International Journal of Pharmaceutics 373 (2009) 24–40

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

An interesting relationship between drug absorption and melting point

Katherine A. Chu*, Samuel H. Yalkowsky

University of Arizona, College of Pharmacy, 1703 E Mabel Street, Tucson, AZ 85721, United States

ARTICLE INFO

Article history:
Received 6 December 2008
Received in revised form 26 January 2009
Accepted 30 January 2009
Available online 12 February 2009

Keywords:
Absorption
Absorption potential
Bioavailability
Dose
Fraction absorbed
Melting point
Partition coefficient
Passive absorption
Solubility
Suspension

ABSTRACT

The ability to predict the extent of passive intestinal drug absorption is very important for efficient lead candidate selection and development. Physicochemical-based absorption predictive models previously developed use solubility, partition coefficient and pK_a as drug input parameters for intestinal absorption. Alternatively, this study looks at the relationship between melting point and passive transport for poorly soluble drugs. It is based entirely on the expression derived from the General Solubility Equation (GSE) that relates melting point to the *product* of intrinsic solubility and partition coefficient. Given that the melting point of a compound is one of the first and more reliable physical properties measured, it can be advantageously used as a guide in early drug discovery and development.

This paper elucidates the interesting relationship between the melting point and dose to the fraction absorbed of poorly soluble drugs, i.e., class II and IV compounds in the Biopharmaceutics Classification System. The newly defined melting point based absorption potential (MPbAP) parameter is successful at distinguishing 90% of the 91 drugs considered being well absorbed (FA > 0.5) or poorly absorbed. In general, lower melting compounds are more likely to be well absorbed than higher melting compounds for any given dose. The fraction absorbed for drugs with high melting temperatures is limited by the dose to a greater degree than it is for low melting compounds.

1. Introduction

The discovery of new drugs is becoming progressively more difficult and more expensive. Pharmaceutical companies spend $1 billion dollars in research and development for every drug that reaches the market (Herper, 2007). According to Oprea (2002) approximately one in a million compounds, from those initially tested via high throughput screening, is likely to reach the market. There are a multitude of factors responsible for the time and cost of bringing new therapies to market. Any guideline to streamline the drug discovery and development process and design lead candidates for clinical success can help sustain a competitive industry.

Rational drug design and automated in vitro screening have produced promising compounds with respect to intrinsic activity, yet their physicochemical properties are often not optimized to promote passive intestinal absorption. It is generally recognized that the pharmacokinetic profile of a drug is influenced by its physical chemical properties, i.e., molecular weight, lipophilicity, polar surface area, hydrogen-bond donors and acceptors, etc. (Ajay et al., 1998; Sadowski and Kubinyi, 1998; Oprea et al., 2001; Biswas et al., 2006). These molecular descriptors can be manipulated to obtain drugs with the desired physicochemical properties governing passive intestinal drug transport, i.e., solubility and permeability.

A number of physicochemical and physiological factors affect oral drug absorption. Factors such as drug solubility, lipophilicity, dissolution, formulation, food composition, gastric emptying time, GI fluid volume, GI fluid pH, bile salts, intestinal motility, and specialized membrane transport can all affect absorption. Clearly, intestinal absorption is a complex process and any model that attempts to encompass all the physicochemical and physiological properties governing transport of drug molecules will not be straightforward. For poorly soluble drugs that are not subject to active or efflux transport mechanisms, a few simple physicochemical parameters are sufficient for determining the fraction of drug absorbed by passive transport.

Since oral drug delivery is the most popular and preferred route of administration, the ability to predict the extent of intestinal absorption is very important for efficient drug selection. Hence, various models have been proposed for predicting the fraction of drug absorbed (Dressman et al., 1985; Macheras and Symillides, 1989; Johnson and Swindell, 1996; Wessel et al., 1998; Balon et al., 1999; Sanghvi et al., 2001, 2003; Zhao et al., 2001; Willmann et al., 2004; Obata et al., 2005; Yalkowsky et al., 2006; Hou et al., 2007).

Lipinski's Rule of Five (Lipinski et al., 1997) and the Biopharmaceutics Classification System (Amidon et al., 1995) provide a qualitative and a semi-quantitative understanding, respectively, of how solubility and permeability affect oral absorption. Others have proposed predictive models that provide a more quantitative perspective of how aqueous solubility, S_w^{int}, partition coefficient, K_{ow}, and dose affect the extent of passive intestinal absorption

* Corresponding author. Tel.: +1 520 626 2014; fax: +1 520 626 2466.
E-mail address: chu@pharmacy.arizona.edu (K.A. Chu).

0378-5173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2009.01.026

(Dressman et al., 1985; Balon et al., 1999; Sanghvi et al., 2001). Another model utilizes the first-order absorption rate constant, intrinsic solubility, and particle size to determine the maximum absorbable dose (Johnson and Swindell, 1996). Again, this study proposes the use of the melting point of a compound to predict the fraction of drug absorbed.

1.1. Membrane transport of nonelectrolytes

The numerous models proposed for predicting oral absorption can be broadly classified as in vivo, in situ, in vitro, and in silico, in order of biological relevancy. They range from simple to complex models that are developed based on any number of molecular descriptors or physiological variables. However, only in silico models can be used in drug design and early drug discovery.

Virtually all in silico absorption prediction models are based on the theory of Stehle and Higuchi (1972a,b) on the mass transport of a solute across a membrane by passive diffusion. In these models the transport rate, or flux F, is given by

$$F \propto \Delta C \cdot K_{mw} \tag{1}$$

where ΔC is the concentration gradient across the membrane and K_{mw} is the membrane–water partition coefficient. Eq. (1) is applicable at steady-state conditions where the concentrations have no time dependence, that is, the concentration differential across the membrane is constant. Using silicone rubber membranes, Flynn and Yalkowsky (1972) showed that in the case of drug suspensions, the flux is given by

$$F \propto S_w^{int} \cdot K_{mw} \tag{2}$$

where S_w^{int} is the molar intrinsic solubility of the unionized form of the drug in water and K_{mw} is its membrane–water partition coefficient. Yalkowsky et al. (1973) then showed that the above relationship can be applied to the transport of alkyl-p-aminobenzoates across the gills of goldfish by replacing the membrane–water partition coefficient with the octanol–water partition coefficient, K_{ow}.

1.2. Absorption potential

Using similar reasoning, Dressman et al. (1985) and Balon et al. (1999) developed absorption potential, AP, models to estimate the intestinal absorption of drugs by passive transport. Dressman's absorption potential is calculated from S_w^{int}, K_{ow}, and the fraction of unionized drug at pH 6.5, F_{non}, luminal volume in liters, V, and administered dose in moles, D. The volume of the lumen is usually assumed to be 0.250 l (Dressman et al., 1985). Balon's model is more quantitative and is based on the solubility of the drug in water at pH 6.8, $S_T^{6.8}$, and the distribution coefficient at the same pH, $K_D^{6.8}$, instead of their intrinsic counterparts.

$$AP_{Balon} = \log\left(\frac{S_T^{6.8} \cdot K_D^{6.8} \cdot V}{D}\right) \tag{3}$$

A sigmoidal relationship between the absorption potential and the human fraction of drug absorbed has been observed by Dressman for 7 drugs and Balon for 20 drugs.

1.3. Effect of pH on transport for saturated solutions

The pH dependence of the total solubility and the octanol-buffer distribution coefficient are well understood and can be reliably modeled on the basis of the intrinsic solubility, intrinsic partition coefficient, pH and pK_a values. Although it is not especially difficult to experimentally determine the pK_a and log D values for compounds, it may not be practical to do so when thousands of compounds are being screened for passive intestinal absorption. A useful simplification that requires no prior knowledge of dissociation constants and pH has been put forward. In saturated solutions, Ni et al. (2002) showed that as the total solubility, S_T, of a weak electrolyte increases with pH, there is an accompanying and proportionate decrease in the distribution coefficient, K_D, such that the product of the two ($S_T \cdot K_D$) is a constant and equal to the product of their intrinsic counterparts ($S_w \cdot K_{ow}$).

$$S_T \cdot K_D = S_w^{int} \cdot K_{ow} \tag{4}$$

This relationship assumes that ion pair partitioning and salt precipitation are negligible. The average absolute difference between the two products for the 25 acids, bases, and ampholytes that Ni et al. studied is 0.116 log units. This error is small relative to the typical errors associated with calculated solubility and partition coefficient values. The small error confirms the applicability of Eq. (4).

The basis for the relationship between the two products ($K_D \cdot S_T$ and $K_{ow} \cdot S_w^{int}$) is the concentration of the uncharged species in octanol. First, the distribution coefficient is the ratio of the total concentrations (i.e., the sum of the concentrations of the unionized and ionized forms) of the drug in the octanol phase to that in the aqueous phase. That is:

$$K_D = \frac{[HA]_{oct} + [A^-]_{oct}}{[HA]_w + [A^-]_w} \tag{5}$$

where [HA] is the concentration of the unionized species and [A^-] is the concentration of the ionized form, and the subscripts 'oct' and 'w' represent the octanol and aqueous phases, respectively. If it is assumed that the concentration of the ionized form in octanol is negligible, then the total concentration of the drug in octanol can be approximated by the concentration of the uncharged form. Therefore, the distribution coefficient can be simplified as:

$$K_D = \frac{[HA]_{oct}}{S_T} \tag{6}$$

or

$$S_T \cdot K_D = [HA]_{oct} \tag{7}$$

Secondly, since the intrinsic octanol–water partition coefficient only measures the unionized species in the two phases, the product of $S_w^{int} \cdot K_{ow}$ also results in a constant:

$$S_w^{int} \cdot K_{ow} = [HA]_w \left(\frac{[HA]_{oct}}{[HA]_w}\right) = [HA]_{oct} \tag{8}$$

Eqs. (7) and (8) show that the two products ($K_D \cdot S_T$ and $K_{ow} \cdot S_w^{int}$) approximate the concentration of the uncharged species in octanol. In saturated solutions this value is constant and independent of pH. Thus it provides the basis for the equivalence of $K_D \cdot S_T$ and $K_{ow} \cdot S_w^{int}$ (i.e., Eq. (4)). The use of the terms S_w^{int} and K_{ow} provides an advantage since they are easier to measure and to calculate than S_T and K_D and consequently it is not necessary to consider the pK_a of the drug. Furthermore, their use eliminates the potential inaccuracies of determining distribution coefficients and solubilities at a specific pH. It also avoids the inability of a single pH value to model the entire absorbing region of the small intestines where according to Willmann et al. (2004) the pH can range from 5.0 to 7.5. This can translate into a 100-fold or more difference in solubility, depending on the pK_a of the drug substance.

Based on the above rationale, Sanghvi et al. (2001) proposed a modified absorption potential (MAP) that requires only S_w^{int} and K_{ow} as molecular input parameters. By combining Eqs. (3) and (4) they get:

$$MAP = \log\left(\frac{S_w^{int} \cdot K_{ow}}{4 \cdot Dose}\right) \tag{9}$$

For the combined 27 compounds analyzed by Dressman and Balon, Sanghvi reported that the fraction of drug absorbed is correlated as

well as or better with MAP than with AP. It should be emphasized that the above-modified absorption potential is only valid for drugs that are in suspension in the GI fluid volume, as noted in a subsequent paper by Sanghvi et al. (2003). If the MAP is applied to drugs in solution, the intrinsic solubility term used in the MAP model would be an overestimate of the concentration of the uncharged species, resulting in an artificially high MAP value.

2. Method

2.1. Compound selection

Only passively transported drugs are evaluated in this study. Compounds known to have active or efflux transport mechanisms and compounds known to be extensively metabolized in the gut or liver are excluded from the data set. Low solubility drugs are defined here as those drugs that form saturated solutions in the gut. A drug is assumed to form a saturated solution if its molar solubility is less than the concentration of the dose in moles dispersed in 0.250 l of aqueous medium, i.e., if

$$S_w^{int} < 4 \cdot \text{Dose} \quad (10)$$

Salts are excluded in this study since the General Solubility Equation (GSE) (Jain and Yalkowsky, 2001) is only applicable to nonelectrolytes and the uncharged form of weak electrolytes.

2.2. Absorption data

Experimentally derived human intestinal absorption data for 219 structurally diverse compounds were compiled from literature (Zhao et al., 2001; Sanghvi et al., 2003; Willmann et al., 2004). Due to the compound selection criteria for passively absorbed low solubility drugs, only 91 compounds are evaluated in the model and are listed in Table 1. If more than one fraction absorbed value is given, an average was used. Most of the doses were taken from these references. Additional sources are cited in the table. If multiple doses are available for a given compound, the average dose was taken. For doses given in mg/kg, a body weight of 70 kg was used. Some of the cephalosporin antibiotics are not available as oral drugs and thus their doses were not reported. Therefore an average among typical oral doses ranging from 200 to 1000 mg (MayoClinic.com, 2008) for members of this class of compounds is used. Although the uptake of some cephalosporin antibiotics is mediated by PEPT1 transporters (Kohda-Shimizu et al., 2001) the seven cephalosporins in this dataset were determined to be passively absorbed (Kohda-Shimizu et al., 2001; Willmann et al., 2004).

2.3. Physical data

Experimental melting point, MP, intrinsic aqueous solubility, S_w^{int}, and molecular weight, MW, values were obtained from the Estimation Programs Interface (EPI) Suite (United States Environmental Protection Agency, 2000–2007) SciFinder Scholar (American Chemical Society, 2006) the AQUASOL dATAbASE (Yalkowsky, 1999), or the Merck Index (Merck Research Laboratories, 2001) as well as from the literature sources mentioned in the previous section. The octanol–water partition coefficient was calculated using ClogP for Windows (Biobyte Corp, 1995–1999). Experimental solubility values were only available for 61 drugs, thus solubility data for the remaining 32 drugs were estimated using the GSE. The melting temperatures for Ceftazidime and Cefmetazole were estimated using EPI Suite since their experimental melting data could not be found. The experimental fraction absorbed data and the physical data of the 91 drugs analyzed in this study are listed in Table 1.

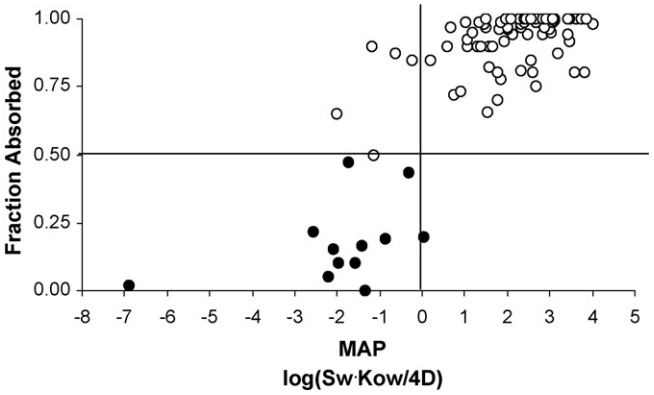


Fig. 1. Relationship between MAP (Eq. (9)) and fraction absorbed. (●) Compounds with FA < 0.5. (○) Compounds with FA > 0.5.

3. Results and discussion

3.1. Modified absorption potential for saturated compounds (MAP)

Sanghvi's modified absorption potential assumes the drug is completely dissolved or reaches its solubility in the gut. This represents the best case scenario. Obviously, if this condition is not met, absorption will be altered. The application of the MAP at saturation to 91 passively absorbed low solubility compounds is illustrated in Fig. 1. The figure can be divided into four quadrants by a horizontal line at 50% absorption and a solid vertical line at MAP = 0, that is, $\log(S_w^{int} \cdot K_{ow}) = \log(4D)$. Compounds with MAP values greater than zero ($\log(S_w^{int} \cdot K_{ow}) > \log(4D)$) are expected to be well absorbed while those that have MAP values less than zero ($\log(S_w^{int} \cdot K_{ow}) < \log(4D)$) should be poorly absorbed. In fact, about 92% of the drugs fall into the upper right and lower left quadrants.

The six compounds in the upper left quadrant (allopurinol, carbamazapine, etoposide, pindolol, sulfamethizole, and tetracycline) and the one drug in the lower right quadrant (thiacetazone) cannot be explained based on any apparent pattern among their structural features. Active and efflux transport mechanism, again, are not expected for these compounds. In examining the effects of using calculated log *P* versus experimental log *P* values in the model, there was no difference in the correlation between MAP and FA. All seven of the outliers had experimental solubility data.

Sources of error may come from any one or a combination of errors in: solubility, partition coefficient, dose, human absorption data, or simply from the failure of the model. In addition, it is not possible to know what, if any, the effects of formulation factors are on the experimental absorption data. Formulations that lead to supersaturated solutions in the gut may increase the amount absorbed. A prediction rate of 92% is very good in light of the different degrees of uncertainty for all of the measured data.

The fortuitous effectiveness of a delineator of MAP = 0 in Fig. 1, indicates that for at least 50% absorption,

$$\text{MAP} = \log\left(\frac{S_w^{int} \cdot K_{ow}}{4 \cdot \text{Dose}}\right) \geq 0 \quad (11)$$

or

$$\log(S_w^{int} \cdot K_{ow}) \geq \log(4 \cdot \text{Dose}) \quad (12)$$

Eq. (12) gives rise to the product of S_w^{int} and K_{ow} versus 4·Dose plotted in Fig. 2. As in Fig. 1, the filled and open circles represent compounds with FA < 0.5 and FA > 0.5, respectively. The solid line with a slope of unity is described by Eq. (12) when $\log(S_w^{int} \cdot K_{ow}) = \log(4 \cdot \text{Dose})$. This corresponds to the vertical line in Fig. 1 at

Table 1
Physical properties, dose and human intestinal absorption data.

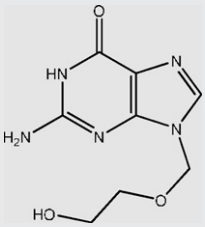
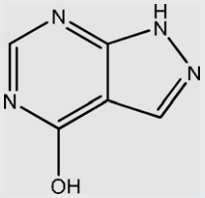
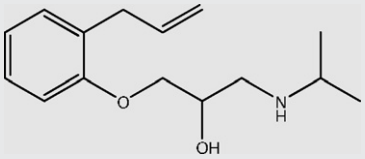
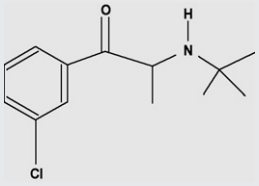
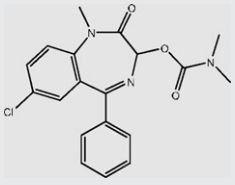
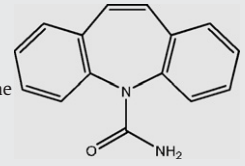
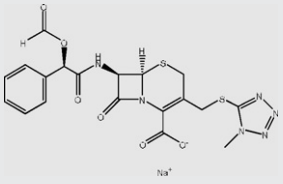
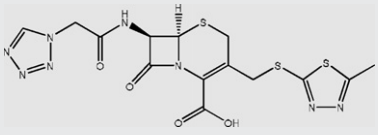
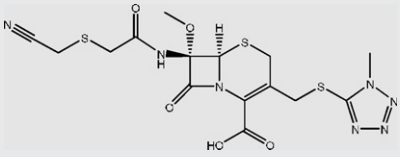
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Acyclovir		225	255	g	0.22	b, c(avg)	350	b, c(avg)	−2.24	e	−2.52
Allopurinol		136	350	f	0.90	f	300	f	−2.38	g	−0.86
Alprenolol		249	108	g	0.95	b, c(avg)	100	b, c	−2.98	h	2.65
Bupropion		240	25	n	0.87	c	125	c(avg)	−3.23	c	3.43
Camazepam		372	174	g	1.00	c	20	c	−4.63	h	3.64
Carbamazepine		236	190	g	0.85	f, b(avg)	733	f, b(avg)	−4.12	b	1.98
Cefamandole nafate		462	190	j, d	0.00	f	2000	f	−3.43	f	0.31
Cefazolin		455	199	j, d	0.05	b	600	i	−3.33	b	−1.16
Cefmetazole		472	330	g, q	0.10	b	600	i	−2.97	b	−1.28

Table 1 (*Continued*)

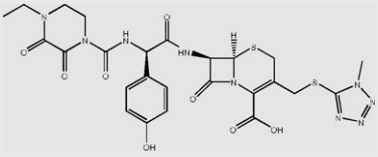
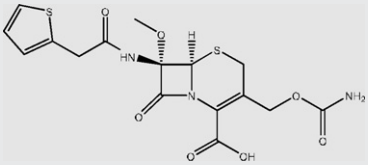
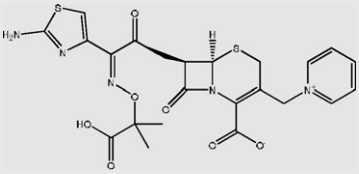
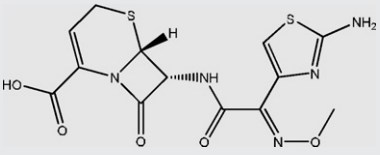
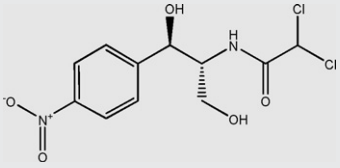
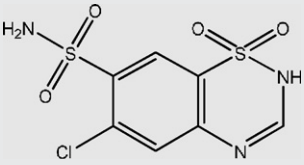
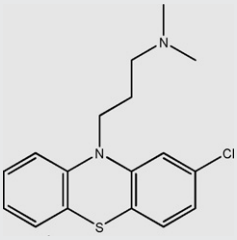
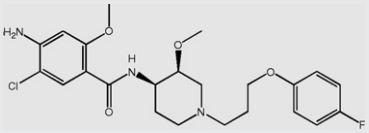
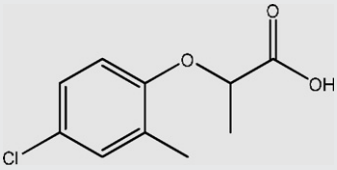
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Cefoperazone		646	170	g	0.10	b	600	i	−4.00	b	−0.02
Cefoxitin		427	150	j	0.15	b	600	i	−3.61	b	−0.75
Ceftazidime		546	350	g, q	0.02	b	600	i	−3.04	b	−6.22
Ceftizoxime		382	227	r	0.72	c	500	c	−2.47	h	0.95
Chloramphenicol		323	151	f	0.90	f	1000	f	−2.11	f, g	1.28
Chlorothiazide		296	342	d, f	0.19	f	250	f	−3.05	f, g	−0.31
Chlorpromazine		319	25	g	1.00	b	75	b(avg)	−5.10	b, g	5.80
Cisapride		466	109	j	1.00	c	12.5	c(avg)	−3.99	h	3.65
Clofibrate		243	25	j	0.97	c	1500	c	−3.40	e	4.12

Table 1 (*Continued*)

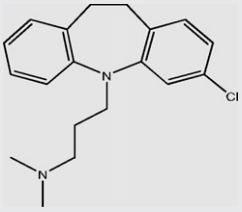
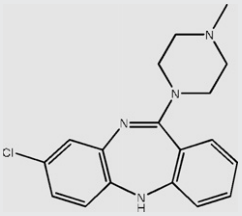
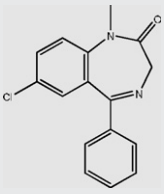
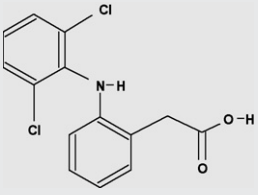
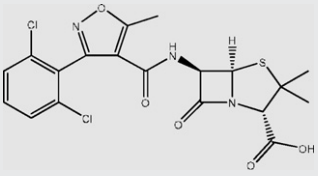
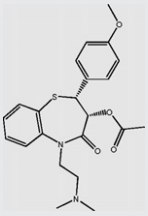
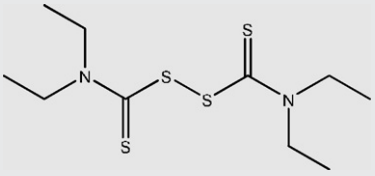
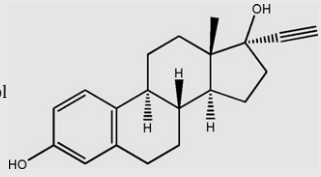
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Clomipramine		315	190	j	1.00	b	50	b	−6.03	b	5.92
Clozapine		309	183	j	1.00	b	450	b(avg)	−4.42	b	4.75
Diazepam		285	132	g	0.99	b, c(avg)	15	b, c(avg)	−3.76	g	3.16
Diclofenac		295	157	n	1.00	b, c, f(avg)	50	b, c	−4.37	f	4.32
Dicloxacillin		470	218	j, d	0.85	b	375	b	−5.11	b	2.80
Diltiazem		415	214	j	0.92	b	180	b	−2.95	j	3.65
Disulfiram		296	71	g	0.97	c	250	c	−4.86	c, g	3.88
Ethinylestradiol		296	183	g	1.00	c	30	c	−4.42	g	3.86

Table 1 (*Continued*)

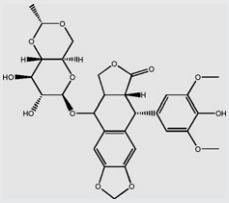
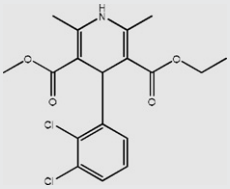
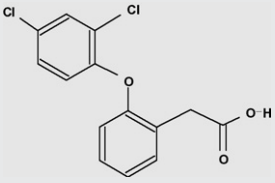
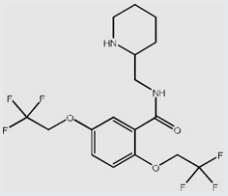
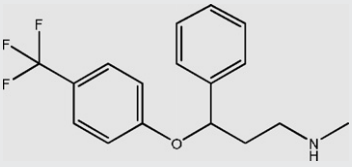
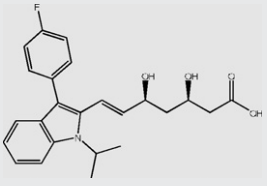
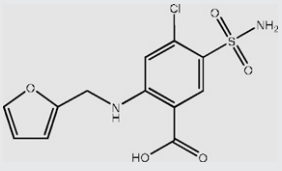
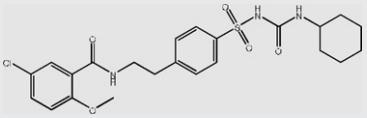
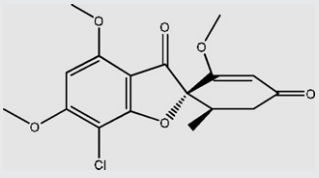
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Etoposide		589	239	g	0.50	b, c	305	b, c(avg)	−3.47	e	−0.35
Felodipine		384	145	j	0.94	b, c	27.5	b, c	−5.68	c	5.58
Fenclofenac		297	112	g	1.00	c	400	c	−4.55	e	4.71
Flecainide		414	146	g	0.81	c	100	c	−5.35	h	4.64
Fluoxetine		309	158	f	0.80	f	30	f	−5.40	h	4.57
Fluvastatin		411	195	j	1.00	b, c	6	b, c(avg)	−5.25	h	4.05
Furosemide		331	295	g	0.65	b, c, f(avg)	40	b, c	−3.66	g	1.87
Glyburide		494	169	g	1.00	c	3	c(avg)	−5.09	g	4.23
Griseofulvin		353	220	f	0.43	f	250	f	−4.61	f	1.75

Table 1 (*Continued*)

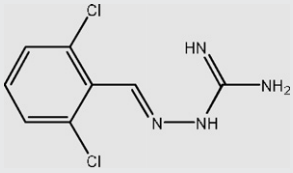
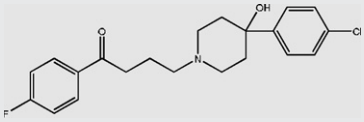
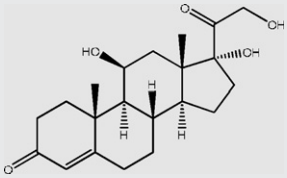
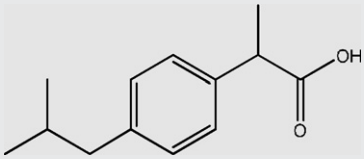
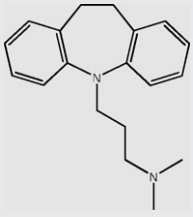
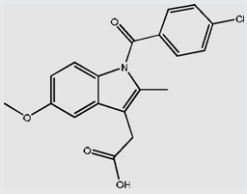
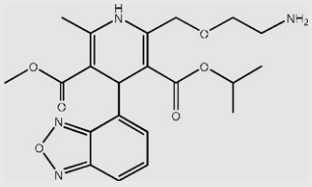
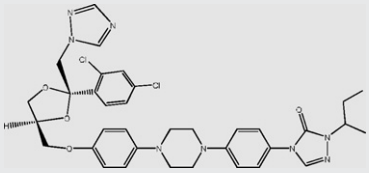
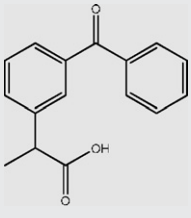
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Guanabenz		231	228	d, g	0.78	b, c(avg)	24	b, c(avg)	−4.49	h	2.96
Haloperidol		376	152	g	1.00	b	20	b	−4.43	g	3.85
Hydrocortisone		362	220	g	0.90	b, c, f(avg)	175	b, c, f(avg)	−3.05	g	1.70
Ibuprofen		206	76	g	0.92	b, c, f(avg)	300	b, c, f(avg)	−3.99	g	3.68
Imipramine		280	175	g	0.98	b, c, f(avg)	50	b, c(avg)	−4.19	g	5.04
Indomethacin		358	158	g	0.99	b, c(avg)	50	b, c	−5.58	g	4.18
Isradipine		430	169	j	0.96	b, c(avg)	12.5	b, c(avg)	−5.14	h	4.20
Itraconazole		706	166	b	0.80	k	200	l	−5.85	l	6.50
Ketoprofen		254	94	g	0.96	b, c, f(avg)	112.5	b, c(avg)	−3.70	g	2.76

Table 1 (*Continued*)

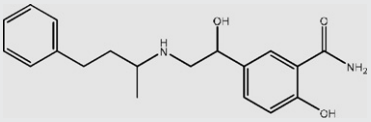
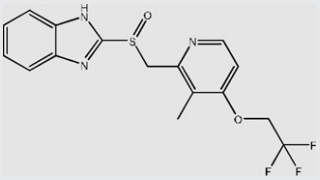
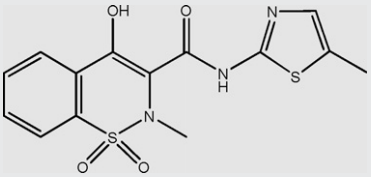
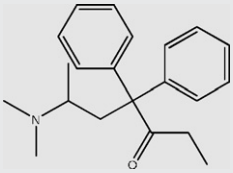
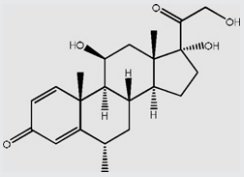
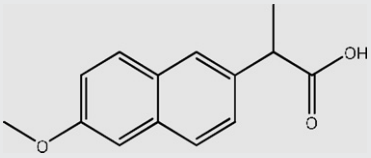
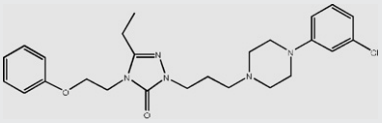
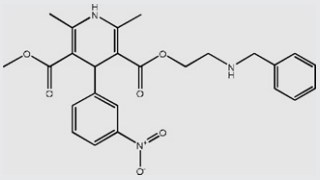
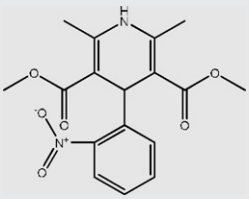
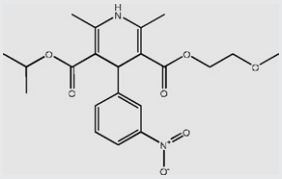
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Labetalol		328	188	g	0.95	b, c, f	600	b, c	−3.45	g	2.50
Lansoprazole		369	169	j, d	0.85	c	30	c	−5.18	h	4.24
Meloxicam		351	255	d, g	0.90	c	30	c	−4.08	h	2.28
Methadone		309	100	j	0.80	c	6.71	m(avg)	−4.42	h	4.17
Methylprednisolone		374	233	g	0.82	b, c	42	b, c	−3.49	g	1.70
Naproxen		230	153	g	0.99	b, c, f	250	b, c	−4.16	g	2.82
Nefazodone		470	84	g	1.00	c	100	c	−5.65	h	5.56
Nicardipine		466	137	g	1.00	b	25	b(avg)	−5.33	e	5.51
Nifedipine		346	173	g	1.00	b	45	b(avg)	−3.79	b	3.41
Nimodipine		418	125	j	1.00	b	30	b	−4.24	b	4.14

Table 1 (*Continued*)

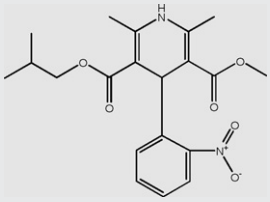
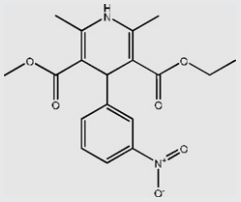
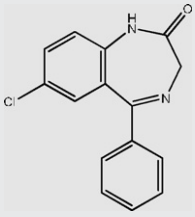
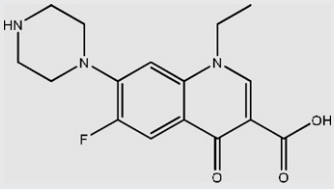
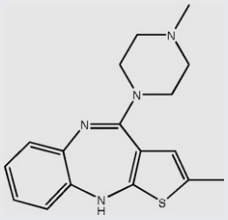
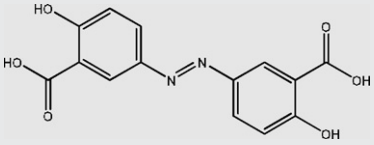
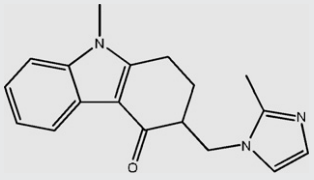
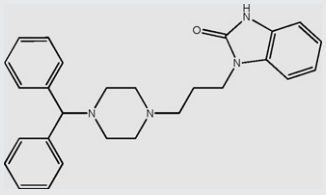
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Nisoldipine		388	152	j	0.95	b, c(avg)	15	b, c(avg)	−5.63	h	4.86
Nitrendipine		360	158	j	0.94	b, c(avg)	20	b, c	−4.85	h	4.02
Nordazepam		270	217	g	0.99	b, c	10	b, c	−4.43	h	3.01
Norfloxacin		319	221	n	0.47	b, c, f, m(avg)	400	b, c, f, m	−3.06	n	−0.99
Olanzapine		312	195	j	0.75	f	10	f	−5.09	h	3.89
Olsalazine		302 > 300		j	0.17	c, f(avg)	2500	c, f(avg)	−7.42	e	4.50
Ondansetron		293	232	j	1.00	b, c, f	8	b, c, f	−4.29	h	2.72
Oxatomide		426	154	g	1.00	c	60	c	−6.43	h	5.64

Table 1 (*Continued*)

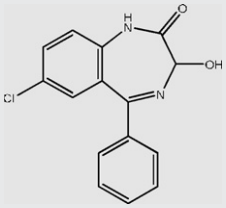
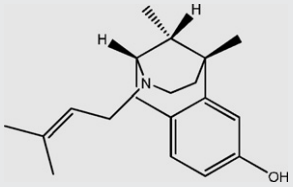
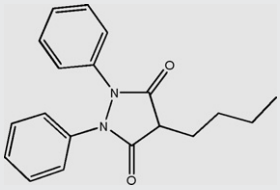
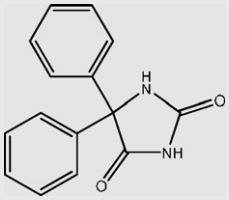
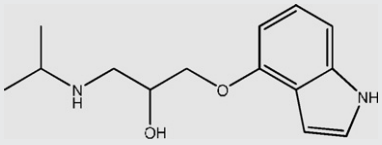
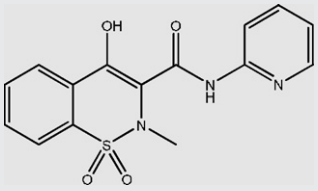
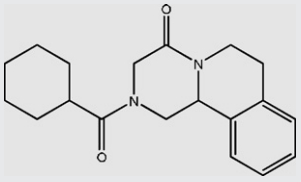
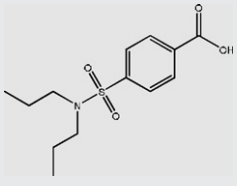
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Oxazepam		287	206	g	0.97	f	15	f	−3.97	f	2.29
Pentazocine		285	146	g	1.00	b	50	b	−5.38	h	4.67
Phenylbutazone		308	105	g	1.00	b	300	b	−3.81	b, g	3.38
Phenytoin		252	286	g	0.90	b, c, f	250	b, c, f(avg)	−3.90	g	2.08
Pindolol		248	171	g	0.87	c	1050	c	−2.45	h	1.49
Piroxicam		331	199	g	0.99	f	20	f	−4.16	g	1.89
Praziquantel		312	136	g	1.00	c	1960	c	−2.89	g	3.36
Probenecid		285	195	g	1.00	b	500	b	−4.02	b	3.37

Table 1 (*Continued*)

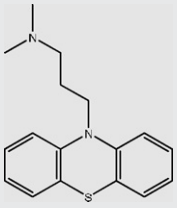
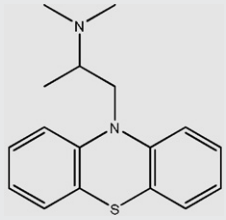
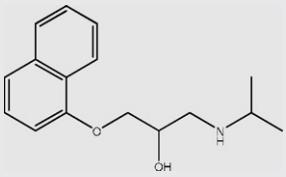
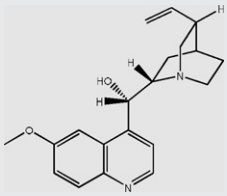
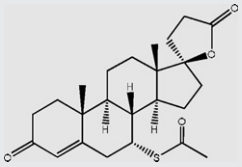
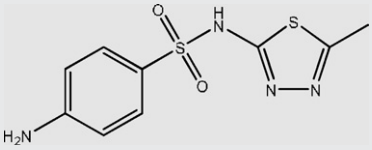
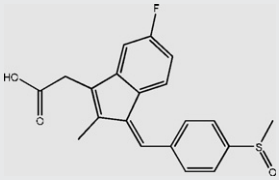
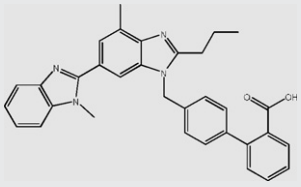
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Promazine		284	25	g, p	1.00	b	100	b	−4.30	b	4.90
Promethazine		284	60	g	1.00	b	113	b(avg)	−4.26	b, g	4.90
Propranolol		259	96	j	0.95	b, c(avg)	300	b, c	−2.96	h	2.75
Quinidine		324	174	g	0.81	b, c, f(avg)	330	b, c, f	−3.42	c, g(avg)	2.79
Spironolactone		417	135	g	0.73	c	125	c(avg)	−4.28	g	2.25
Sulfamethizole		270	208	j	0.85	b	750	b(avg)	−2.41	b	0.22
Sulindac		356	183	g	0.90	c	200	c	−4.24	h	3.16
Telmisartan		514	262	n	0.90	c	40	c	−9.33	h	7.46

Table 1 (*Continued*)

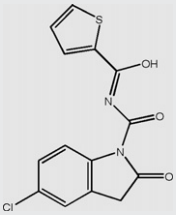
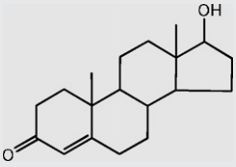
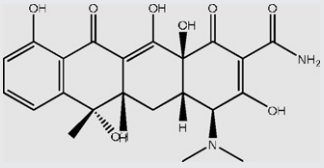
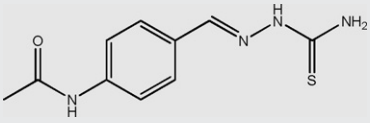
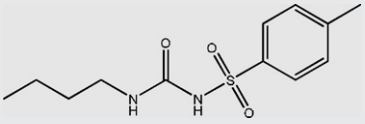
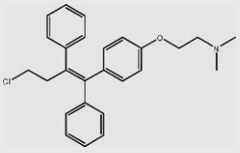
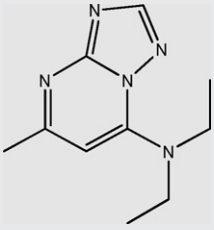
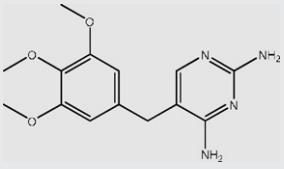
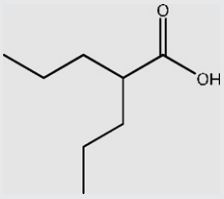
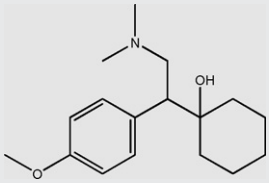
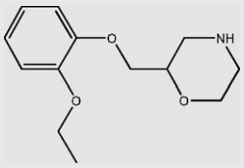
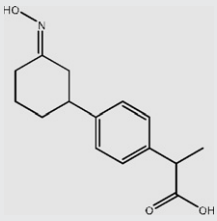
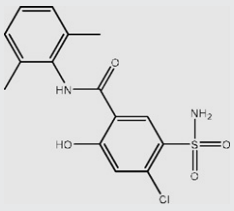
Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Tenidap		321	230	j, d	0.90	c, f(avg)	116	c, f(avg)	−3.49	h	1.94
Testosterone		288	155	g	0.99	b, c, f(avg)	20	b, c, f	−4.09	g	3.22
Tetracycline		444	173	g	0.65	b	750	b(avg)	−3.28	b	−0.91
Thiacetazone		236	225	g	0.20	c	150	c	−3.43	g	0.88
Tolbutamide		270	129	g	0.93	b, c(avg)	1000	b	−3.27	b	2.50
Toremifene		406	109	j	1.00	c	120	c	−6.87	h	6.53
Trapidil		205	100	g	0.96	c	275	o	−2.46	h	2.21
Trimethoprim		290	201	g	0.97	f	160	f	−2.86	f	0.88
Valproic Acid		144	25	n, p	1.00	b, c	600	b, c	−2.48	h	2.98

Table 1 (*Continued*)

Compound Name	Structure	MW	Melting point (°C)	Reference for MP	Fraction absorbed	Reference for FA	Dose (mg)	Reference for dose	log S_w	Reference for log S_w	log P^a
Venlafaxine		277	103	j	0.97	c	50	c	−3.55	h	3.27
Viloxazine		237	178	j	0.98	c	200	c	−2.79	h	1.76
Ximoprofen		261	178	g	0.98	c	30	c	−3.36	h	2.33
Xipamide		355	256	j	0.70	f	20	f	−3.79	g	1.89

(a) ClogP for Windows, v4.0 (Biobyte Corp.); (b) Willmann et al. (2004). (c) Zhao et al. (2001). (d) Decomposition temperature; (e) *AQUASOL dATAbASE of aqueous solubility*; (f) Sanghvi et al. (2003). (g) Estimation Program Interface (EPI) Suites, EPA. (h) General Solubility Equation; (i) cephalosporins not available as oral dose so typical oral dose is used; (j) SciFinder Scholar, American Chemical Society; (k) Hou et al. (2007). (l) Branchu et al. (2007). (m) Physicians' Desk Reference (2002). (n) Merck Research Laboratories (2001). (o) Dose taken from online patent www.patentstorm.us/patents/6015578-description.html; (p) compound is liquid at room temperature. A MP of 25 °C is given to liquid solutes in order to eliminate the crystalline solubility term in the GSE; (q) Estimated melting temperature from EPI Suites; (r) Yalkowsky et al., 2006.

MAP = 0. Cleary the vast majority of the well-absorbed compounds lie to the right of the diagonal line.

Fig. 2 provides a quantitative perspective of the roles of the *product* of solubility and partition coefficient and dose on fraction absorbed. Without sufficient drug available in solution, absorption will be limited. Inadequate membrane partitioning to the solute will also reduce the extent of passive intestinal absorption. A dose that is significantly oversaturated (i.e., doses above the diagonal line) will likely lead to a decrease in absorption efficiency. According to Curatolo (1998) the hallmarks of a well-absorbed drug are high solubility and moderate lipophilicity. While there is no question that drugs with these physicochemical characteristics typically do not have problems with absorption, Fig. 2 indicates that for discrete combinations of solubility and partition coefficient values (i.e., the product of S_w^{int} and K_{ow}) even drugs that are poorly soluble or very lipophilic have the potential of being well absorbed if given at a sufficiently low dose.

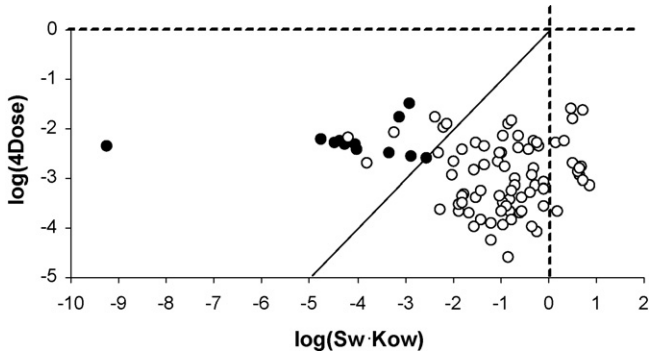


Fig. 2. Relationship between $S_w^{int} \cdot K_{ow}$, dose and fraction absorbed. The line is described by Eq. (12) with a slope of 1 and intercept of 0. (●) Compounds with FA < 0.5. (○) Compounds with FA > 0.5.

The significance of dose in the MAP model might be better appreciated under the following context. For a given compound, if the logarithm of the product of S_w^{int} and K_{ow} is greater than the logarithm of 4·Dose, the drug is likely to be well absorbed. Or put another way, the absorption of a drug with the requisite solubility and partitioning properties (i.e., $\log(S_w^{int} \cdot K_{ow}) \geq \log(4 \cdot \text{Dose})$) is not expected to be limited by a high dose. In this regard, the dose quantifies what is meant by adequate values of aqueous solubility and membrane partitioning for improved drug absorption. Interestingly, MAP is analogous to the concept of the maximum absorbable dose, MAD, developed by Johnson and Swindell (1996). However, while MAD requires biological data, MAP only requires physicochemical data.

3.2. General Solubility Equation

Jain and Yalkowsky (2001) revised the General Solubility Equation (GSE) in which the aqueous solubility of an unionized organic compound is related to its octanol–water partition coefficient and

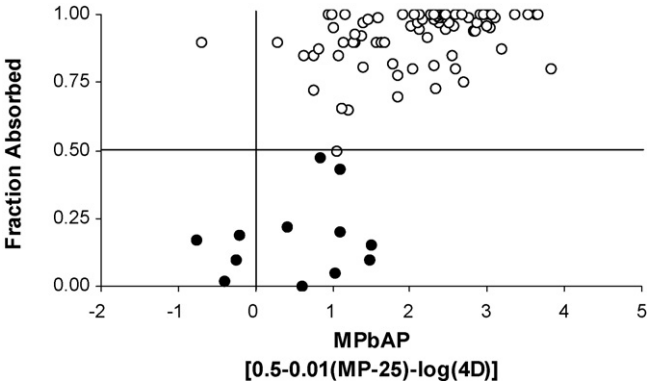


Fig. 3. Relationship between MPbAP (Eq. (15)) and fraction absorbed. (●) Compounds with FA < 0.5. (○) Compounds with FA > 0.5.

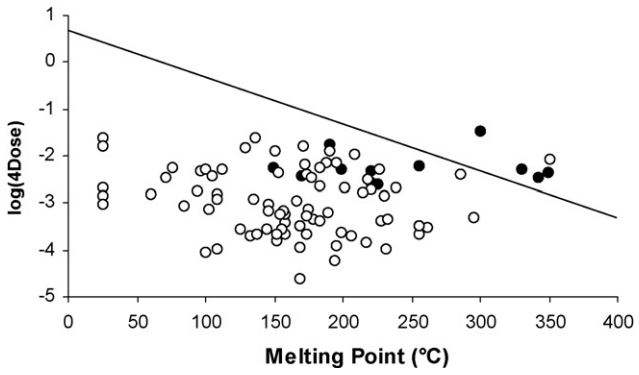


Fig. 4. Relationship between Melting point, dose and fraction absorbed. The line is described by Eq. (17) with a slope of −0.01 and intercept 0.75. (●) Compounds with FA < 0.50. (○) Compounds with FA ≥ 0.50. Some data points are covered.

its melting point by,

$$\log S_w^{int} = 0.5 - 0.01(MP - 25) - \log K_{ow} \quad (13)$$

where MP is the melting point of the drug in degrees Celsius. Rearranging this equation gives

$$\log(S_w^{int} \cdot K_{ow}) = 0.5 - 0.01(MP - 25) \quad (14)$$

This enables us to replace the S_w^{int} and K_{ow} product in Eq. (9) with the MP term. Although solubility and dissolution rates have typically been correlated with melting temperatures, the melting point of a drug has not been used as a predictive tool for oral absorption efficiency of poorly soluble drugs. Given that the melting point of a compound is one of the first and more reliable physical properties measured, it can be advantageously used to guide the screening and selection of lead compounds.

3.3. Melting point based absorption potential (MPbAP)

Dressman's (Dressman et al., 1985), Balon's (Balon et al., 1999) and Sanghvi's (Sanghvi et al., 2001) passive intestinal drug absorption models are based on a few physical parameters. Here, we distil the model down to one fundamental physical property and introduce a simpler yet meaningful tool to evaluate oral absorption efficiency. Replacing the log of the product of S_w^{int} and K_{ow} in Eq. (9) with the right-hand side of Eq. (14) results in the melting point based absorption potential, MPbAP:

$$MPbAP = 0.5 - 0.01(MP - 25) - \log(4 \cdot Dose) \quad (15)$$

where the dose is in moles. Note that the above equation is applicable only if the dose exceeds the amount of drug that can be dissolved in 250 ml of water. Eq. (15) and Fig. 3 describe this interesting relationship between the fraction of drug absorbed, the dose, and melting point.

Fig. 3 is analogous to Fig. 1, where a vertical line at MPbAP = 0 and a horizontal line at FA = 0.5 create four quadrants with a delineator that discriminates between well-absorbed and poorly absorbed drugs. Again most compounds with MPbAP values greater than 0 are shown to be well absorbed (FA > 0.50) and fall in the upper right quadrant while those that are poorly absorbed tend to fall in the lower left quadrant and have MPbAP values less than 0. Using a delineator at MPbAP = 0 gives 90% correct designations of drugs falling in the upper right and lower left quadrants.

The prediction rate of the MPbAP model can be considered quite good given the additional assumptions of the GSE. Two of the outliers (allopurinol and thiacetazone) in Fig. 3 are the same as in Fig. 1 while the other seven outliers may be attributed to the lack of exactness of the GSE, particularly for the four cephalosporin compounds having the only common structural features observed among the outliers (acyclovir, allopurinol, cefamandole nafate, cefoperazone, cefoxitin, cefazolin, griseofulvin, norfloxacin, and thiacetazone).

It is also important to note that the General Solubility Equation assumes the melting point of the crystal does not change in the presence of water. In addition, if a drug has a true melting point that is significantly higher than the decomposition temperature, the GSE may overestimate the solubility and shift the drug to higher MPbAP values. None of the melting temperatures for the outliers were reported as decomposition temperatures. Salts were excluded in the study since the GSE is only applicable to nonelectrolytes and the uncharged form of weak electrolytes.

3.4. Melting point, dose and fraction absorbed

The relationship illustrated in Fig. 3 may be interpreted in a somewhat more intuitive manner if we evaluate the combined effects of melting temperature and dose on the fraction absorbed. In order to observe their individual roles in MPbAP, they are plotted separately in Fig. 4 where filled circles represent compounds with FA < 0.5 and open circles are compounds with FA > 0.5. From Fig. 3 we have distinguished between efficient and poor absorption using MPbAP = 0. When MPbAP ≥ 0, Eq. (15) becomes

$$[0.5 - 0.01(MP - 25)] - \log(4 \cdot Dose) \geq 0 \quad (16)$$

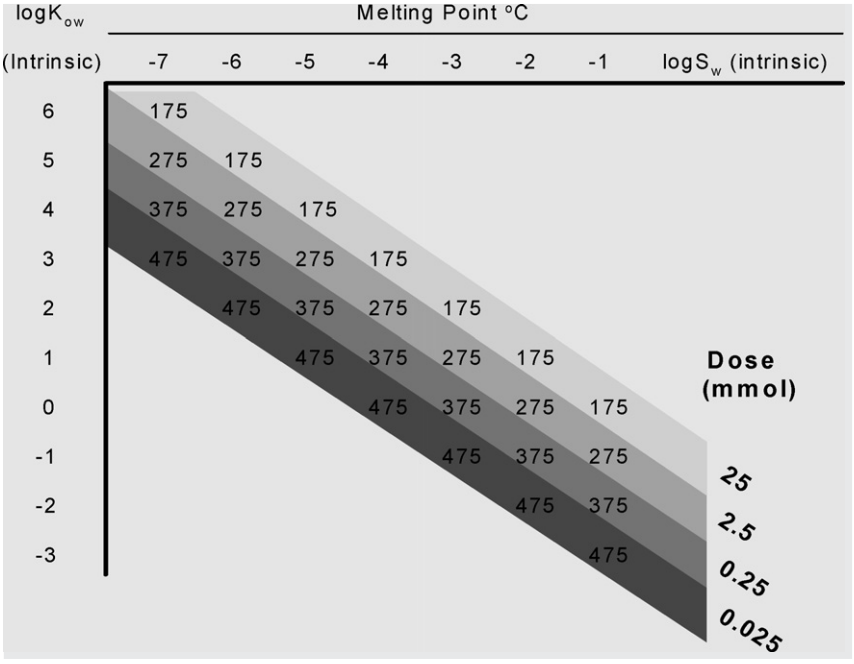
which is analogous to Eq. (11). Rearranging gives

$$0.75 - 0.01MP \geq \log(4 \cdot Dose) \quad (17)$$

which describes the condition for a minimum of 50% absorption. Eq. (17) is plotted as the line with a slope of −0.01 and a *y*-intercept of 0.75 in Fig. 4.

It is clear that most of the well-absorbed drugs fall below the line. Fig. 4 is analogous to Fig. 2 and can be interpreted in the same way but using one term, MP, instead of two terms, S_w^{int} and K_{ow}. Based on the GSE, the lower the melting temperature, the greater is the product of S_w^{int} and K_{ow}. Therefore, for any given dose, lower melting compounds are more likely to be well absorbed than higher melting compounds, just as compounds that have greater $S_w^{int} \cdot K_{ow}$ values are more likely to be well absorbed than compounds with lower $S_w^{int} \cdot K_{ow}$ products. For a minimum of 50% absorption, the MP term of Eq. (17) or the product of S_w^{int} and K_{ow} of Eq. (12) must be greater than 4·Dose. For example, using the diagonal line in Fig. 4 as the cut-off, a drug with a melting point of 275 °C would be expected to have good absorption up to a dose of 2.5 mmoles, versus a similar drug with a melting point of 375 °C that can only be dosed up to 0.25 mmoles for adequate absorption. For a given dose level, every one hundred degrees increase in melting temperature brings the drug ten times

Table 2
Interrelationship of solubility, partition coefficient, melting point, and dose for at least 50% absorption.



closer to intersecting the point of decreased absorption efficiency (i.e., the cut-off line).

Again, the significance of dose can be better understood in the following perspective. The fraction absorbed is independent of dose for drugs that are completely dissolved in the GI lumen. At high enough doses the GI lumen becomes saturated. Beyond this point, increasing the dose reduces absorption efficiency. The MPbAP model, as well as the MAP model, defines the maximum dose to achieve a minimum of 50% absorption.

The MPbAP model essentially collapses the two key physicochemical properties of passive intestinal absorption into a single, more easily measured property. While the convenience of the model allows the use of melting point to estimate fraction absorbed, fundamentally, the prediction is still based on the product of solubility and partition coefficient. Table 2 illustrates the interdependencies of S_w^{int}, K_{ow}, MP, and Dose in determining FA. If the solubility and partition coefficient values, found along the horizontal and vertical axes, respectively, are known, then the corresponding melting temperature can be found in the table. Likewise, if the melting point of a drug is known, the product of S_w^{int} and K_{ow} is defined. The various combinations of solubility and partition coefficients can be determined.

The dose requirement for a minimum of 50% absorption as described by Eqs. (12) and (17) should be less than the product of S_w^{int} and K_{ow} or the MP term, respectively. Combining Table 2 with dose levels completes the prediction of fraction absorbed. For a 275 °C melting drug, the maximum acceptable dose for 50% absorption is 2.5 mmoles. Higher doses for a 275 °C melting drug will lead to decreased absorption efficiency and lower doses should lead to improved absorption efficiency. Another way to look at it is drugs with a dose of 2.5 mmoles will not be well absorbed if they have melting temperatures greater than 275 °C or have a value for the product of the logarithm of S_w^{int} and K_{ow} that is less than −2. Drugs that have melting temperatures of 175 °C should be well absorbed up to a maximum dose of 25 mmoles. Basically, the lower the melting point, the less likely that absorption will be limited by dose. Translating melting temperatures or dose values into solubility and partition coefficient values is easily accomplished by referring to Table 2.

4. Conclusion

Sanghvi's modified absorption potential has expanded our appreciation of the balancing act that solubility, partitioning, and dose play on passive absorption. In general, if the product of S_w^{int} and K_{ow} is greater than 4 times the dose, the compound is expected to be at least 50% absorbed. The ability to predict the extent of absorption is further facilitated by the General Solubility Equation which combines the product of aqueous solubility and membrane partitioning into one term. In spite of the complex process of intestinal absorption, the MPbAP model describes an interesting and potentially useful relationship between the fraction absorbed and a drug's melting point. In this model, the melting point acts as a surrogate for the product of solubility and partition coefficient and it allows one to assess whether a drug is likely to be well absorbed or not at a given dose level. In general, low melting compounds will be better absorbed than high melting compounds. For every one hundred degrees increase in melting temperature, there is a 10-fold decrease in the maximum dose that will provide at least 50% absorption. Again, the interdependencies of melting point, solubility, partition coefficient, and dose in determining fraction absorbed are illustrated in Table 2. The MPbAP model may be a convenient tool to help facilitate rational drug design and development and provide a means to rank-order lead candidates in a more systematic and meaningful context. Appreciation for the dose limit to achieve at least 50% absorption has many implications on development time and costs.

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