1.23	–0P
33	RA	Good	16	21	–5	3.94	6.54	2.13	6.12	6.14	–0P
34	RAP	OK	16	29	–14	2.08	3.00	1.76	2.72	1.79	–0P
35	RA	Good	2	–20	22	3.31	4.47	2.53	6.19	4.38	–0P
36	RA	Good	1.4	28	–28	3.13	5.12	2.32	4.09	4.16	–0P
37	RA	Good	1	6	–5	2.80	2.71	1.20	5.40	3.36	–0P
38	RA	Good	0.6	18	–18	1.95	2.57	1.70	3.53	2.23	–0P
Test set											
39	BIO	Good	100	99	1	2.63	2.56	0.00	1.84	2.67	–0P
40	BIO	Good	100	99	1	2.39	2.72	0.59	1.19	2.53	–0P
41	BIO	Good	100	101	–1	1.79	2.46	0.43	1.18	2.58	–0P
42	BIO	Good	100	76	24	2.82	3.51	0.58	2.08	2.17	–0P
43	BIO	Good	100	76	24	1.93	1.84	0.42	1.38	1.22	–0P
44	EF	Good	100	96	4	3.43	2.83	0.33	2.25	3.40	–0P
45	EU	Good	100	106	–6	1.99	1.57	0.09	1.04	2.26	–0P
46	EU	Good	100	101	–1	1.80	1.76	0.59	0.62	1.98	–0P
47	EU	Good	100	107	–7	1.97	1.56	0.00	1.15	2.40	–0P
48		Good	100	100	0	2.69	2.37	0.10	1.39	2.26	–0P
49	RA	Good	100	92	8	1.97	1.88	0.78	0.87	2.03	–0P
50	RA	Good	100	83	17	2.18	2.53	0.37	2.03	2.45	–0P

Table 5. (Continued)

51	RA	Good	100	101	-1	1.61	2.32	0.35	1.13	2.38	-0P
52	REV	Good	100	85	15	1.94	1.81	0.00	1.47	1.36	-0P
53	REV	Good	100	91	9	1.90	2.98	0.53	1.71	2.74	-0P
54	REV	Good	100	89	11	2.12	2.50	0.97	1.16	2.39	-0P
55	REV	Good	100	80	20	2.47	3.53	0.58	1.92	2.21	-0P
56	REV	Good	100	79	21	2.95	3.60	0.58	2.04	2.30	-0P
57	REV	Good	100	90	10	1.05	1.09	0.00	1.11	1.37	-0P
58	REV	Good	100	100	0	2.13	2.15	0.00	1.46	2.27	-0P
59	REV	Good	100	78	22	2.84	3.61	0.58	2.06	2.25	-0P
60	REV	Good	100	108	-8	1.70	2.48	0.00	2.07	3.79	-0P
61		Good	100	111	-11	1.58	2.47	0.00	1.16	2.62	-0P
62	BIO	Good	100	71	29	1.91	2.06	0.49	1.77	1.56	-0P
63	BIO	Good	100	123	-23	2.43	2.03	0.02	1.11	3.30	-0P
64	BIO	Good	100	111	-11	2.07	3.17	0.00	1.57	3.09	-0P
65	REV	Good	100	99	1	1.94	2.42	0.00	1.60	2.45	-0P
66	RA	Good	100	84	16	1.26	1.55	1.19	1.44	3.03	-0P
67	EU	Good	100	94	6	1.78	1.78	0.00	1.37	1.87	-0P
68	BIO	Good	99	94	5	2.33	2.21	0.28	1.24	1.93	-0P
69	EU	Good	99	83	16	2.83	3.31	0.56	2.47	3.20	-0P
70	EU	Good	99	82	17	2.19	3.26	0.72	2.00	2.75	-0P
71	EU	Good	99	98	1	1.85	1.36	0.10	1.29	2.15	-0P
72	EF	Good	98	83	15	1.15	1.42	0.32	1.47	1.87	-0P
73	EU	Good	98	94	4	2.30	2.43	0.55	1.26	2.31	-0P
74	RA	Good	98	90	8	1.44	1.71	0.35	1.48	2.28	-0P
75	REV	Good	98	75	23	2.46	2.87	0.50	1.71	1.59	-0P
76	BIO	Good	97	106	-9	0.93	1.23	0.00	0.69	1.82	-0P
77	BIO	Good	97	83	14	2.52	2.81	0.50	1.76	2.18	-0P
78	EU	Good	97	93	4	1.24	1.32	0.35	1.36	2.37	-0P
79	RA	Good	97	95	2	1.53	1.58	0.00	1.05	1.48	-0P
80	RA	Good	96	70	26	2.20	2.73	1.41	1.76	2.64	-0P
81	BIO	Good	96	99	-3	1.68	1.52	0.00	0.98	1.63	-0P
82	BIO	Good	95	84	11	1.69	2.30	0.35	1.62	2.01	-0P
83	BIO	Good	95	74	21	1.54	1.98	0.74	1.74	2.10	-0P
84	EU	Good	95	86	9	2.02	1.78	0.26	1.75	2.21	-0P
85	EU	Good	95	90	5	1.80	2.38	0.00	1.76	2.09	-0P
86	EU	Good	95	97	-2	0.86	0.84	0.59	0.50	1.78	-0P
87	EU	Good	95	86	9	2.20	2.13	0.77	1.62	2.64	-0P
88	EU	Good	95	93	2	1.26	1.18	0.10	1.49	2.22	-0P
89	EU	Good	95	80	15	1.45	1.95	0.58	1.64	2.18	-0P
90	REV	Good	95	84	11	1.47	1.81	0.10	2.03	2.38	-0P
91	EU	Good	93	97	-4	1.25	1.03	0.10	1.25	2.16	-0P
92	REV	Good	93	79	17	1.84	2.11	0.53	1.29	1.40	-0P
93	BIO	Good	92	95	-3	1.63	1.78	0.59	0.86	1.98	-0P
94	RA	Good	91	83	8	2.06	3.16	0.72	1.98	2.80	-0P
95	BIO	Good	90	99	-9	1.33	1.29	0.10	1.44	2.57	-0P
96	BIO	Good	90	85	5	1.69	2.02	0.59	1.23	1.87	-0P
97	BIO	Good	90	82	8	2.88	3.57	0.58	1.91	2.32	-0P
98	BIO	Good	90	89	1	2.21	1.68	0.48	1.21	1.87	-0P
99	EU	Good	90	94	-4	0.94	0.77	0.18	0.63	1.24	-0P
100	EU	Good	90	79	11	1.86	2.46	0.66	1.62	2.07	-0P
101	EU	Good	90	83	7	1.44	1.48	0.70	1.12	1.77	-0P
102	EU	Good	90	77	13	1.87	2.55	0.20	2.41	2.46	-0P
103	BIO	Good	90	103	-13	2.58	2.22	0.00	1.32	2.20	-0P
104	EU	Good	90	88	2	1.24	1.30	0.35	1.50	2.23	-0P
105	RA	Good	90	111	-11	1.71	2.43	0.32	1.54	2.92	-0P
106	RA	Good	89	88	1	2.51	2.33	0.38	1.49	1.99	-0P

**Table 5.** (Continued)

No	Method for obtaining %Abs.	Quality of the %Abs. Data	Observed %Abs.	Predicted %Abs.	Obs. Pred.	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	Error Code <sup>a</sup>
107	BIO	OK	89	94	-5	2.70	2.63	0.68	1.04	2.07	-0P
108	EU	OK	89	87	2	1.88	1.68	0.26	1.73	2.25	-0P
109	RA	Good	88	101	-13	1.75	2.17	0.32	1.37	2.71	-0P
110	EU	OK	88	97	-9	1.72	2.47	0.32	1.53	2.64	-0P
111	RAP	OK	88	79	9	1.59	2.14	0.68	0.95	1.15	-0P
112	BIO	OK	88	57	31	1.62	2.06	0.61	2.34	1.67	-0P
113	EU	OK	87	98	-11	1.14	1.31	0.09	1.07	1.94	-0P
114	EU	OK	87	81	6	1.68	1.48	0.47	1.58	2.01	-0P
115	BIO	OK	87	69	18	2.34	2.36	0.51	1.92	1.53	-0P
116	EU	OK	85	78	7	2.10	1.68	0.55	1.76	2.06	-0P
117	BIO	OK	85	85	0	2.02	3.15	0.42	1.84	2.37	-0P
118	BIO	OK	85	93	-8	1.85	1.94	0.19	1.74	2.54	-0P
119	RA + EF	Good	84	80	4	1.15	1.68	0.50	1.31	1.62	-0P
120	BIO	OK	84	88	-4	2.48	2.46	0.28	1.54	1.94	-0P
121	EU	OK	84	84	0	0.93	1.35	0.59	0.80	1.29	-0P
122	RA	Good	82	57	25	2.55	2.71	0.93	2.39	2.00	-0P
123	BIO	OK	82	84	-2	2.18	3.23	0.72	2.02	2.90	-0P
124	EU	OK	82	80	2	0.76	2.38	0.00	2.28	2.36	-0P
125	BIO	OK	81	91	-10	0.82	1.80	0.54	1.41	2.60	-0P
126	BIO	OK	81	89	-8	2.30	1.90	0.26	1.88	2.55	-0P
127	BIO	OK	81	78	3	1.77	2.08	0.61	1.37	1.60	-0P
128	REV	Good	80	83	-3	1.60	2.40	0.58	1.97	2.76	-0P
129	REV	Good	80	76	4	0.78	0.79	0.22	1.81	1.83	-0P
130	BIO	OK	80	73	7	1.27	1.81	1.02	0.85	1.17	-0P
131	BIO	OK	80	83	-3	2.09	3.22	0.77	2.01	2.91	-0P
132	EU	OK	80	84	-4	1.85	1.60	0.11	1.51	1.56	-0P
133	EU	OK	80	66	14	1.21	1.89	0.55	1.51	1.03	-0P
134	EU	OK	80	82	-2	2.35	3.41	0.42	2.16	2.52	-0P
135	BIO	OK	80	109	-29	1.61	1.59	0.00	1.25	2.71	-0P
136	BIO + RAP	OK	77	88	-11	1.98	2.71	0.25	1.83	2.34	-0P
137	RA	Good	64	86	-22	2.84	3.09	0.81	1.59	2.50	-0P
138	RA	Good	60	50	10	2.21	2.16	1.82	2.05	2.36	-0P
139	RA	DP?	57	77	-20	1.61	1.63	0.70	1.88	2.49	-0P
140	BIO + RAP	OK	50	79	-29	1.45	1.89	0.55	1.75	2.18	-0P
141	RAP	OK	44	72	-28	1.84	2.93	0.75	2.21	2.53	-0P
142	RA	Good	44	56	-12	1.41	1.44	1.28	1.71	1.70	-0P
143	BIO + RAP	OK	38	57	-19	2.61	2.53	1.07	2.47	2.26	-0P
144	RA	Good	17	25	-8	0.79	1.76	1.78	1.93	0.70	-0P
145	RAP	OK	3	20	-17	2.15	3.08	2.02	2.96	1.85	-0P
146	EF		92	96	-4	1.67	2.46	0.32	1.62	2.71	-0P
147			62	58	4	1.41	1.40	1.28	1.74	1.84	-0P
148	REV		60	50	10	3.23	3.15	1.28	3.06	2.81	-0P
149	REV		28	56	-28	1.88	2.36	0.84	3.17	3.10	-0P
150	REV		1	-4	5	3.50	3.75	0.81	6.78	4.02	-0P
151	RA	IVL	100	84	16	2.39	2.45	1.28	1.60	3.13	-0P
152	BIO	OK?	78	80	-2	2.98	2.99	0.20	2.81	3.02	-0P
153	BIO	OK?	76	78	-2	1.34	1.40	0.55	1.12	1.28	-0P
154	EU	OK?	71	88	-17	1.26	1.58	0.59	1.33	2.30	-0P
155	EU	OK?	73	66	7	0.88	1.11	0.19	1.55	0.70	-0P
156	EU	OK?	69(65-72)	55	14	2.19	3.13	1.49	1.78	1.73	-0P
157	EU	OK?	60	53	7	1.39	1.59	1.08	2.22	1.94	-0P
158	EU	OK?	57	73	-16	1.87	2.33	0.82	1.88	2.27	-0P

**Table 5.** (Continued)

159	EU	OK?	50	54	-4	2.54	3.25	0.95	2.23	1.51	-0P
160	EU	OK?	16	37	-21	1.00	1.83	1.63	1.97	1.31	-0P
161	EU	OK?	3	55	-52	2.52	2.89	1.08	2.18	1.72	-0P
162	EU	OK?	1	-6	7	3.33	3.13	0.87	6.94	4.28	-0P
163	EU	OK?	0.3	-8	8	2.74	3.51	2.20	5.05	3.26	-0P
164		Check	100	90	10	1.61	1.89	0.32	1.59	2.39	-0P
165		Check	100	110	-10	1.29	1.38	0.00	1.20	2.79	-0P
166		Check	100	90							
167		Check	95	82	13	1.64	1.96	0.35	1.84	2.23	-0P
168		Check	91	90							
169		Check	60	100	-40	3.47	3.04	0.28	1.81	2.92	-0P
170		Check	50	77	-27	1.62	1.99	0.11	1.83	1.55	-0P
171		Check	28	54	-26	2.20	2.44	0.91	2.44	1.92	-0P
172		Check	Poor	45		2.16	1.84	0.04	4.80	3.65	-0P
Zwitterionic drugs											
173	BIO	Good	100	53	47	2.72	3.07	1.12	2.80	2.49	-10P
174	BIO	Good	100	80	20	2.27	2.64	0.00	2.54	2.50	-10P
175	BIO	Good	100	85	15	2.05	2.45	0.00	2.22	2.41	-10P
176	EU	Good	100	69	31	2.54	2.77	0.58	2.50	2.43	-10P
177	EU	Good	100	72	28	2.34	2.74	0.58	2.32	2.39	-10P
178		Check	100	70	30	0.47	0.59	0.52	0.89	0.56	-10P
179	BIO + RAP	Good	93	52	41	2.53	2.90	1.12	2.85	2.54	-10P
180	BIO	Good	90	100	-10	1.93	1.56	0.59	1.23	2.89	-10P
181		Check	90	113	-23	3.90	3.15	0.59	1.71	3.98	-10P
182	BIO	OK	88	88	0	2.84	3.20	0.17	2.20	2.63	-10P
183	EU	OK	88	94	-6	2.10	2.07	0.59	1.50	2.81	-10P
184	EU	OK	88	77	11	0.86	1.11	0.59	0.78	0.89	-10P
185	BIO	OK	86	55	31	1.36	1.30	1.36	1.50	1.43	-10P
186	BIO + RAP	OK	75	37	38	3.65	4.11	1.73	3.48	3.04	-10P
187	RAP	OK	62	67	-5	2.36	2.60	0.58	2.56	2.48	-10P
188	EU	OK?	58	72	-14	0.56	0.76	0.77	0.93	1.09	-10P
189	RA	Good	55	76	-21	0.62	0.83	0.77	0.91	1.30	-10P
190	RAP	OK	55	65	-10	0.46	0.74	0.79	1.34	1.26	-10P
191		Good	41	56	-15	1.35	1.26	1.36	1.54	1.57	-10P
192		Check	1	43	-42	4.47	5.36	1.28	4.08	3.48	-10P
Drugs with missing fragments from ABSOLV program											
193	RA	Good	8	96	-88	1.75	2.23	0.00	2.30	3.32	-20P
194	RA	Good	100	70	30	2.10	1.99	0.49	2.01	1.82	-60P
195	BIO	Good	98	89	9	1.31	1.34	0.94	0.79	2.07	-60P
196	BIO	Good	95	80	15	1.60	1.49	0.64	1.16	1.53	-60P
197	EU	OK	85	-70	155	4.31	6.77	4.02	7.65	4.91	-60P
198	RA	Good	72	60	12	2.62	3.23	0.97	2.58	2.43	-60P
199	EU	OK?	50	-45	95	3.96	6.12	3.18	7.20	4.84	-60P
200	RA	Good	32	65	-33	1.45	1.89	0.43	2.01	1.47	-60P
201	BIO + RAP	OK	23	116	-93	0.87	0.62	0.00	0.13	1.72	-60P
Dose-limited, dose-dependent, and formulation-dependent drugs											
202	EUB	DL	73	108	-35	2.25	3.74	0.00	1.82	3.17	-0P
203	BIO	DL	50(25-75)	68	-18	3.03	3.81	0.38	3.81	3.90	-0P
204	RAP	DL	47	78	-31	2.97	4.16	0.31	3.22	3.49	-0P
205	RA	DL	44(36-52)	70	-26	2.58	3.89	0.41	3.31	3.36	-0P
206	RAP + BIO	DL	37	58	-21	1.97	3.26	0.93	5.04	6.00	-0P
207	RA	DL	36	90	-54	1.61	3.25	0.50	2.92	4.47	-0P
208	RA	DL?	34	73	-39	1.37	2.08	1.63	1.81	3.37	-0P
209	BIO	DL	28(10-65)	36	-8	3.97	6.84	1.54	8.65	10.02	-0P
210	REV	DL	28	66	-38	3.94	4.38	0.84	4.03	4.48	-0P

Table 5. (Continued)

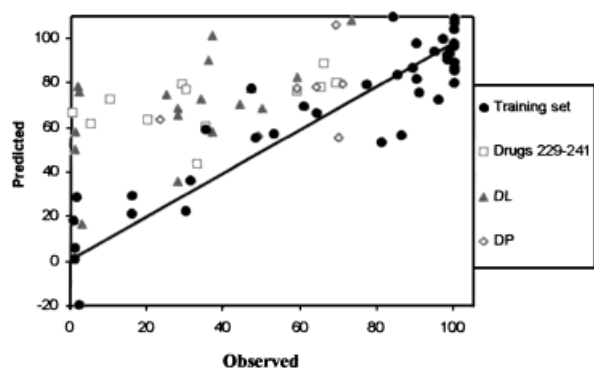
No	Method for obtaining %Abs.	Quality of the %Abs. Data	Observed %Abs.	Predicted %Abs.	Obs. Pred.	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>	Error Code <sup>a</sup>
211	BIO + EU	DL	120(0.7–23)	76	–74	3.51	2.91	0.81	2.93	3.73	–0P
212	RAP	DL?	1	58	–57	2.66	3.38	0.91	2.93	2.73	–0P
213	RAP	DL	1.9	78	–76	3.44	3.39	1.57	1.33	2.50	–60P
214	EU	DL?	59(56–61)	83	–24	3.18	3.10	1.27	1.49	2.70	–10P
215	EU	DL?	≥ 37	101	–64	2.34	2.43	0.28	1.84	3.27	–10P
216	BIO + EF	DL?	28(25–50)	69	–41	1.79	2.42	0.96	2.56	3.19	–10P
217	EU	DL?	25(10–40)	74	–49	1.60	2.18	0.78	2.08	2.66	–10P
218	EU	DL	3(2–5)	17	–14	3.70	5.37	3.37	5.70	7.12	–10P
219	RA	DL?	1	50	–49	2.77	4.36	1.15	3.18	2.76	–10P
220	BIO	DP	69(37–100)	106	–37	2.28	2.57	0.43	1.91	3.89	–0P
221	BIO	DP	64(39–88)	78	–14	1.60	2.29	0.20	2.28	2.40	–0P
222	RA	DP	49(36–61)	56	–7	2.18	3.12	1.21	1.97	1.69	–0P
223	BIO	DP	23(15–30)	63	–40	2.34	2.67	0.83	1.87	1.52	–0P
224	EF	DP	71	79	–8	2.08	2.46	0.31	2.10	2.27	–10P
225	RA	DP	70(57–83)	56	14	3.91	4.73	1.80	2.77	3.22	–10P
226	BIO + EU	DP	59(43–74)	78	–19	0.63	0.83	0.77	0.93	1.44	–10P
227	EUB	FD	86(77–95)	87	–1	3.40	3.81	0.25	2.38	2.74	–0P
228	EU	DL? + M	24(17–31)	80	–56	2.21	1.61	1.43	0.81	2.03	–0P
Drugs expected to have higher absorption											
229	RAP		≥ 69	80	–11	2.27	2.57	0.31	2.10	2.30	–10P
230	BIO + RAP		≥ 33	44	–11	1.71	2.66	1.13	2.44	1.58	–0P
231	RAP		≥ 29	80	–51	1.41	1.75	0.67	2.01	2.84	–0P
232	RAP		≥ 10	73	–63	2.84	3.17	1.46	1.50	2.34	–10P
233	RAP		≥ 5	62	–57	1.80	2.37	0.74	2.66	2.57	–0P
234	EU + EF		66(61–71)	89	–23	1.50	2.29	0.28	2.09	2.94	–10P
235	EU~EF		59(49–68)	76	–17	2.20	2.58	0.40	2.28	2.44	–0P
236	EU		≥ 65	78	–13	1.85	2.52	0.77	1.76	2.36	–0P
237	EU	DL?	≥ 30	77	–47	2.18	2.49	0.56	2.06	2.38	–0P
238	EU		≥ 20	64	–44	2.05	2.25	0.98	1.82	1.77	–0P
239	EU	DL	≤ 10	109	–99	1.29	2.22	0.35	1.32	3.29	–0P
240	EU		≥ 0.4	67	–66	3.10	3.64	1.35	2.41	3.04	–0P
241	BIO		≥ 35	61	–26	1.97	3.55	1.02	4.71	5.77	–0P

<sup>a</sup>Error code:

1. –0P: The descriptors are OK by ABSOLV program.
2. –10P: Zwitterionic molecule. The program calculates descriptors for the neutral form, but in many environments the charged form will dominate.
3. –20P: Charged molecule. There are no fragments for these molecules, such as CO<sub>2</sub><sup>–</sup> or NR<sub>4</sub><sup>+</sup>.
4. –60P: Missing fragment. The molecule has an atom or atoms for which no fragment values have been defined. The descriptors calculated from ABSOLV will be wrong.
5. All the drugs and drug-like materials with the error code of –10P, –20P, and –60P were not used in all of the regression analyses.
6. Dose-limited drugs are defined as  $100 \times [\text{Dose} \times (1 - \text{fraction absorbed}) - 0.25 \times \text{WS}] / \text{Dose} > 20\%$ .

for 16 drugs. The average of these standard deviations is 9%, so that it is unreasonable to expect any equation to correlate percent absorption to less than this value. The RMSE values of Palm et al.<sup>11</sup> and Wessel et al.<sup>10</sup> in Table 6 thus represent about the limit of correlative equations. Of course, predictions of percent absorption for a

test set cannot be expected to be better than correlations, as shown by the RMSE of 16% for 10 drugs in the test set of Wessel et al.<sup>10</sup> By comparison, our RMSE of 14% for a test set of no less than 131 drugs represents a very good prediction, bearing in mind the experimental error in the data.



**Figure 4.** Plot of absorption observed and predicted by Model 1.

In conclusion, the Abraham descriptors are able to successfully predict absorption for a diverse set of drugs. The significant descriptors are the summation of solute hydrogen bond acidity (**A**) and the summation of solute hydrogen (**B**), but the volume term may also contribute to the absorption. The predicted absorption could also be fitted very well with the observed absorption for large drugs (molecular weight > 500) if they were not dose-limited (Drugs 150, 163 and 197). Most of the dose-limited drugs satisfied the “rule of 5”; that is, they have molecular weight of > 500 and number of hydrogen bond donors > 5 or number of hydrogen bond acceptors > 10. They usually have low solubility and their absorption varies considerably among different preparations.<sup>264</sup> The absorption is usually higher dosed in solution than in solid form.<sup>26</sup> The absorption of these drugs may not only be controlled by the passive diffusion rate, but also by the *in vivo* dissolution rate in small intestinal fluid. Therefore, the solubility and dose are very important pieces of information that should be known before QSAR analysis is attempted on the human absorption because the drug may be dose limited and have lower absorption. The absorption model allows prediction of

**Table 6.** Comparison of Statistics for Equations for Percent Absorption

Source	Training Set			Test Set	
	$r^2$	$n$	RMSE, %	$n$	RMSE, %
Palm et al. <sup>11</sup>	0.94	20	9	—	—
Wessel et al. <sup>10</sup>	—	67	9	10	16
No. 1, Table 3	0.83	38	14	131	14
No. 5, Table 3	0.74	169	14	—	—

human intestinal absorption to about  $\pm 15\%$  and can be used to determine how to modify drug structure to improve absorption.

In a following paper, we aim to discuss the mechanism of human intestinal absorption and factors such as the rate-limiting step of absorption and the contribution of ionized and unionized species.

## ACKNOWLEDGMENTS

Y. H. Zhao and J. Le are grateful to Glaxo Wellcome and Roche Products Ltd. for a postdoctoral research fellowship and a research studentship.

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