Prediction of Intestinal Drug Absorption Properties by Three-Dimensional Solubility Parameters

Jörg Breitkreutz[1,2]

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Purpose. The purpose of this study was to investigate the use of solubility parameters for the prediction of gastrointestinal absorption sites and absorption durations of drugs.

Methods. Three-dimensional solubility parameters of drug substances were calculated using an advanced parameter set based on the group contribution methods of Fedors and Van Krevelen/Hoftyzer. The results of the calculations were illustrated via Bagley diagram and related to absorption data reported in the literature.

Results. Solubility parameters of drugs which are known to be absorbed over a long period in human's digestive tract were found in a limited area within the Bagley diagram. From the three-dimensional solubility parameters of these substances, a region for optimal absorption with the centre coordinates δ_v = 20.3 $(J \cdot cm^{-3})^{0.5}$ and δ_h = 11.3 $(J \cdot cm^{-3})^{0.5}$ could be derived. Drugs with absorption sites along the whole gastrointestinal tract were found in this area. Drugs which are preferably absorbed from upper parts of the intestine are located in another typical region with partial solubility parameters δ_h of more than 17 $(J \cdot cm^{-3})^{0.5}$.

Conclusions. The method which is presented in this paper appears as a simple but effective method to estimate the absorption behaviour of new substances in drug research and development.

KEY WORDS: Hansen solubility parameters; regional gastrointestinal uptake; sustained-release dosage forms; site-specific delivery; passive diffusion; carrier-mediated transport.

INTRODUCTION

Physiological, chemical and physicochemical factors influence the absorption of drug molecules from the gastrointestinal tract (1). Some drugs exhibit different absorption rates at the absorption sites of the digestive tract (2). Different permeation mechanisms, e.g. passive diffusion and carrier-mediated transport, and pathways have been described (3). Several attempts have been made to predict oral drug absorption in humans from theoretical considerations of the physicochemical properties of the drug, from in vitro model data, pharmacokinetic simulations and animal studies (4–6). Since the early work of Hansch (7) correlations between biological activity and partition coefficients as well as solubility parameters have been performed. Methods including polar interaction forces and hydrogen bond formation ability seem to be favourable to the original Hildebrand solubility parameter δ, e.g. the solvatochromic parameter approach (8) or Hansen's three-dimensional solubility parameters (9). In Hansen's approach, the Hildebrand solubility parameter of a compound is sub-divided into three partial parameters which represent the contribution of dispersion forces, polar interactions and hydrogen bond formation to the total solubility parameter of the substance. Several descriptors have been introduced to estimate properties of drug substances from three-dimensional molecular structures (10–12). Dynamic polar molecular surfaces calculated by molecular modeling methods show better sigmoidal correlations when related to intestinal drug absorption than octanol/water partition coefficients or hydrogen bond numbers (13).

Recently it was reported that Hansen's three-dimensional solubility parameters can accurately predict permeation rates for human skin (14) and absorption rates of drugs from the rectum (15). Therefore, the purpose of this study was to utilize this method for the prediction of gastrointestinal absorption sites.

METHODS

The use of Hildebrand's solubility parameter δ is restricted to nonpolar substances. It is defined as

$$\delta = \sqrt{\frac{E_{coh}}{V_M}}$$

$$E_{coh} = \text{cohesive energy [J/mol]} \qquad (1)$$

$$V_M = \text{molar volume [cm}^3\text{/mol]}$$

By separate consideration of the sum of the intermolecular forces that form cohesive energy, Hansen (9) extended the application of the concept of solubility parameters to polar systems. He defined three partial solubility parameters: δ_d for components of intermolecular dispersion or Van der Waals' forces, δ_p for components of intermolecular polar forces and δ_h for components of intermolecular hydrogen bonding. The total solubility parameter δ_{tot} is calculated by

$$\delta_{tot} = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2}$$

$$\delta_d = \text{dispersion components} \qquad (2)$$

$$\delta_p = \text{polar components}$$

$$\delta_h = \text{hydrogen bonding components}$$

The partial solubility parameters describe the ability of a molecule to interact with another one of the same or a different type via intermolecular forces. The molecular forces and the molar volume are composed by the sum of the contributions of all structural fragments which are present in the molecule. Fedors (16) supposed group contributions to the molar volume of molecules and Van Krevelen/Hoftyzer (17) group contributions to the molecular forces. By combining both methods, partial solubility parameters can be calculated as follows (14):

$$\delta_d = \frac{\sum_i F_{d_i}}{\sum_i V_i} \qquad (3)$$

$$\delta_p = \frac{\sqrt{\sum_i F_{p_i}^2}}{\sum_i V_i} \qquad (4)$$

[1] Institute for Pharmaceutical Technology, Westphalien Wilhelms University, Münster, Germany.

[2] To whom correspondence should be addressed. (e-mail: breitkr@uni-muenster.de)

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$$\delta_h = \frac{\sqrt{\sum_i E_{h_i}}}{\sqrt{\sum_i V_i}} \quad (5)$$

i = structural group within the molecule

F_d = group contributions to dispersion forces

F_p = group contributions to polar forces

E_h = group contributions to hydrogen bond energy

V_i = group contributions to molar volume

The three-dimensional solubility parameters for each drug substance were calculated according to eqs. 3–5 by the self-made computer program SPWin, version 2.1, containing an advanced parameter set for the calculation of three-dimensional parameters (18). The parameter set is based on the group contribution methods of Fedors (16) and Van Krevelen/Hoftyzer (17). The contributions are fitted to an experimental based training data set (19). Variations from the original contributions have been implemented into the program and some new fragments have been added (18, Table I). The computer calculates the three-dimensional solubility parameters immediately after user's input of the frequency of molecular fragments within the molecule.

Bagley (20) introduced combined solubility parameters δ_v and δ_a, defined as

$$\delta_v = \sqrt{\delta_d^2 + \delta_p^2} \quad (6)$$

$$\delta_a = \sqrt{\delta_p^2 + \delta_h^2} \quad (7)$$

With these composed solubility parameter a projection of the three-dimensional solubility parameter space into a two-dimensional plot is achieved. A figure which demonstrates the relation of δ_v versus δ_h is called Bagley diagram.

RESULTS

Three-dimensional solubility parameters of several drug molecules were calculated. As a first step, the calculations were performed for substances with available data of estimated absorption durations after peroral application to fasting subjects determined by the numerical deconvolution method (21).

The calculated three-dimensional solubility parameters (Table II) were transferred into the Bagley diagram (Fig. 1). In this presentation an area can be observed which contains the substance-specific locations of all substances which exhibit oral absorption durations of 10 hours or more. In another typical region, substances with an absorption duration of less than 3 hours are located. These substances exhibit large values for δ_h. Locations of substances with oral absorption durations between 4 and 9 hours are widely spread over the Bagley diagram, but rather poorly found in regions with short or long absorption durations.

From these findings a virtual point with an oral absorption of maximal duration was supposed. Its coordinates in the Bagley diagram were calculated as $\delta_v = 20.3$ $(J \cdot cm^{-3})^{0.5}$ and $\delta_h = 11.3$ $(J \cdot cm^{-3})^{0.5}$. Consequently it was assumed that drugs which are preferably absorbed in the upper parts of the gastrointestinal tract, but less in the cecum and colon should be located outside of the area of longest absorption duration. On the other hand, substances which are located in this area of the Bagley diagram should be absorbed from all regions of the digestive tract. Several methods for in vivo detection of drug-specific absorption sites have been reported (2,22). A classification for drug substances was assumed as follows:

group 1: drugs which are only absorbed from the upper parts of the gastrointestinal tract

group 2: drugs which are preferably absorbed from the upper parts of the small intestine, but to a lower extent also from the other sites

group 3: drugs which are absorbed along the whole gastrointestinal tract, or even better absorbed from the cecum or colon than from small intestine.

Several drugs with accurately investigated absorption behaviour in humans were selected and classified into the three groups. Their three-dimensional solubility parameters (Table III) were transferred into the Bagley diagram (Fig. 2). Drugs of the classification group 3 are located in the postulated area for absorption along the whole gastrointestinal tract. Drugs of the classification

Table I. Contributions to Molecular Forces and Molar Volume From Molecular Structural Groups (Deviating Contributions from Fedors' and Van Krevelen/Hoftyzer's Values)

Structural Group i	F_{d_i} $[(J \cdot cm^3)^{0.5}/mol]$	F_{p_i} $[(J \cdot cm^3)^{0.5}/mol]$	E_{h_i} [J/mol]	V_i [cm^3/mol]
-CHO (aldehyde)	400	800	5200	22.8
-O-, not at adjacent C-atoms	100	400	3000	3.8
-O-, at adjacent C-atoms	120	530	3500	4.5
-OH, not at adjacent C-atoms	210	520	22000	10.0
-OH, at adjacent C-atoms	210	450	20000	13.0
$-NH_2$	300	440	8600	17.5
>N- (tetraedric)	20	800	5000	−9.0
-N=(planar)	20	800	5000	5.0
>S=O	472	1170	7418	4.3
$-SO_2-$	1129	1358	11670	51
-F	220	540	400	18.0
ring closure 3–4 atoms	190	0	0	18.0
ring closure ≥ 5 atoms	190	0	0	16.0
conjugated double bond in ring system	50	37	0	−2.2

Table II. Solubility Parameters and Absorption Durations of Various Drugs

Drug	No.	δ_d $[(J \cdot cm^{-3})^{0.5}]$	δ_p $[(J \cdot cm^{-3})^{0.5}]$	δ_h $[(J \cdot cm^{-3})^{0.5}]$	δ_v $[(J \cdot cm^{-3})^{0.5}]$	δ_{tot} $[(J \cdot cm^{-3})^{0.5}]$	Molar Volume $[cm^3/mol]$	Absorption Duration[b] [h]
Digoxin	1	20.73	3.69	17.61	21.06	27.45	490.1	1–2
Allopurinol	2	25.63	23.68	25.19	34.90	43.04	63.2	1–2
Riboflavin	3	23.75	9.65	22.25	25.64	33.95	206.3	1–2
Erythromycin[a]	4	18.09	3.35	15.65	18.40	24.16	577.2	2
Ampicillin	5	21.98	6.69	11.70	22.98	25.78	224.3	3
Tetracycline[a]	6	24.99	8.53	22.25	26.40	34.53	235.4	3
Doxycycline[a]	7	24.70	8.49	22.20	26.12	34.28	236.5	3
Metacycline[a]	8	25.61	8.84	22.66	27.09	35.32	227.0	3
Oxytetracycline[a]	9	25.85	9.08	24.64	27.40	36.85	228.3	3
Phenoxymethylpenicillin	10	21.61	6.54	10.50	22.58	24.90	227.7	3
Methaqualone	11	21.62	7.34	8.01	22.83	24.19	186.9	3–4
Pyridoxal-5-phosphate	12	24.79	19.47	16.97	31.50	35.78	116.3	3–4
Acetaminophen	13	21.13	8.62	15.61	22.82	27.65	111.2	3–5
Glibenclamide	14	21.44	5.29	8.87	22.09	23.80	360.9	4
Furosemide	15	23.83	8.00	13.35	25.14	28.46	206.4	4–5
Sulfametoxidiazine	16	21.70	9.50	13.55	23.69	27.29	198.1	4–5
Indometacin	17	23.06	5.98	9.42	23.83	25.62	229.8	4–5
Nitrofurantoin[a]	18	22.14	15.45	16.64	27.00	31.79	126.2	5–6
Prednisolone	19	20.63	5.59	16.65	21.37	27.09	252.6	5–6
Chloramphenicol[a]	20	23.06	9.50	18.68	24.94	31.18	175.4	5–6
Sulfinpyrazone[a]	21	23.44	7.30	10.79	24.55	26.87	263.9	5–6
Hydrochlorothiazide	22	23.86	10.07	13.82	25.89	29.35	200.7	5–6
Betamethasone	23	20.50	5.63	16.18	21.26	26.72	268.8	6–8
Phenytoin	24	22.80	6.69	7.74	23.76	24.99	170.2	6–8
Dicumarol	25	26.25	5.57	17.83	26.83	32.21	182.5	7
Metronidazole	26	19.86	13.94	16.86	24.27	29.55	117.8	8–9
Isosorbide mononitrate	27	20.87	13.37	17.00	24.78	30.05	110.7	9
Quinidine	28	20.72	5.37	11.97	21.40	24.52	244.2	10
Propranolol	29	19.57	3.35	11.04	19.85	22.72	218.2	>10
Metoprolol	30	18.31	3.68	11.52	18.68	21.94	238.1	>12
Phenylbutazone[a]	31	20.91	6.41	9.85	21.87	24.06	237.8	>12
Theophylline	32	17.80	12.85	12.65	21.95	25.33	138.2	>12

[a] Determined as an average of the solubility parameters for keto- and enol-forms.
[b] Absorption durations from ref. 21.

group 1 have extremely high δ_h values and exhibit therefore a large distance to the supposed optimal absorption point. Substances of classification group 2 are located outside the postulated area for optimal absorption. They have higher δ_h or δ_v values than drugs of classification group 3.

DISCUSSION

In the present investigations three-dimensional solubility parameters were used to characterize drug absorption behaviour along the gastrointestinal tract. The results were compared to published pharmacokinetic data. The suitability of the proposed method was demonstrated for several drug substances with heterogenous chemical structure. The concept of the three-dimensional solubility parameters is superior to calculations of octanol/water partition coefficients or total solubility parameters, because polarity and forming of hydrogen bonds are considered. During the present investigations, calculations of log P values (29) were performed. No linear ($r = 0.498$) or sigmoidal correlation was found between log P and the absorption durations of the compounds. Recently it was reported that the absorbed fraction of a drug cannot be predicted by log P calculations (13). It could be demonstrated that log P can predict permeability coefficients of drugs within homologous series of substances but not for compounds with heterogenous structures (30). For these purposes, the Δ log P value, the difference between the octanol/water partition coefficient and an alkane/water partition coefficient of a substance, might be better suitable but show also limitations.

Drug's hydrogen bonding potential which is important for passive diffusion through membranes (30) can be directly seen in the Bagley diagram. Therefore this projection of the calculated three-dimensional solubility parameters was chosen. Additionally, the evaluation of a restricted area for molecules with long absorption durations was found to be more difficult in a diagram type of δ_a versus δ_d than in the Bagley diagram. The hydrogen bonding potential is calculated by weightened group contributions fitted to a training set of molecules and therefore can describe reality better than counting the number of potential hydrogen bond locations within a molecule. Moreover, the hydrogen bonding potential of the solubility parameter concept is related to the molar volume and hence to the molecular size. Substances with very low hydrogen bonding potential

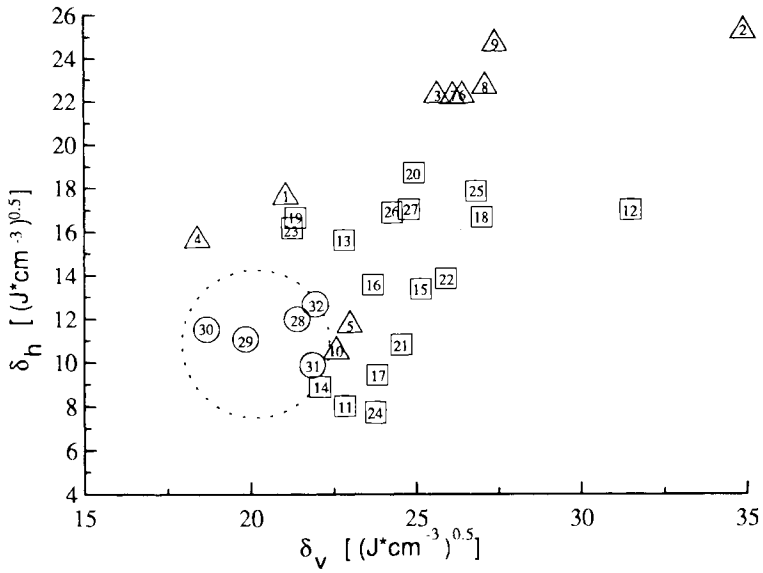

Fig. 1. Position of substance-specific locations of drugs within the Bagley diagram (identification numbers see Table II). ○ drugs with oral absorption duration ≥ 10 h; □ drugs with oral absorption duration 4–9 h; Δ drugs with oral absorption duration ≤ 3 h; --- determined area for absorption along the whole gastrointestinal tract.

are located outside the region of optimal absorption whereas other methods like the dynamic polar molecular surface method or the hydrogen bond method would predict complete absorption for these compounds.

Some of the main constitutional aspects in drug molecules are considered in the present parameter set. There are different fragment types for aliphatic or aromatic fragments and several oxygen atom types can be chosen depending on their vicinity. Nevertheless, the method disregards conformational arrangements and therefore cannot predict chameleonic behaviour of molecules. Molecular modeling methods could be used for such purposes instead (13).

A biopharmaceutical classification for in vitro-in vivo correlation of absorption data has been proposed by Amidon and co-workers (4). Solubilities and permeability are the basis for this generally accepted classification. As the new application of the three-dimensional solubility parameters combines these two drug properties, a classification into three groups of substances characterized exclusively by their absorption pattern in humans was chosen in the present investigations. Unfortunately, from the localization within the Bagley diagram the mechanisms of absorption at a definite site (e.g. passive diffusion, aqueous channel transport or carrier-mediated transport) cannot be derived. Experimental

Table III. Solubility Parameters of Various Drugs of Classification Groups 1, 2, and 3

Drug	δ_d $[(J \cdot cm^{-3})^{0.5}]$	δ_p $[(J \cdot cm^{-3})^{0.5}]$	δ_h $[(J \cdot cm^{-3})^{0.5}]$	δ_v $[(J \cdot cm^{-3})^{0.5}]$	δ_{tot} $[(J \cdot cm^{-3})^{0.5}]$	Molar Volume [cm^3/mol]	Reference
Group 1							
Aciclovir	21.80	14.64	24.06	26.26	35.61	128.0	23
Levodopa	22.34	6.26	21.86	23.20	31.88	122.2	24
Group 2							
Amoxicillin	23.13	7.38	15.65	24.28	28.88	215.3	25
Ciprofloxacin	22.66	7.30	10.97	23.81	26.22	211.8	22
Cyclosporine	18.83	3.25	14.10	19.11	23.96	951.1	26
Piretanide	22.48	6.75	12.18	23.47	26.44	258.0	27
Group 3							
Dilazep	19.79	3.97	9.81	20.19	22.44	467.9	22
Diltiazem	20.44	4.86	8.40	21.01	22.63	311.6	2
Ipsapirone	21.00	7.86	11.31	22.42	25.11	302.4	22
Nifedipine	19.61	5.15	8.59	20.28	22.02	251.9	22
Nimodipine	19.00	4.36	8.30	19.49	21.18	321.1	22
Nisoldipine	19.00	4.31	7.87	19.49	21.01	300.5	22
Nitrendipine	19.44	4.84	8.33	20.03	21.70	268.0	22
Oxprenolol	18.32	3.87	11.34	18.72	21.89	234.2	28

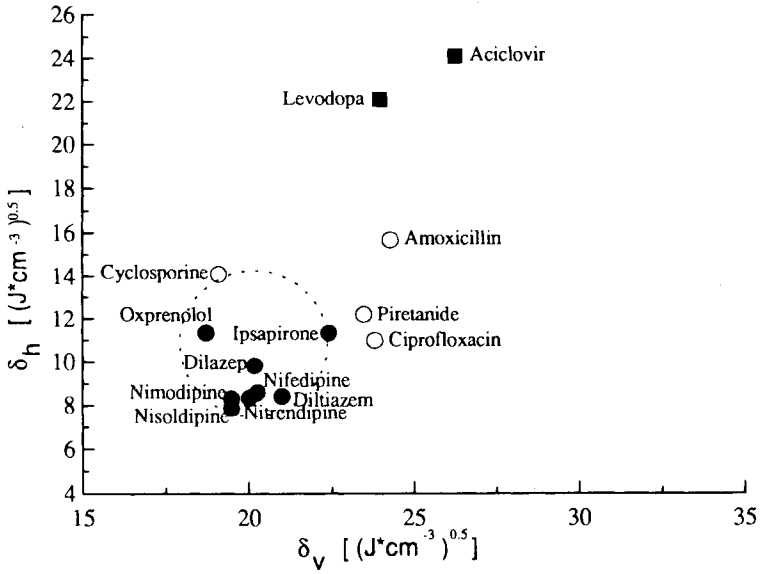

Fig. 2. Prediction of absorption sites with drug-specific locations within the Bagley diagram. ■ drugs of group 1; ○ drugs of group 2; ● drugs of group 3; --- postulated area for absorption along the whole gastrointestinal tract.

studies, e.g. animal in vivo studies or human cell culture methods, and advanced molecular modeling methods (10,13) may be superior for this special subject though they exhibit also limitations to accurate prediction (6). Nevertheless some interesting aspects of permeation mechanisms may be derived from the Bagley diagram: if the drug is absorbed at all sites of the gastrointestinal tract, absorption may be preferably due to passive uptake and therefore, the drug-specific point should be located in the area of optimal absorption. If the drug is absorbed by carrier-mediated transport and its ability of passive diffusion is low, the drug-specific point should be located outside the region of optimal absorption. The prediction of absorption sites and absorption durations by three-dimensional solubility parameters will fail if drug molecules are metabolized to a remarkable extent in gastrointestinal lumen or membranes. Although a molecule first may have a constitution for long absorption duration it can loose its structure and the property of long absorption duration by metabolism or chemical instability. Examples of these substances are penicillines (see Table II and Fig. 1). From the results of the three-dimensional solubility parameters the absorption durations for this group of drugs would be overestimated because their degradation in the gastrointestinal tract is not considered.

In pharmaceutical technology and biopharmaceutics, knowledge of drug absorption properties are important in the rational choice or development of dosage forms e.g. with sustained release kinetics or site-specific delivery. The concept of the three-dimensional solubility parameters calculated by the group contribution methods appears as a simple, fast and effective tool to predict absorption duration and absorption sites before starting detailed experimental investigations in pharmaceutical research and development.

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