Evaluation of rat intestinal absorption data and correlation with human intestinal absorption. Eur J Med Chem 38:233-243

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · APRIL 2003

Impact Factor: 3.45 · DOI: 10.1016/S0223-5234(03)00015-1 · Source: PubMed

Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Medicinal Chemistry 38 (2003) 233–243
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Original article

Evaluation of rat intestinal absorption data and correlation with human intestinal absorption

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Received 16 September 2002; received in revised form 18 December 2002; accepted 23 December 2002

Abstract

The absorption of 111 drug and drug-like compounds was evaluated from 111 references based on the ratio of urinary excretion of drugs following oral and intravenous administration to intact rats and biliary excretion of bile duct-cannulated rats. Ninety-eight drug compounds for which both human and rat absorption data were available were selected for correlation analysis between the human and rat absorption. The result shows that the extent of absorption in these two species is similar. For 94% of the drugs the absorption difference between humans and rats is less than 20% and for 98% of drugs the difference is less than 30%. There is only one drug for which human absorption is significantly different from rat absorption. The standard deviation is 11% between human and rat absorption. The linear relationship between human and rat absorption forced through the origin, as determined by least squares regression, is %Absorption (human) = 0.997%Absorption (rat) ($n = 98$, SD = 11). It is suggested that the absorption in rats could be used as an alternative method to human absorption in pre-clinical oral absorption studies.

Keywords: Human intestinal absorption; Rat intestinal absorption; Correlation; Evaluation

1. Introduction

Modern drug design not only focuses on the pharmacological activity of a compound but also considers its ability to be absorbed and to reach its site of action. One of the methods used to screen the ability of a compound to be absorbed is intestinal permeability in rats. Two quasi in vivo methods were developed some years ago. The methodology of Schanker [1] involves using 30 mL of drug solution, which is recirculated for 3 h through the length of the rat intestine using a pump, and employing a solution reservoir. The amount of drug absorbed and kinetic constant of absorption can be calculated. The advantage of this method is that experimental conditions (i.e. pH) can be controlled and can help in understanding the absorption mechanism [2]. Similar to the Schanker method, another method used to screen the intestinal permeability of a compound in rats was developed by Dolusio [3]. Using this method, 10 mL of drug solution was introduced into the rat small intestine (after appropriate surgery and rinsing), and 0.1 mL aliquots removed for analysis at regular time intervals. A non-animal procedure, diffusion though Caco-2 cell monolayers, has been employed to screen permeability and is especially valuable for examining a large number of compounds [4].

However, the absorption information obtained from the above methods focuses on the rate of diffusion across either the rat small intestine or cell monolayers. It is important to note that this diffusion rate may not be the only factor that controls absorption. Many other factors, such as solubility, formulation, food composition, chemical composition, pH of the intestinal secre-

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0223-5234/03/$ - see front matter
doi:10.1016/S0223-5234(03)00015-1

tions, gastric emptying time, intestinal motility and blood flow [5], can affect absorption. Therefore, pharmacokinetic experiments in animals are usually carried out in order to obtain the percentage of drug absorption. Rat is one of the most common animals employed in pre-clinical oral absorption studies. Chiou and Barve [6] recently reported an excellent overall correlation ($r^2 = 0.97$) between human and rat absorption for 64 drugs with wide physicochemical and pharmacological properties. They concluded that their study indicates that evaluation of in vivo absorption in rats may be employed as an alternative method to predict the extent of oral absorption in humans following oral administration of drugs in a solution or rapidly released dosage form. Chiou's group also showed that for non-linear absorption, excellent correlation between humans and rats for about 100 drugs could be made when doses are normalised to body surface area [7]. Monkey may be another excellent animal model for predicting oral absorption in humans but they are very expensive [8]. Chiou and Buehler found absorption values in monkeys were similar or identical to those in humans. Similar t_{max} values found in monkeys and humans at comparable doses indicate comparable absorption kinetics between the two species. On the other hand, dog may not be a good model. Poor correlation ($r^2 = 0.51$) between the two species was found by Chiou's group [9].

In a previous paper [10], the human intestinal absorption of 241 drug and drug-like compounds with a wide range of physicochemical properties was evaluated. Although many research groups have worked to establish quantitative relationships between human absorption and molecular descriptors [11–18], only the study of Chiou and Barve has compared human and rat absorption for a large data set (80 compounds) [6–9]. The aim of this study is firstly to obtain more absorption data from the literature and secondly to investigate the similarity in absorption between humans and rats.

2. Chemistry

2.1. Rat intestinal absorption data

The rat intestinal absorption dosed orally by gavage was collected and evaluated from 111 sources of literature. The details of the evaluation are shown below. Other absorption data on 48 drugs were taken from Chiou and Barve [6,9].

2.2. Human intestinal absorption data

Two-hundred and forty one human oral absorption data was evaluated from over 250 original papers and reviews. Among them, 198 absorption data were considered to be reliable or relatively reliable. Eighteen drugs were separated from the total of 241 drugs as dose-limited drugs because dissolution may be the rate-determining step of absorption for these compounds. Based on the analysis of solubility, dosage and extent of absorption, these dose-limited drugs cannot be rapidly released into GI gut fluid if a drug is dosed as a tablet or capsule [7]. The details of the evaluation were published previously [10].

2.3. Statistical analysis

The data set was analysed using EXCEL 97. The regression coefficients were obtained by least-squares regression analysis. For each regression, the following information is provided: number of observations used in the analysis (n), square of coefficient of determination (r^2), standard deviation of the estimate (SD) for 95% confidence and Fisher's criterion (F). For equations where the line is forced through the original (no constant), we do not give any value for r^2 as equations 2 and 4 (below). It is known that in these equations r^2 is difficult to interpret [19,20].

3. Results and discussion

3.1. Evaluation of rat intestinal absorption data

The rat is a very common animal employed in preclinical oral absorption studies. Although a large data set of 80 compounds was used by Chiou and Barve [6,9], there were potentially much more data available from the literature.

Methods of obtaining qualified oral absorption have previously been reported [6,10]. One of the best ways of obtaining oral absorption data is from the ratio of cumulative urinary excretion of drug and drug-related materials following oral and intravenous administration; this method being especially used for low absorption. Table 1 lists the absorption data evaluated mostly by this method and also some absorption data obtained from the percentage of urinary and biliary excretion. The following key is used as an indication of the source and quality of the data.

3.1.1. RA

The absorption is evaluated from the ratio of cumulative urinary excretion of compounds following oral and intravenous administration.

3.1.2. EU

The absorption is obtained from the urinary excretion of compounds following oral administration and recovery in urine is greater than 80%.

Table 1
Rat absorption, percentage of excretion in urine, bile and faeces of drugs and drug-like compounds

Number	Names	Percentage of absorption [a]	Excretion in urine [b]	Excretion in bile [c]	Excretion in faeces [d]	Total recovery [e]	Oral dose [f] (mg kg^{-1})	Percentage of absorption [g]	Method for obtaining percentage of absorption [h]	Quality of the percentage of absorption [i] data	References
1	Alprenolol		38/37	/56	44/55	81/92	10 sol	100	RA	OK	[27]
2	Cisapride	~100/100 [j]					40–160 sol	100		OK	[28]
3	Clofibrate	100/100 [j]	87/83		3.6/7	91/90	25 susp	100	RA	OK	[29]
4	Cyclosporin	100 [j]	6.6/8.3	9.1/59	85/77	92/86	10–30 sol	100		OK	[6,30]
5	Etintidine		70/63		28/23	98/86	20 sol	100	RA	OK	[31]
6	Felbamate	100	66(47)/(58)	52/40	24(0)/(0)	90	100sol/susp	100	EBF	OK	[32]
7	Lorcainide		36/29	70	61/67	97/96	5 sol	100	RA	OK	[33]
8	Lormetazepam	100	20/19				0.25 susp	100	RA	OK	[34]
9	Nilvadipine	~100	24/21	/74	69/80	93/101	10 sol	100	RA	OK	[35]
10	Propranolol	99 [j]	68/52		27/24	95/76	10 sol	100	RA	OK	[36]
11	Propylthiouracil	~100	90/75		1.5		20 sol	100	RA	OK	[37]
12	Rimantadine		81–87/81–87				60	100	RA	OK	[38]
13	Salicylicacid	100 [j]	~100	1	1	100	5–50 sol	100	EUB	OK	[39]
14	Sultopride	100 [j]	71–82	29	24–30	95–100	10–100 sol	100	EUB	OK	[40]
15	Timolol		58/51		26/28	84/79	10 sol	100	RA	OK	[41]
16	Tinidazole	100	64/65		25/25	89/90	100 susp	99	RA	OK	[42]
17	Tiopinac	99	60.7/61.3		31/33	92/94	2 sul/susp	99	RA	OK	[43]
18	Acetylsalicylicacid	~100	86/88		2.0/3	88/91	10 sol	98	RA	OK	[44]
19	Exaprolol	98	48/49				1	98	RA	OK	[45]
20	Bumetanide	95–98	15/37		79/61	94/98	5 sol	97	RA(note)	OK	[46,47]
21	Camazepam	97/97 [j]	29/30		58/65	87/95	20 susp	97	RA	OK	[48]
22	Venlafaxine	97 [j]	97			97	22.1 sol	97	EU	OK	[49]
23	Viloxazine	100 [j]	91–101		1–8	95–101	4–250 sol	96	EU	OK	[50]
24	1,3-diphenyl-1-triazene		76/80				20 sol	95	RA	OK	[51]
25	Carfecillin	95 [j]	95		5	100	740 sol	95	EU	OK	[52]
26	Acetaminophen	98 [j]	92				100 sol	92	EU	OK	[53]
27	Granisetron	100/100 [j]	35/38(32)	42/53	61/59	96/97	0.25–5 sol	92	RA	OK	[54]
28	Fenclofenac	100 [j]	2–4	79–84	86(1)	87–91	10 sul/susp	92(84–99)	EUB–EBF	OK	[55]
29	Torasemide		70/78	/30	13/16	83/94	10 cap	90	RA	OK	[56]
30	1,3-diphenylguanidine		32/36		45/46	77/82	321 sol	89	RA	OK	[57]
31	Enciprazine		32/36	/79	59/57	91/93	20 sol	89	RA	OK	[58]
32	Dofetilide	~100	54/61		41/36	95/97	7 sol	88	RA	OK	[59]
33	Omeprazole	100 [j]	23/26		73/72	96/98	34.5	88	RA	OK	[60]
34	Amlodipine		33/38		58/60	91/98	10 sol	87	RA	OK	[61]
35	Ketorolac	87/87 [j]	69/79		24/18	94/98	1 sol	87	RA	OK	[62]
36	Nizatidine	100 [j]	57(55)	22	27(6)	85	10	86(77–94)	EUB–EBF	OK	[63]
37	Trimethoprim		85		10	95	20 susp	85	EU	OK	[64]
38	Ramatroban	83	(79)	4			sol	83	EUB	OK	[65]
39	Tetrapeptide	>75	75/90		14/14	89/104	1 susp	83	RA	OK	[66]
40	Bitolterol		65/79		24/24	89/103	1.14 sol	82	RA	OK	[67]

Table 1 (*Continued*)

Number	Names	Percentage of absorption [a]	Excretion in urine [b]	Excretion in bile [c]	Excretion in faeces [d]	Total recovery [e]	Oral dose [f] (mg kg^{-1})	Percentage of absorption [g]	Method for obtaining percentage of absorption [h]	Quality of the percentage of absorption [i] data	References
41	Casodex	~80	30/37		71/58	101/95	25 susp	81	RA	OK	[68]
42	Felodipine	100 [j]	26/32(15)	/74	55	81	1.92 sol	81	RA	OK	[69,70]
43	Pentacaine	79	32/40				2	79	RA	OK	[71]
44	Saccharin	100 [j]	74–83		16	98–104	16–22 sol	79	EU	OK	[72]
45	MK-711		29.5/38		55/44	85/82	1	78	RA	OK	[73]
46	Terbutaline	60 [j]	12(41)/48	44–29	61/35	73/83	1	78(70–85)	EUB	OK	[74]
47	Dapsone		(45)	24	(22)		5 sol	74(69–78)	EUB–EBF	OK	[75]
48	Acifran		61/84		29/4.8	90/89	10 sol	73	RA	OK	[76]
49	Carvedilol		(3.48)/(12)	68/81	(26)/(1.01)	(98)/(94)	30 susp	71	EUB	OK	[77]
50	Loprazolam	~68	6.7(13)	46	90(15)	97	5 sol	68	Note 1	OK	[78]
51	Valaciclovir		65/95			98/99	25 sol	68	RA	OK	[79]
52	Perindopril		33/44–54		59/41–36	92/86	0.5	67	RA	OK	[80]
53	Pravastatin	65	4/4.8	58/90	87/83	91/88	20 sol	62	EUB	OK	[81]
54	Avitriptan		9.8/22	62/54	85/70	95/92	20 sol	59(45–72)	RA–EUB	OK	[82]
55	Ramipril	56/56 [j]	26		71	97	susp	56	RA(note)	OK	[83]
56	Colterol		43/83		43/23	86/107	1.41 sol	52	RA	OK	[67]
57	Atenolol	48–50 [j]	42–49/88(71–89)	/2.5	51–56/13	99/101(73–91)	9–80 sol	52(48–56)	RA	OK	[84,85]
58	Apovincaminc acid	50	18/44		62/35	80/79	10 sol	50	RA	OK	[86]
59	Prulifloxacin	44	14(15.5)	35	83(44)	97	20 susp	50	EUB	OK	[87]
60	Fosfomycin		46/95	0.07/0.1			100 sol	48	RA(note)	OK	[88]
61	MK-499		10/21.0	40	78/68	88/89	0.25 sol	48	RA	OK	[89]
62	PCE22716		29/61		53/33	82/94	5	43	RA	OK	[90]
63	Fenoterol	42/57 [j]						42	RA(note)	OK	[91]
64	Recainam		25/59		72/39	97/98	8.5 sol	42	RA	OK	[92]
65	Ziprasidone		(22)	20	(55)	(97)	10 susp	42	EUB	OK	[93]
66	Azidocillin		23/56	/52	60/39	83/95	15 sol	41	RA	OK	[94]
67	YM17E	>40	0.4(1)/0.6	39	97/95	97/96	10 sol	40	EUB	OK	[95]
68	Fosmidomycin		34/90	/0.2	61/3	95/93	10	38	RA	OK	[96]
69	Doxycycline		9–11/30		87/71	99/101	10	33	RA	OK	[97]
70	Inogatran	30–35	16–21/52–60		67–72/35–45	95/98	~1 sol	33(30–35)	RA	OK	[98]
71	Bromocriptine	32–40/32–40 [j]		23	(68)	(91)	sol	32	EBF	OK	[99]
72	Pamaqueside		0.1(5.8)/(34)	11/40.6	98(76)/(1.3)	98(93)	100 sol	24	EBF	OK	[100]
73	Xamoterol	19/19 [j]	8.0/43		89/52	97/95	5 sol/susp	19	RA	OK	[101]
74	Nadolol	14–18/18 [j]	8.6–11/62		88–84/31	96/93	20 sol/susp	18	Note		[102,103]
75	Pranolium chloride	8–13	7.2/40	<5/25	76/40	83/80	1 sol	18	RA	OK	[104]
76	Reproterol	18			58			18	RA(note)	OK	[105]
77	Oxitropium bromide	14	/~50	12.0/14	/~50			14	RA(note)	OK	[106]
78	CGS 16617		6.3/93	0.1–2.4	89/5.3	95/98	10 sol	7	RA	OK	[107]
79	NAD394		3.4/63		93/33	96/96	20 susp	5.4	RA	OK	[87]
80	Iothalamatesodium	2.1–7/1.9 [j]	3.8–4.9/98				20–800 sol	4.2	RA(note)	OK	[108]

Table 1 (*Continued*)

Number	Names	Percentage of absorption [a]	Excretion in urine [b]	Excretion in bile [c]	Excretion in faeces [d]	Total recovery [e]	Oral dose [f] (mg kg^{-1})	Percentage of absorption [g]	Method for obtaining percentage of absorption [h]	Quality of the percentage of absorption [i] data	References
81	Acarbose	1–2/1.5 [j]	3.2–14/94	0/0.2	(80–103)/(0.91)		2–200 sol	2	RA	OK	[109]
82	Alendronate	~0.9	/35		/0.36	/35	10 sol	0.9	RA(note)	OK	[110]
83	Pamidronate	0.5	0.12	/0.07			20	0.5	Note	OK	[111]
Drugs with less-reliable absorption											
84	Mespirenone		15.5/10		63/31	79/41	2–200 susp	100	RA	TL	[112]
85	Toremifene		2.8/3.5		70/62	73/65	3–48 sol	80	RA	IVL	[113]
86	Nufenoxole		8	60	61	69	1 sol	79(68–99)	EUB–EBF	TL	[114]
87	L-canavanine		61/83		2.0/0	63/83	2000	73	RA	TL	[115]
88	Amodiaquine		7.0/10		77/91	84/101	8.6 sol	70	RA	IVL	[116]
89	(−)-6-aminocarbovir		32/47				60 sol	68	RA	OK?	[117]
90	Diflubenzuron	~50	23(21)	32–41	50–69	73–92	4 susp	68(58–77)	EUB+EBF	DP	[118]
91	Prazosin		8.3/12.5	40(24h)	81/75	89/88	1 sol	66	RA	IVL	[119]
92	Crisnatol		6.8/10.7		90/83	97/94	5 sol	64	RA	IVL	[120]
93	Ranitidine	63 [j]	63		33	96	sol	>63	EU	OK?	[121]
94	Spironolactone		4.69/7.46		74.19/90.18	79/97	5 sol	63	RA	IVL	[122]
95	Bromerguride		4.5/7.5		87/89	92/97	0.25 susp	60	RA	IVL	[123]
96	Benidipine hcl		9–20(6–17)	42–51	73–91		1–0.5 susp	58(48–68)	EUB	V	[124]
97	Carbidopa		16/66	8/1.0	52/10	68/76	20 sol	24–54	RA–EBF	TL	[125]
98	Idarubicin	~50	5.3/16		76/81	81/97	1 sol	~50	RA	IVL	[126]
99	Lacidipine		3–8/5–14		88–95/76–96	97/96	2.5 susp	~50	RA	IVL	[127]
100	Sumatriptan	~50/50 [j]	12–30/45–71		63–71/17–23		1–5 sol	~50	RA	V	[128,129]
101	Sulpiride		15–20	20–30	75	90–95	sol	43(35–50)	EUB	V	[130]
102	Nileprost		12/27.0	/83	67/59	79/86	0.2 sol	44	RA	TL	[131]
103	Pidotimod		31/76				100 sol	41	RA	OK?	[132]
104	Carbovir		30–18/77–42		41–60/4–31	71–78/81–73	10–60	~40	RA	V	[133]
105	Ipratropium bromide	17–35	5.5/58	3.2/18				17–35	RA	OK?	[134]
106	Lovastatin	29/29 [j]	0.6/2.1		78/96	79/98	sol	29	RA	IVL+TL	[81]
107	Pafenolol	16–31	10–20/58–69		80/30	95/95	0.34–8.4sol	24(16–31)	RA	V	[135]
108	ANSA		7–8/60		58–80/16	77/76	45	13	RA	TL	[136]
109	BMS-18374	2.9	2.2(0.5)/18(14)	0.6/41	103/95	104/109	0.015 sol	12	RA	IVL	[137]
110	Acyclovir	21 [j]	8.0/90		88/9.5		100–900 sol	9	RA	DP	[138]
111	Tripeptoid	3–8	0.44/5.52		94/91	94/97	1 susp	6	RA	IVL	[66]

Notes for some of drugs. Drug 50: absorption is evaluated from the percentage of cumulative excretion in urine, faeces and amount in intestine gut (16%). Drugs 60 and 80: absorption is obtained from the ratio of urinary excretion of parent drug following oral and intravenous administration. Drugs 55, 63, 76 and 77: absorption is obtained from the ratio of urinary excretion following oral and

intravenous administration. Drug 20: The absorption value is obtained from references [46,47]. More recent studies using the HPLC method have demonstrated that the drug is virtually completely absorbed. Drug 74: absorption is evaluated from the ratio of urinary excretion of the drug following oral and intraperitoneal administration. Drug 82: absorption is based on the ratio of amount in bones following oral and intravenous administration. Drug 83: amount absorbed within 72 h was means used as radioactivity in urine and organs.

[a] Absorption data was given from the original literature.
[b] Percentage of cumulative drug and its metabolites in urine following oral/intravenous administration to intact (bile duct-cannulated) rats.
[c] Percentage of cumulative drug and its metabolites in bile by oral/intravenous administration to bile duct-cannulated rats.
[d] Percentage of cumulative excretion in faeces by oral/intravenous administration to intact (bile duct-cannulated) rats.
[e] Total recovery of cumulative excretion in urine and faeces by oral/intravenous administration to intact (bile duct-cannulated) rats.
[f] Dose in solution or (and) suspension or capsule.
[g] Absorption data (or averaged values) chosen here based on the analysis of excretion in urine, bile and faeces.
[h] Method for obtaining absorption data (%Absorption [f]).
[i] Quality of the absorption data based on the analysis of literature values.
[j] Absorption is from Chiou data set [6,9].

3.1.3. EUB

The absorption is obtained from the sum of urinary and biliary excretion of compounds following oral administration and total recovery in urine and faeces is greater than 80%.

3.1.4. EBF

The absorption is evaluated from the excretion in faeces and bile to bile duct-cannulated rats and total recovery in urine and faeces is greater than 80%.

3.1.5. OK

The absorption is evaluated from the original papers; or from the ratio of urinary excretion of compounds following oral and intravenous administration and urinary excretion following oral and intravenous administration is greater than 20%; or from biliary excretion to bile duct-cannulated rats and total recovery in urine and faeces is greater than 80%.

3.1.6. OK? (uncertain)

The absorption is evaluated from the RA but the total recovery is not given. If the total recovery in urine and faeces following ether oral or intravenous administration is lower than 80%, a large estimation error will result.

3.1.7. IVL

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

3.1.8. TL

The total recovery in urine and faeces is lower than 80%. The absorption may not be reliable.

3.1.9. V

Absorption is variable because of variable excretion in urine or bile.

3.1.10. DP

Absorption is dose-dependent based on original papers.

The single oral dose level to intact or bile duct-cannulated rats (mg kg^{-1}) by gavage in solution or suspension is also listed in Table 1. All of the values in urine, faeces and bile were obtained from studies using radio-labelled compounds except drugs 45 and 111. The above methods may mis-estimate drug absorption if metabolism occurs in the gastrointestinal tract.

Table 2
Human and rat absorption data (% absorbed of dose)

Number	Names	Rat	Human
1	Alprenolol	100	93
2	Antipyrine	100 [a]	97
3	Bornaprine	100 [a]	100
4	Bumetanide	97	96
5	Caffeine	100 [a]	100
6	Cimetidine	100 [a]	> 64/98 [a]
7	Cisapride	100/100 [a]	100
8	Clofibrate	100/100 [a]	97
9	Clonidine	100 [a]	95
10	Codeine	100 [a]	95
11	Cyclosporin	100 [a]	100 [a]
12	Diclofenac	100 [a]	100
13	Doxazosin	100 [a]	100 [a]
14	Ethinylestradiol	100 [a]	100
15	Felbamate	100	90
16	Flumazenil	100 [a]	95
17	Fluvastatin	100 [a]	98 [a]
18	Imipramine	100 [a]	100
19	Isradipine	100 [a]	92
20	Ketanserin	100 [a]	100 [a]
21	Ketoprofen	100 [a]	92
22	Lormetazepam	100	100
23	Miglitol	100 [a]	100 [a]
24	Morphine	100 [a]	85
25	Nimodipine	100 [a]	100 [a]
26	Oxatomide	100 [a]	100
27	Phenglutamide	100 [a]	100
28	Progesterone	100 [a]	100
29	Propranolol	100/99 [a]	99
30	Propylthiouracil	100	76
31	Remoxipride	100 [a]	100 [a]
32	Salicylicacid	100/100 [a]	100
33	Sultopride	100/100 [a]	89
34	Tamsulosin	100 [a]	100 [a]
35	Timolol	100	95
36	Tolmesoxide	100 [a]	98
37	Verapamil	100 [a]	100
38	Ximoprofen	100 [a]	98
39	Isoxepac	99 [a]	98 [a]
40	Acetylsalicylicacid	98	100
41	Camazepam	97/97 [a]	100
42	Theophylline	97 [a]	100
43	Venlafaxine	97/97 [a]	97
44	Levodopa	97 [a]	86
45	Viloxazine	96/100 [a]	98
46	Bisoprolol	96 [a]	100 [a]
47	Carfecillin	95/95 [a]	99
48	Cefadroxil	95 [a]	100
49	Hydrocortisone	95 [a]	91
50	Acetaminophen	92/98 [a]	100 [a]
51	Fenclofenac	92/100 [a]	100
52	Granisetron	92/100 [a]	100
53	Naproxen	92 [a]	99
54	Nitrendipine	90 [a]	88 [a]
55	Torasemide	90	96
56	Omeprazole	88/100 [a]	80/97 [a]
57	Ketorolac	87/87 [a]	90
58	Nizatidine	86/100 [a]	90
59	Trimethoprim	85	97
60	Felodipine	81/100 [a]	88
61	Toremifene	80	100
62	Gabapentin	79 [a]	59(43–74)
63	Saccharin	79/100 [a]	88
64	Terbutaline	78/60 [a]	62
65	Captopril	≥ 71 [a]	84
66	Pelrinone	71 [a]	98 [a]
67	Prazosin	66	86(77–95)
68	Hydrochlorothiazide	65 [a]	69(65–72)
69	Ranitidine	> 63/63 [a]	64(39–88)
70	Spironolactone	63	73
71	Pravastatin	62	34
72	Chlorothiazide	60 [a]	49(36–61)
73	Furosemide	60 [a]	61
74	Ramipril	56/56 [a]	60 [a]
75	Atenolol	52/49 [a]	50
76	Benazepril	50 [a]	> 37
77	Sumatriptan	−50/50 [a]	57
78	Fosfomycin	48	31
79	Azithromycin	45 [a]	37
80	Sulpiride	43(35–50)	44
81	Fenoterol	42/57 [a]	60
82	Recainam	42	71
83	Ziprasidone	42	60
84	Fosmidomycin	38	30
85	Enalapril	34 [a]	> 66(61–71)
86	Bromocriptine	32/36 [a]	28
87	Lovastatin	29/29 [a]	> 10
88	Pafenolol	24(16–31)	> 29
89	Bretyliumtosylate	20 [a]	23
90	Xamoterol	19/19 [a]	8.6 [a]
91	Nadolol	18/18 [a]	57/20 [a]
92	Reproterol	18	60
93	Enalaprilat	11 [a]	25(10–40)
94	Acyclovir	9/21 [a]	23(15–30)
95	Adefovir	8 [a]	16
96	Amphotericin B	5 [a]	3(2–5)
97	Iothalamatesodium	4/2 [a]	2
98	Acarbose	2	2/1.5 [a]

[a] The absorption is obtained from reference [6,9].

3.2. Relationship between human and rat intestinal absorption

Recently, Chiou and Barve [6] reported an excellent linear correlation for the percentage of oral dose absorbed between humans and rats for 64 drugs (equation 1). Regression analysis through the origin results in the same standard error (equation 2, $S = 5.6$). However, the correlation between dogs and human was relatively poor for 43 drugs ($r^2 = 0.51$) [9]. Their study indicates that the evaluation of in vivo absorption in rats may be used as an alternative method to satisfactorily predict the extent of GI absorption in humans following oral administration of drugs in a solution or rapidly released dosage form.

$$\%\text{Absorption (rat)} = 0.990\%\text{Absorption (human)} + 0.164 \quad (1)$$

$n = 64$, $r^2 = 0.97$, SD = 5.6 $F = 2176$

$$\%\text{Absorption (rat)} = 0.996\%\text{Absorption (human)} \quad (2)$$

$n = 64$, SD = 5.6, $F = 2211$.

In order to further compare the similarity between the human and rat absorption, 98 drugs that have both human and rat absorption values were selected and are listed in Table 2. Among the data listed in Table 2, 21 rat absorption data are evaluated from original references (Table 1). Twenty-nine rat absorption data were also evaluated from original references although these values were previously reported in the Chiou and Barve paper [6,9] as well. A further 48 rat absorption data were directly obtained from the Chiou's data set [6,9]. Most of the human absorption data were obtained from reference [10] and some were obtain from references [6,9]. The relationship between human and rat absorption for these compounds is shown in Fig. 1 (the line is the unity line with 95% confidence intervals), from equation 3.

$$\%\text{Absorption (human)} = 0.91\%\text{Absorption (rat)} + 6.89 \quad (3)$$

$n = 98$, $r^2 = 0.88$, SD = 11, $F = 675$

$$\%\text{Absorption (human)} = 0.997\%\text{Absorption (rat)} \quad (4)$$

$n = 98$, SD = 11, $F = 640$.

The data in Table 2 shows that for 94% of the drugs the absorption difference between humans and rats is less than 20% and for 98% of drugs the difference is less than 30%. There are only two drugs, enalapril and reproterol, for which human absorption is significantly different from rat absorption (difference $>30\%$) (see Table 3 and Fig. 1). It is not surprising to see the difference for enalapril because it is a dose-dependent drug. For reproterol, the human absorption was given in a review paper [10]. The method from which this absorption data was obtained needs to be checked; large estimation errors may result for low absorption drugs if intravenous administration is very low or total recovery in urine and faeces is lower than 80% following oral and intravenous administration (e.g. drugs 84–104 in Table 1). Regression analysis through the origin results in nearly the same standard deviation (equation 4). Because the equation coefficient is nearly equal to 1 (0.997), this suggests that there is no bias in the two data sets.

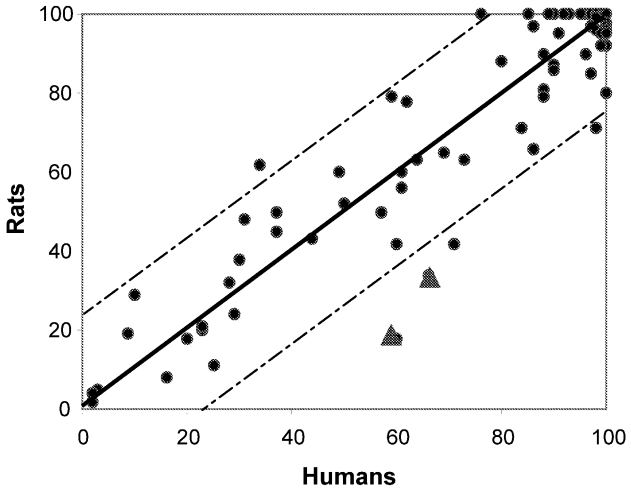

Fig. 1. Plot of human percentage of absorption against rat percentage of absorption for 98 compounds.

Absorption is a complex kinetic process that is dependent on numerous biochemical, physiological and physicochemical factors. It is difficult to be absolutely sure that some data refer to true absorption. It is also difficult to evaluate the error of absorption data. The ratio of cumulative urinary excretion using radio-labelled compounds following oral and intravenous administration is a popular method to obtain absorption data, especially for low absorption. However, this method has no specification in identifying the parent and its metabolisms. For example, oral absorption of bumetanide in rats was reported to be 41% based on a radioactive method [46]. Using an HPLC method it was recently demonstrated that bumetanide is virtually completely absorbed in rats [47].

Sometimes, it is difficult to give a certain or reliable value of absorption. Absorption for some drugs is highly dose-dependent (i.e. chlorothiazide) and the reported data are based on 'intrinsic absorption' at low doses [7]. The differences of absorption for some drugs, such as enalapril, acyclovir, gabapentin and

Table 3
Standard deviation (SD) and average absolute error (AAE) between human and rat absorption

Absorption (%)	Data set in this paper			Chiou and Barve data set		
	Number [a]	SD	AAE [b]	Number [a]	SD	AAE [b]
0–100	98	11	−0.7	64	5.6	3.0
0–89	43	15	−3.4	25	8.3	5.2
0–49	21	16	−4.9	15	9.2	5.1
0–19	8	15	−6.0	7	3.4	2.6

[a] The number of compounds is based on the rat absorption values.
[b] AAE = Σ|%Absorption (human) − %Absorption(rat)|/n.

adefovir, between humans and rats are most likely attributed to dose-dependent absorption phenomenon [6,7,10]. The methods used to obtain absorption may be another source for the difference. Percentages of 62, 85 and 98 for human absorption of cimetidine were reported in references [4,11,6], respectively. Some absorption values with 100% have been given in the literature from the high urinary excretion of compounds (usually $\geq 80\%$) following oral administration [10]. The 100% values were obtained based on the words of 'almost and nearly complete absorption' from the original papers. The absorption values of 80 and 100% do not make any difference to pharmacokinetic scientists because the two absorption values may have errors of about 20%. However, 20% error is quite high for QSAR studies. For example, if an absorption value was given as 85%, the range of absorption could be from 70–100% if the error is 15%. However, this range is still reasonable for pharmacokinetic workers. Therefore, it is suggested that the present model will be useful except in the following two cases: first, the predicted absorption is high or medium but the observed absorption is low, and second, the predicted absorption is low and the observed absorption is medium or high. By inspection of the human and rat absorption data, we find only reproterol that does not satisfy these rules. As explained above, the method of obtaining the absorption data may cause the difference.

Since oral administration to rats is in solution or suspension, it is reasonable to assume that in vivo dissolution rate does not significantly affect the extent of rat intestinal absorption [6,9,10]. This situation does not apply to human absorption in which drugs with poor solubility may exhibit incomplete dissolution and hence incomplete absorption [21–24]. Dissolution rate is the rate-determining step of absorption for these drugs [7,10,24–26]. Nearly all drug administration in humans was by tablet or capsule with 100–300 mL of water. In contrast to humans, all the rat oral administration listed in Table 1 was dosed in solution or suspension, and in some cases with a certain amount of organic solvent such as ethanol, methylcellulose or corn oil. Examining the human absorption administered orally both in solution and tablet form, it is evident that absorption for drugs dosed in solution is usually equal to or higher (sometimes significantly higher) than in solid forms [102,103]. For solid drug forms, absorption may not only be controlled by passive diffusion, but also by the in vivo dissolution rate in small intestinal fluid. Furthermore, drugs dosed with organic solvents used in the administration, such as ethanol, may precipitate out when the level of solvent effectively decreases. Dissolution can still be the rate-limited step for low solubility drugs.

Transporting difference in intestine between human and rat may be another source of difference between humans and rats. If metabolism occurs during passage across the gastrointestinal tract, absorption data cannot be reliably obtained from the method. Absorption data will be underestimated if the absorption of metabolites is lower than their parent drug. On the other hand, the absorption data will be overestimated if the absorption of metabolites is higher than their parent drug. Correlation of absorption between human and rat may not be linear, but curved. Chiou's recent results showed that the absorption between human and rat is linear for drugs not limited by the solubility problem and non-linear for the dose-dependent drugs when doses are normalised to body surface area or $BW^{0.67}$ [7]. The physiological difference between humans (or rats) can also result in difference of absorption [55].

4. Conclusions

Absorption is a complex kinetic process that is dependent on numerous biochemical, physiological, and physicochemical factors. Experimental error for obtaining absorption value is quite high, especially for low absorption. It is un-realistic to attempt to obtain QSAR models that can accurately predict human or rat absorption. Statistical analysis shows that standard deviations between human and rat absorption are 11 for 0–100% absorption and 16 for 0–49% absorption (Table 3); this is considered to be in the range of experimental error. After comparison of data on 98 drugs, it is apparent that rat absorption is similar to human absorption. This is in agreement with the result reported from Chiou et al. [6] although the coefficient of determination and standard error ($r^2 = 0.88$, SD = 11) obtained in this paper is not as significant as that in the Chiou paper ($r^2 = 0.97$, S = 5.6). Our results suggest that evaluation of in vivo absorption in rats could be used as an alternative method to predict the extent of intestinal absorption in humans following oral administration.

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