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Note

Solubility parameter and oral absorption

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Abstract

The solubility parameter (δ) for a series of structurally diverse compounds was determined using a group contribution method devised by Fedors, and then related to the degree of oral absorption. Solubility parameter values around 22.5 $MPa^{1/2}$ were shown to be associated with compounds that were well absorbed, whereas, compounds with a high δ (30–40 $MPa^{1/2}$) showed poor absorption. A correlation was also evident between the number of H-bonding acceptor groups in a compound and the extent of oral absorption. Surprisingly, when *C* Log *P* values were used in comparison, no obvious correlation existed. The conclusion from this work is that the solubility parameter may be a more reasonable predictor of absorption than using *C* Log *P* values.

Keywords: Solubility parameter; Cohesion energy density; Absorption; Polarity

1. Introduction

The cohesive energy of a material is the amount of energy required to separate the material into its constituent atoms or molecules. Hence, the cohesive energy is a measure of the attraction that atoms or molecules have for one another. An understanding of cohesive energies may help determine how a drug substance will behave when processed or when dosed in vivo, since the cohesive energy has been related to physico-chemical properties such as melting point, surface free energy, tensile strength and solubility [1]. The most common approach in quantifying the cohesive energy for a drug substance is to determine its solubility parameter, δ, which is defined as the square root of its cohesive energy density (CED), expressed as the energy of vaporisation per unit volume [2–5]

$$\delta = (CED)^{1/2} = \left((\Delta E_V/V_m)\right)^{1/2} = \left((\Delta H_V - RT)/V_m\right)^{1/2} \quad (1)$$

where ΔE_v is the energy of vaporisation, ΔH_v is the heat of vaporisation and V_m is the molar volume (molecular weight/density). The units for the solubility parameter are $MPa^{1/2}$. The solubility parameter for a particular material will lie on a scale from about 10 (non-polar) to 48 (polar, value for water). When the solubility parameters for two materials are similar one would expect them to be miscible. In contrast they would be immisicible if they differ largely in value. For example, triacetin ($\delta = 22$) is more likely to be soluble in isopropanol ($\delta = 23$) then in water ($\delta = 48$) or mineral oil ($\delta = 14$). An analogy to 'like dissolves like' is appropriate. Although, the concept of solubility parameters was developed for simple liquid mixtures, its application has been extended to simple solid/liquid systems under the assumption that the solid in question is treated as a 'supercooled liquid' with a low degree of crystallinity [1]. Therefore, the use of such parameters has found diverse applications in the cosmetics and packaging industries [6,7], as well as uses in the dyeing of textiles [8], chromatographic separation [9], polymer blending [10] and solvent selection for nanoparticle preparation [11]. Studies have also shown that the solubility parameter may predict the absorption of simple solutes or complex drug molecules across a variety of substrates including in vitro model membranes [12–14], skin [12,15] and the cell walls of erythrocytes [16]. Evidence also exists for a correlation between the solubility parameter and the pharmacological activity of a number of barbituric acids and the antimicrobial activity for a series of linear and branched dihydroxybutane derivatives [17,18].

It was the purpose of this study to investigate whether a correlation existed between the solubility parameters for a number of structurally diverse compounds and their oral absorption in man, and whether the determination of such

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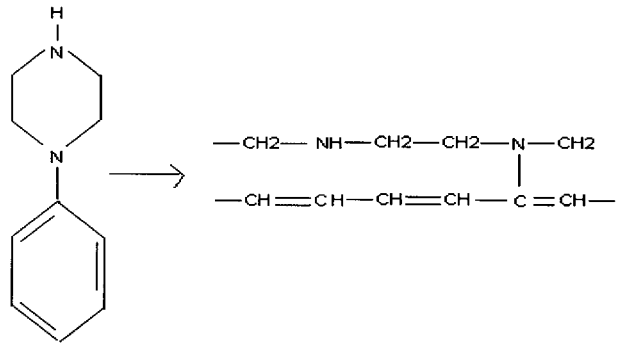

Fig. 1. The structure of Piperazine subjected to Fedors' method [20].

a parameter would afford any advantages over existing methods for predicting the absorptive potential of drug substances.

2. Methods

2.1. Selecting a method for estimating the solubility parameter

There are a number of indirect and direct methods available that can be used to determine solubility parameter. These include vapour pressure or boiling point determinations, solubility/miscibility measurement in liquids with known cohesive energy, solution calorimetry, surface energetic measurements by inverse gas chromatography, or by calculation using the group contribution method [1]. In this work, a group contribution method was used to calculate the solubility parameter from a knowledge of the drug structure alone. Such an approach is especially useful at the start of the pharmaceutical discovery or development process, where the properties of a new chemical entity (which very often is in short supply) can be estimated in light of very little experimental data. However, the disadvantage of using such a method is that it relies upon a database of a large number of appropriately characterised functional groups being made available.

The most common group contribution method employed is that derived by Van Krevelen and Hoftyzer from their studies in polymer chemistry [19]. This method does, however, require knowledge of the molar volume for the material in question. The molar volume can be determined experimentally but is more commonly calculated using the group contribution method devised by Fedors [20]. The Fedors contribution method also allows the calculation of the solubility parameter for both liquids and for high molecular weight amorphous polymers and was therefore employed accordingly in this study.

Table 1
Derived contributions for the functional groups of Piperazine

Group	Δ_{ei} (cal/mol)	Δ_{vi} (cal/mol)
4 CH2	4720	64.4
1 NH	2000	4.5
1 N	1000	−9.0
5 CH═	5150	67.5
1 C═	1030	−5.5
3 (Conjugated bonds)	1200	−6.6
2 (6-Membered rings)	500	32.0
Total	15 600	147.3

2.2. Calculation of solubility parameters

Fedors' [20] method was used in this investigation for the main reason that it contains the contributions for a large number of functional groups and chemical structures. In this method, the following equation is used for directly determining, δ,

$$\delta = \left[\sum_i \Delta_{ei} / \sum_i \Delta_{vi} \right]^{1/2} \quad (2)$$

where Δ_{ei} and Δ_{vi} are the additive atomic and group contribution for the energy of vaporisation and molar volume, respectively. The Δ_{ei} and Δ_{vi} terms for each functional group are found in reference tables prepared by Fedors [20].

Fedors approach to aromatic compounds was to open ring structures and to treat the resultant structure as a linear-chain compound, and then apply a correction for ring closure, for example, if we consider piperazine (refer to Fig. 1 and Table 1),

$$\delta = [\Sigma_i \Delta_{ei} / \Sigma_i \Delta_{vi}]^{1/2} = [15600/147.3]^{1/2} = 10.30\ (\text{cal/cm}^3)^{1/2} \quad (3)$$

The value for δ can then be converted to $\text{MPa}^{1/2}$ by multiplying by 2.04, i.e. producing a value for Piperazine of 21.01 to $\text{MPa}^{1/2}$.

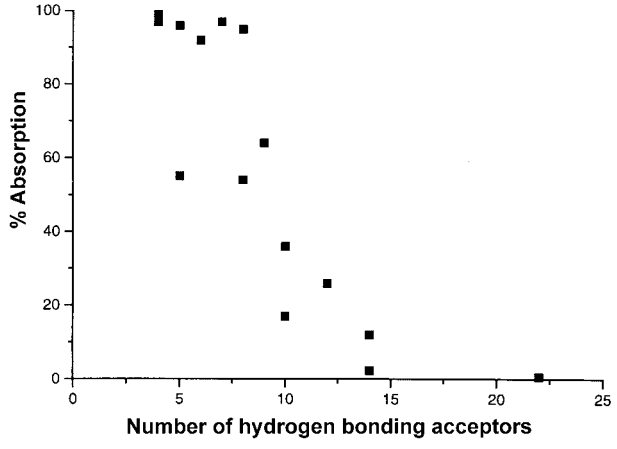

Fig. 2. The relationship between oral absorption in humans of 18 structurally diverse compounds and their number of hydrogen bonding acceptor groups [21].

Table 2
Absorption and structural properties of the investigated compounds [21]

Compound	% Oral absorption	No. of hydrogen acceptors	Calculated Log *P*	Solubility parameter (M $Pa^{1/2}$)
Metoprolol	102	7	1.2	22.3
Nordiazepam	99	4	3.0	24.7
Diazepam	97	4	3.0	23.5
Oxprenolol	97	7	1.7	22.5
Phenazone	97	4	0.4	20.6
Alprenolol	96	5	2.6	22.2
Practolol	95	8	0.8	23.3
Pindolol	92	6	1.7	24.7
Metolazone	64	9	1.9	32.1
Tranexamic acid	55	5	−1.8	22.7
Atenolol	54	8	−0.1	27.0
Sulpride	36	10	1.1	29.2
Mannitol	26	12	−4.7	37.8
Foscarnet	17	10	−1.8	38.0
Sulphasalazine	12	14	3.8	34.7
Olsalazine	2.3	14	4.5	35.5
Lactulose	0.6	22	−5.7	39.2
Raffinose	0.3	32	−8.1	38.2

2.3. Selection of model drug compounds

The model compounds were selected from those previously used by Palm et al. [21]. They covered compounds with a varying extent of oral absorption and of physico-chemical properties such as lipophilicity, charge and the number of H-bonding acceptor groups. These are all properties that Lipinski et al. [22] have used to derive their 'developability' criteria. In addition, the effects of low solubility and pre-systemic metabolism had been judged to be negligible for these compounds or had already been accounted for in the determination of the absorbed drug fraction [21]. Two compounds, namely ciprofloxacin and oxazepam, were excluded from analysis. Ciprofloxacin was excluded due to evidence of fluoroquinolones being subjected to trans-intestinal elimination [23] and oxazepam on the basis that it would have been the third benzodiazepine used in this investigation.

3. Results and discussion

Table 2 summarises the derived absorption and structural values for the investigated compounds. Fig. 2 shows the sigmoidal relationship between the percentage of drug absorbed orally and the number of hydrogen bonding acceptor groups, as reported by Palm et al. [21]. From Fig. 2, it can be seen that as the number of hydrogen bonding groups increased, the percentage of drug absorbed orally decreased. This relationship correlates well with the findings of Lipinski [22], who claimed that poor absorption or permeability would result if a compound possessed greater than

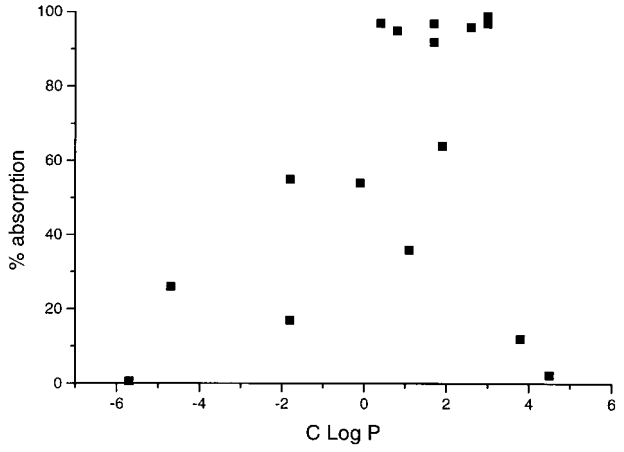

Fig. 3. The relationship between oral absorption in humans and C Log P values [21].

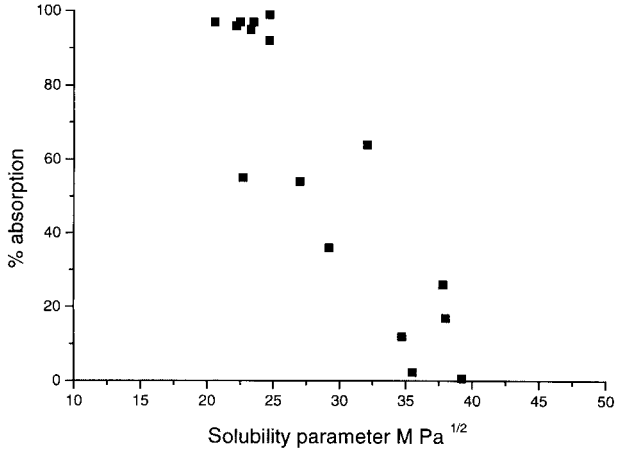

Fig. 4. The relationship between oral absorption in humans and calculated solubility parameters.

Table 3
Solubility parameters derived for biological membranes [7,12,16,24]

Membrane	Solubility parameter (M $Pa^{1/2}$)
Rat gut wall	25.7
Frog synaptic nerve	23.7
Porcine stratum corneum	20.0
Erythrocyte cell wall	21.4
Hairless mouse skin	20.8

ten H-bonding acceptor groups. Fig. 3 shows no correlation when the calculated Log *P* values are plotted as a function of the percentage of drug absorbed orally. In Fig. 4, the calculated solubility parameter values have been plotted versus the percentage of oral absorption, and, although a precise sigmoidal relationship as noted in Fig. 2 for hydrogen bond acceptors, is not evident, there is clearly a trend. Compounds with solubility parameters in the range 20–25 $MPa^{1/2}$ generally have high oral absorption (greater than 80%). As the solubility parameter values increased beyond 30 $MPa^{1/2}$, the extent of oral absorption decreased markedly. Since an increase in the solubility parameter reflects a corresponding increase in polarity, it is not surprising that the extent of absorption has been reduced. Polar molecules are less likely to be absorbed across the lipid bilayers of the gastrointestinal membrane. It was surprising; however, that this relationship was not expressed as clearly by the C Log *P* values in Fig. 3.

A number of workers have derived a solubility parameter for biological membranes (Table 3) which range from 20–26 $MPa^{1/2}$ [7,12,16,24]. Mullins [25] suggested whilst reviewing the physical mechanisms involved in narcosis, that the membrane acceptance of a narcotic depends upon it having a δ value close to that of the biological membrane. From their observations, Miller et al. [26] suggested a solubility parameter range of 15–19 $MPa^{1/2}$ as optimum for the activity of general anaesthetics. Drug compounds studied in rats and humans by Shanker, Shore and others [27,28] that have shown good absorption, all had a δ value of around 23.5 $MPa^{1/2}$. Findings by Khalil and Martin [29] and by Shrove and Shaw [14] from their in vitro studies showed that the closer the δ value was to that of the biological barrier, the greater the extent of drug transport across that barrier. Comparing Fig. 4 with the solubility parameter values in Table 2, it is possible to see that highly bioavailable compounds have solubility parameters which match the values determined for the biological membranes and it is therefore possible that such a mechanism was in operation for the compounds studied.

In conclusion, the results from this study reinforce the usefulness of estimating the solubility parameter for drug compounds not only for developmental purposes, but also for refining the drug discovery process. A knowledge of the solubility parameter (which can be easily and rapidly computated) would serve as a useful compliment to predictive tools such as Lipiniski's Rule of 5 [22] when constructing novel molecular entities as potential medicinal agents.

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