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A rapid screening tool for estimating the potential of 2-hydroxypropyl-β-cyclodextrin complexation for solubilization purposes

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Abstract

Quantitative structure–property relationships (QSPRs) were developed for predicting the solubility enhancement (expressed as $\log S/S_0$) of compounds in 45% (w/v) aqueous solution of HP-β-CD. A set of 25 structurally different drugs, whose $\log S/S_0$ values were taken from literature, was used as a training set for building the computational models. Thirteen molecular descriptors, including parameters for size, lipophilicity, cohesive energy density and hydrogen-bonding capacity, were calculated and together with the experimental melting point (MP), used in multivariate analysis. Eight pertinent variables were detected after looking at the results of principal component analysis (PCA) and cluster analysis, and two reliable four-descriptor models generated by multiple linear regression (MLR) and by the partial least squares-projection to latent structures (PLS) methods. In both cases, satisfactory coefficients of determination values were obtained (i.e., R^2 equal to 0.793 or 0.763 for MLR and PLS, respectively). The models were validated using a test set of six compounds. The equations generated can predict the aqueous solubility increase of poorly soluble compounds by complexation in 45% (w/v) aqueous solution of HP-β-CD with a reasonable accuracy. These equations can allow formulation scientists to rapidly estimate, at the early stage of drug development, the potential of HP-β-CD in increasing solubility of poorly water-soluble drugs.

Keywords: Solubility enhancement; Hydroxypropyl-β-cyclodextrin; Prediction; Multivariate regression

1. Introduction

The aqueous solubility of a drug is an important molecular property that mainly influences the extent of its oral bioavailability. Due to their poor aqueous solubility, many drug candidates become unsuccess-

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ful to reach the market in spite of exhibiting potential pharmacodynamic properties (Lipinski et al., 1997; Venkatesh and Lipper, 2000). Therefore, it is very useful to find appropriate formulation approaches to improve aqueous solubility and thus the bioavailability of poorly soluble drugs. Among the known strategies aimed at improving the aqueous solubility, complexation of drugs with cyclodextrins has a relevant place in the pharmaceutical field. Cyclodextrins (CDs) are cyclic macromolecules, obtained by the degradation of starch by α-1,4-glucan-glycosyltransferase. They are composed of 6(α-CD), 7(β-CD), or 8(γ-CD) α(1–4) linked glucose units. In the past two decades, cyclodextrins (CDs) have been widely used in drug formulations as solubility enhancers because of their ability to form water-soluble inclusion complexes (Loftsson and Brewster, 1996). They have been also used to improve drug stability, bioavailability or toxicity profiles. Moreover, chemically modified cyclodextrins have been extensively used to increase the solubility, dissolution rate and bioavailability of poorly water-soluble drugs as well as to increase the stability of labile drugs (Loftsson and Brewster, 1996; Szejtli, 1991; Uekama and Otagiri, 1987; Rajewski and Stella, 1996). Among the chemically modified CDs, 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) deserves special attention due to its favorable physicochemical and biological properties (Pitha et al., 1986; Brewster et al., 1990; Irie and Uekama, 1997). Direct measurements of solubility in the presence of CDs are time-consuming and often difficult, mainly due to the low availability of the guest molecule at the early stage of drug development. Computational models for estimating the solubility increase of chemical entities in the presence of CDs are highly desirable because, before any direct measurements, they allow to decide whether or not the inclusion complexation strategy with CDs can be considered for solubilization purposes.

The aim of the present study was to develop a method for predicting the solubility enhancement of a chemical compound in concentrated (45%, w/v) aqueous solution of HP-β-CD that can be applied to different drugs using calculated molecular descriptors. As a consequence, an estimate of the behaviour at more appropriate HP-β-CD can be obtained. Although a variety of methods for predicting aqueous solubility has been reported in literature, including Yalkowsky's semi-experimental equation, the group contribution methods, and the quantitative structure–property relationships (QSPR) (Yalkowsky and Valvani, 1980; Klopman et al., 1992; Myrdal et al., 1995; Huibers and Katritzky, 1998; Jorgensen and Duffy, 2002; Nelson and Jurs, 1994; Huuskonen, 2000; Bodor and Huang, 1992; Zhong and Hu, 2003), to the best of our knowledge, a computational model for estimating the solubility increase of chemical entities in the presence of CDs have has never been suggested. Herein, we report on models helpful in estimating drug solubility enhancement in the presence of HP-β-CD.

2. Methods

The solubility enhancement of guest molecules due to HP-β-CD is quantified by $\log S/S_0$, where S and S_0 correspond to the solubilities of the drug in a 45% (w/v) aqueous solution of HP-β-CD and in water, respectively. The following computational strategy was pursued to develop models able to predict solubility enhancement: (i) retrieval of 25 liquid and solid structurally different drugs with experimental $\log S/S_0$ values from the literature; (ii) selection of 14 potentially relevant descriptors (melting point and computed descriptors); (iii) selection of pertinent descriptors through principal component analysis (PCA) on the autoscaled matrix of the dataset, combined with a cluster analysis based on correlation coefficients among variables; (iv) search for a relationship between the experimentally determined $\log S/S_0$ values and the computed variables, through multiple linear regression (MLR) and the partial least squares projection to latent structures (PLS) methods; (v) testing the derived equations on a test set of compounds.

2.1. Selection of drugs

The reliability of a QSPR prediction depends greatly on the size, quality and diversity of the training set. The case under examination is complicated by a general lack of detailed information to evaluate the quality of experimental solubility data, especially taking into account that the solubility values are dependent upon the type of HP-β-CD utilized. We mostly used the experimental solubility data reported by Szente and Strattan (1991) that are intended to provide a convenient source of information on complexes with HP-β-CD.

Literature data were selected according to the following criteria: (a) to consider only solubility increase values of unionized species in water at or around 25 °C; (b) to rule out solubility increase values for multicomponent systems; (c) to rule out compounds with very high (>1500-fold) or very low (<10-fold) solubility increases by HP-β-CD complexation. These criteria were motivated by the fact that it is well established that complexation of unionized drugs with neutral CDs (as HP-β-CD) is more effective than with the corresponding ionized forms (Li et al., 1998); furthermore, the solubilizing power of CDs can be enhanced by several orders of magnitude in multicomponent systems (Redenti et al., 2000); lastly, for compounds showing a very low (<10-fold) solubility increase, the data may be affected by large experimental errors when S is very close to S_0, whereas for compounds with high solubility increases, formation of higher-order inclusion complexes and/or self-association of CD complexes to form water-soluble aggregates are possible (Loftsson et al., 2002).

It should be noted that in some cases the original Szente and Strattan (1991) compilation was amended by taking into account the results reported by others (Loftsson et al., 1991) and issues related to the influence of pH on the solubility of ionizable drugs. Thus, Albers and Müller (1991, 1992) in their works on the HP-β-CD solubilizing ability for 17-methyl-testosterone and testosterone, proved the steepest linear solubility increase for the former. Therefore, it seems unlikely that a $\log S/S_0$ value for 17-methyl-testosterone would be much lower than that of testosterone (i.e., 2.30 and 3.26, respectively) as reported in the Szente and Strattan (1991) compilation, the intrinsic solubilities (S_0) of the two drugs being quite comparable. In our regression analysis, we used the values taken from Albers and Müller (1991, 1992). On the other hand, examination of the literature reveals that different values of intrinsic solubilities (S_0) are reported for ketoprofen and ibuprofen. This should be related to the fact that the aqueous solubility of these drugs is pH dependent. Taking into account the criterion for ionizable drugs of considering only solubility increase values of unionized species, the S_0 values for ketoprofen suggested by Orienti et al. (1991) and Zecchi et al. (1987) (0.00027 and 0.00057 M, respectively) as well as the stability constant (K_c) value reported by Junquera and Aicart (1997) (1430 M^{-1} at 25 °C) should be more appropriate since they were obtained at pH 2. Similarly, for ibuprofen having a pK_a value of 4.4, the most appropriate S_0 value should be 0.00004 M, obtained at pH 2 (Zecchi et al., 1987). Again, for this drug we used the $\log S/S_0$ corrected in the light of these findings. Thus, the 25-compound dataset selected for the present study spans a solubility increase range of more than 2 log units (from +1.00 to +3.18).

2.2. Molecular descriptors selection

In our study, we preferred to use global molecular descriptors, thus avoiding problems generally related to 3-D descriptors (e.g., conformation, orientation, alignment). They are listed in Table 1. We selected these parameters because they, as physicochemical descriptors for size, lipophilicity, cohesive energy density and hydrogen-bonding capacity, have been widely used in predictions of aqueous drug solubility (Jorgensen and Duffy, 2002; Chen et al., 2002; Liu and So, 2001). Parameters of size and polarizability [i.e., molecular weight (MW), molecular volume (MV), and molar refractivity (MR)] are highly interrelated. The melting point (MP) which is considered a key index of the cohesive interactions in the solid state (Jorgensen and Duffy, 2002), should provide an assessment of the effect of the solute's crystal structure on solubility (Peterson and Yalkowsky, 2001). As lipophilicity parameter we used the log P (log of octanol/water partition coefficient) which inversely correlates with aqueous solubility (Yalkowsky and Valvani, 1980). The commercially available ACD/Labs and CLOG P computer programs provided us with the MV and $C\log P$ and CMR calculation, respectively (ACD/Labs package, release 5.0 (Advanced Chemistry Development Inc., Toronto, Ont., Canada; CLOG P for Windows Version 4.0 (BioByte Corp., Claremont, CA, USA). The most obvious measure of hydrophilicity of a solute is its ability to form hydrogen bonds. In many studies, the total number of hydrogen bonds (H_{tot}) (Ren et al., 1996), the number of oxygen and nitrogen atoms (n_{ON}), and the number of OH and NH groups (n_{OHNH}) have been used as hydrogen bonding descriptors. However, simple count of H_{tot}, n_{ON} and n_{OHNH} can give rise to inaccurate measure of hydrogen bonding capacity, whereas polar surface area (PSA, molecular surface area contributed by polar atoms, i.e., atoms capable of hydrogen bonding such as nitrogen and oxygen) has been proposed as an

Table 1
Molecular descriptors for the drugs studied

ID	Descriptors	Type of descriptor and/or calculation
X1	Molecular weight, MW (g/mol)	
X2	Molecular volume, MV (cm^3)	ACD/Labs computer program. ACD/Labs package, release 5.0 (Advanced Chemistry Development Inc., Toronto, Ont., Canada)
X3	Melting point (MP)	The melting point data came from several sources: the Merck index, Chemfinder website, and the Analytical profile of drug substances[a]
X4	Calculated molecular refractivity (CMR)	CLOG P for Windows Version 4.0 (BioByte Corp., Claremont, CA, USA)
X5	Calculated $\log P_0/w$ ($C\log P$)	CLOG P for Windows Version 4.0 (BioByte Corp., Claremont, CA, USA)
X6	Topological surface area, TPSA ($Å^2$)	Calculated by the procedure of Ertl et al. (2000)
X7	Total number of hydrogen bonds (H_{tot})	Calculated according to Ren et al. (1996)
X8	Number of oxygen and nitrogen atoms (n_{ON})	Calculated by the chemical formula
X9	Number of OH and NH groups (n_{OHNH})	Calculated by the chemical formula
X10	δ_{tot} (total solubility parameter)	[b]
X11	δ_d (partial solubility parameter, dispersion component)	[b]
X12	δ_p (partial solubility parameter, polar component)	[b]
X13	δ_h (partial solubility parameter, hydrogen bonding component)	[b]
X14	δ_v (combined partial solubility parameter)	[b]

[a] To account also for liquid compounds they were included in the dataset by using for them a MP value of 25 °C.
[b] Calculated by the SPWin Version 2.11 computer program (Breitkreutz, 1998). Ethysterone cannot be parametrized by the SPWin program because of missing ethinyl-fragment. Rough estimation was derived by using the $H_2C{=}$ fragment.

appropriate descriptor of hydrogen bonding capacity (Bergström et al., 2002). A simple protocol to evaluate PSA based on topological information was proposed by Ertl et al. (2000), who termed such a descriptor as topological PSA (TPSA). This protocol was used for quickly assessing TPSA of the chemicals investigated herein.

The solubility parameter is a molecular descriptor, which is related to the cohesive energy density (CED) (i.e., the cohesive energy per unit of volume) of a substance in its condensed state. CED can be transformed into Hildebrand solubility parameter $\delta = (\mathrm{CED})^{1/2} = (\Delta H - RT/V_m)^{1/2}$ in which ΔH is the heat of vaporization, V_m the molar volume at the desired temperature, R the gas constant, and T the absolute temperature. Subsequently, to extend the original Hildebrand theory of solubility to polar systems, partial solubility parameters were introduced by Hansen (2000). The sum of the squares of the partial parameters gives the total squared solubility parameter, that is:

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

in which δ_d, δ_p, and δ_h account for non-polar (dispersive), polar, and hydrogen bonding effects, respectively. According to Fedors report, calculation of solubility parameters for solutes can be made using the group contribution method (Fedors, 1974). Recently, the computer program SPWin Version 2.1 based on the group contribution procedures has became available and we used it to calculate both total and partial solubility parameters and the combined solubility parameter δ_v defined as $\delta_v = (\delta_d^2 + \delta_p^2)^{1/2}$ (Breitkreutz, 1998).

2.3. Regression analysis

Principal component analysis (PCA), cluster analysis, the multiple linear regression (MLR) and the partial least squares (PLS) methods, were performed using the Unscrambler software (v. 7.5, CAMO ASA, Oslo, Norway).

3. Results

3.1. Model development

PCA can be used as useful tool for extracting uncorrelated information from large matrices of predictors

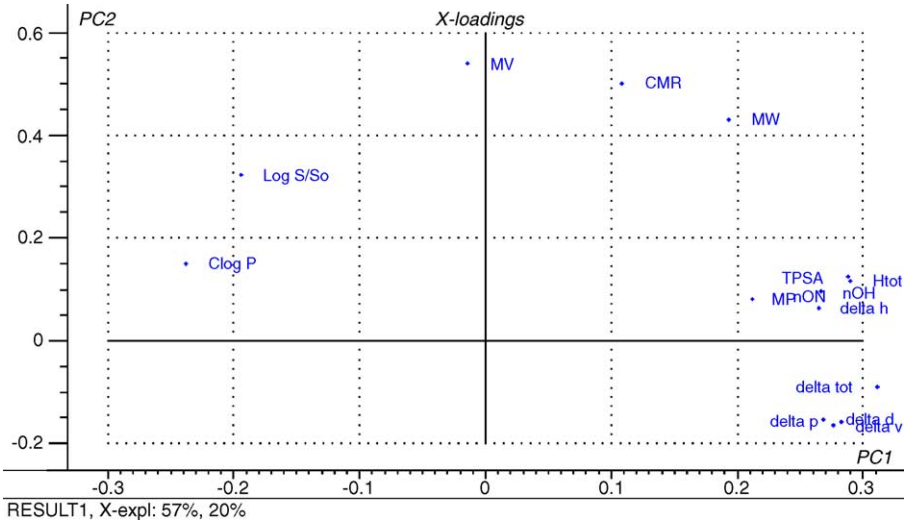

Fig. 1. PCA loadings plot of the two first principal components of the molecular descriptors examined. The first component explains 57% of the variation and the second component 20%.

(independent variables) (Katritzky et al., 2001). The PCA of the autoscaled data matrix made up of 25 rows (compounds) and 14 columns (descriptors) showed that the first two principal components accounted for more 77% of the total variance. The loading plot of the first two PCs (Fig. 1) shows that the hydrogen-bonding descriptors TPSA, H_{tot}, n_{OHNH}, n_{ON}, and δ_h are grouped in a cluster and contain similar information. The parameters of size such as MW, MV, and CMR are found in the upper part of the plot. $C\log P$ is found well separated from the other independent variables. On the other hand, a cluster analysis based on correlation coefficients among variables (Fig. 2) showed which parameters contain comparable information. Thus, looking at PCA and cluster analysis results, seven calculated predictors (MW, MV, CMR, $C\log P$, TPSA, H_{tot}, and δ_{tot}) and the experimental one (MP) were selected and used in the subsequent regression calculations. Since there are a total of 2^{n-1} possible combinations for a dataset consisting of n descriptors, in the case under examination there are $2^8 - 1$ combinations of descriptors. However, it is usually recommended to have at least five compounds per variable in linear regression to produce reliable models (Yasri and Hartsough, 2001). Hence, we considered only models containing no more than five terms (descriptors) out of the 25 training set compounds as initial input. The coefficient of determination (R^2) and the leave-one-out (LOO) cross-validation procedures were performed to obtain an estimate of the predictive performance (i.e., squared cross-validated coefficient of determination, Q^2). Other statistical parameters including the root-mean-square-error and F Fisher-test values were also used to assess the model's predictive power. A multiple linear regression (MLR) analysis, carried out by using uncorrelated variables and following the unambiguous criterion of maximizing the cross-validated explained y-variance, yielded a four-parameter equation (Eq. (1)) which explains 79%

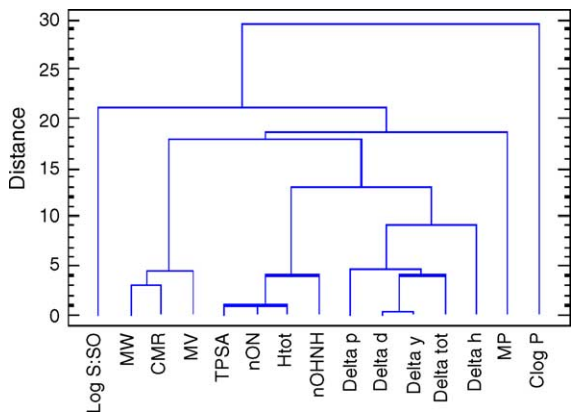

Fig. 2. Dendrogram of similarity among all variables (molecular descriptors and $\log S/S_0$) obtained using a hierarchical cluster analysis (nearest neighbor method, squared euclidean distance) based on correlation coefficients.

Table 2
Predictive power of the devised models[a]

Variables	No. of X-Vars or PLS-LV	Method	R^2	Q^2
14	4	PLS	0.785	0.566
8	5	PLS	0.806	0.685
MW, MV, $C\log P$, TPSA	4	PLS	0.763	0.601
MV, $C\log P$, TPSA, δ_{tot}	4	MLR	0.802	0.697
$C\log P$, TPSA, CMR, δ_{tot}	4	MLR	0.793	0.711
MV, $C\log P$, δ_{tot}, H_{tot}	4	MLR	0.766	0.628
MW, $C\log P$, TPSA, δ_{tot}	4	MLR	0.767	0.654
MV, $C\log P$, TPSA, δ_{tot}, MP	4	MLR	0.811	0.688
$C\log P$, TPSA, CMR, δ_{tot}, MP	5	MLR	0.807	0.712
$C\log P$, TPSA, CMR, δ_{tot}, H_{tot}	5	PLS	0.823	0.682
MV, $C\log P$, TPSA, δ_{tot}, H_{tot}	5	PLS	0.790	0.677

[a] R^2 is the coefficient of determination, Q^2 the cross-validated coefficient of determination.

of the $\log S/S_0$ data variance.

$$\log\frac{S}{S_0} = 3.766 + 0.182\,\mathrm{CMR} - 0.150\,C\log P - 0.00683\,\mathrm{TPSA} - 0.0844\,\delta_{tot},$$
$$n = 25,\ R^2 = 0.793,\ Q^2 = 0.711,$$
$$F\text{-value} = 19.17 \qquad (1)$$

Table 2 shows further MLR models obtained. However, they were left out because characterized by a lower Q^2 value or require incorporation of the experimental measurement of the melting point. In Table 3 observed and calculated (by Eq. (1)) $\log S/S_0$ and residuals are reported.

The squared correlation matrix of the parameters (Table 4) shows that CMR, $C\log P$, TPSA, and δ_{tot} are poorly interrelated ($R^2 < 0.500$) in the molecular dataset examined.

The partial least squares (PLS) method is particularly suited for the extraction of a few highly significant factors from large sets of correlated descriptors. Therefore, in this study, correlation between the eight selected descriptors and $\log S/S_0$ values was also established by PLS. Table 2 shows the PLS models generated and they all include the descriptor δ_{tot}. However, this parameter is computationally more demanding and time consuming, thus thwarting the objective to accelerate the process of calculation. Moreover, it should be also considered that some molecular fragments are missing in the database of the SPWin Version 2.1 program employed to calculate δ parameters. Therefore, although characterized by a lower statistic quality, the following four-term model (Eq. (2)) involving MW, MV, $C\log P$ and TPSA with a maximum of four PLS components is more appropriate when a rapid estimation of the $\log S/S_0$ value is required:

$$\log\frac{S}{S_0} = 1.827 - 0.00508\,\mathrm{MW} + 0.0122\,\mathrm{MV} - 0.179\,C\log P - 0.00547\,\mathrm{TPSA},$$
$$n = 25,\ R^2 = 0.763,\ Q^2 = 0.605 \qquad (2)$$

Since the descriptors cover significantly different numerical ranges, to detect the relative contribution of each independent variable to $\log S/S_0$, the procedure of MLR and PLS analyses was repeated on the matrix of autoscaled data. The values for the MLR and PLS coefficients of the models expressed by Eqs. (1) and (2) with autoscaled parameters are given in Table 5.

A plot of the predicted versus observed solubility increase of the compounds according to Eq. (1) is shown in Fig. 3.

3.2. Model validation using testing set

In this work, we used both the internal (cross-validation procedures) and external model validation approaches employing a testing set of six compounds that were representative of the training set used. The testing set was made up of liquid and solid structurally different drugs with experimental $\log S/S_0$ values reported in the literature (entries 1, 3, 4, in Table 6). It should be noted that the $\log S/S_0$ values of three com-

Table 3
Observed and predicted log S/S_0 for compounds in the training set[a]

No.	Drugs	log S/S_0 observed[b]	log S/S_0 predicted[c] (Eq. (1))	Residual[d] (%)	log S/S_0 predicted[c] (Eq. (2))	Residual[d] (%)
1	Alphaxalone	3.20	2.68	16.25	2.76	13.75
2	Betamethasone	2.72	2.35	13.60	2.49	8.45
3	Carmofur	2.15	1.99	7.44	2.01	6.51
4	Cholesterol	2.69	2.74	−1.86	2.80	−4.09
5	Citronellol	2.30	2.39	−3.91	2.45	−6.52
6	Diazepam	2.17	2.43	−11.98	2.52	−16.13
7	Ethisterone	2.81	2.83	−0.71	2.81	0.00
8	Furosemide	1.38	1.64	−18.84	1.70	−23.19
9	Hydrocortisone	2.18	2.32	−6.42	2.55	−16.97
10	Ibuprofen	2.67	2.44	8.61	2.29	14.23
11	Indomethacin	2.32	2.36	−1.72	2.29	1.29
12	Ketoprofen	2.42	2.41	0.41	2.32	4.13
13	Limonene	2.38	2.56	−7.56	2.30	3.36
14	Lorazepam	2.14	2.08	2.80	2.34	−9.35
15	Methotrexate	2.23	2.27	−1.79	1.88	15.70
16	Naproxen	2.30	2.33	−1.30	2.25	2.17
17	Oxazepam	2.18	2.04	6.42	2.17	0.46
18	Phenytoin	2.47	2.26	8.50	2.30	6.88
19	Piroxicam	1.74	1.91	−9.77	1.96	−12.64
20	Prednisolone	2.27	2.37	−4.40	2.56	−12.77
21	Progesterone	3.00	2.99	0.33	2.88	4.00
22	Retinol	2.74	2.86	−4.38	2.70	1.46
23	Spironolactone	3.13	3.30	−5.43	3.15	−0.64
24	Testosterone	2.69	2.69	0.00	2.72	−0.01
25	17-Methyl-testosterone	2.66	2.72	−0.02	2.74	−0.03

[a] The original literature sources used by Szente and Strattan (1991) for their compilation are quoted in Table 2.
[b] Observed experimental aqueous solubility enhancement.
[c] Calculated experimental aqueous solubility enhancement.
[d] Residual = (log S/S_0 observed − log S/S_0 calculated/log S/S_0 observed) × 100.

pounds in the testing set were experimentally measured by us (entries 2, 5, 6 in Table 6). To test the predictive power of the models for compounds with strong solubility increases, some compounds with enhancement factor greater than 3.18 log units were also considered (entries 7–9 in Table 6). The aqueous solubility increase of compounds in the testing set was predicted using Eq. (1). For the six compounds in the testing set, the present model was able to estimate their solubility increase with a reasonable degree of accuracy. Out of the six compounds in the testing set, only one compound, namely Zolpidem, had a residual of 1.09 log unit, whereas the remaining five compounds were predicted with a residual of <1 log unit. Compounds with

Table 4
The squared correlation matrix of the physico-chemical variables

	MW	MV	$C\log P$	CMR	δ_{tot}	TPSA	MP	H_{tot}
MW	1							
MV	0.584	1						
$C\log P$	0.028	0.149	1					
CMR	0.878	0.822	0.010	1				
δ_{tot}	0.212	0.022	0.393	0.049	1			
TPSA	0.395	0.012	0.479	0.156	0.443	1		
MP	0.217	0.015	0.239	0.118	0.376	0.206	1	
H_{tot}	0.383	0.009	0.455	0.138	0.476	0.962	0.206	1

Table 5
Autoscaled MLR and PLS regression coefficients of the models based on Eqs. (1) and (2) and on the selected set of variables

Descriptors	Eq. (1)	Eq. (2)
CMR	0.835	–
$C\log P$	−0.672	−0.803
TPSA	−0.719	−0.576
δ_{tot}	−0.759	–
MW	–	−0.933
MV	–	1.641

log S/S_0 values >3.18 (entries 7–9 in Table 6) were underestimated by the model derived and showed residuals in the range of 1.2–1.5 log units.

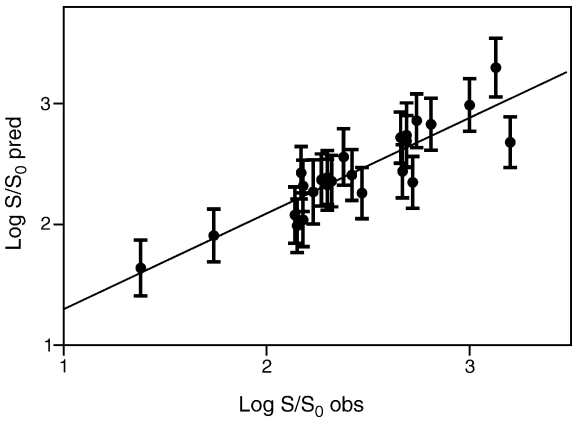

Fig. 3. Relationship between observed and predicted log S/S_0 values by using Eq. (1). Bars represent the standard error of prediction.

4. Discussion

4.1. Data set selection and physico-chemical meaning of the models derived

The dataset used in the present work meets the criteria recognized for developing sound computational models, i.e., size, quality and diversity. In fact, the 25 compounds included in the training set represent acidic, neutral, and basic compounds covering diverse structural classes. They are solid or liquid drugs at room temperature and representatives of steroids, benzodiazepines, and anti-inflammatory agents. The quality of the data plays a crucial role in developing a reliable computational model. We were aware of the limits of Szente and Strattan (1991) dataset, due to the fact that no complete characterization, for instance in terms of substitution degree (Blanchard and Proniuk, 1999), of the HP-β-CD used in deriving the experimental solubility values is reported. Furthermore, it should be also taken into account that (i) many of the compounds examined have very low S_0 values and an accurate measurement of the solubility is difficult from the experimental point of view and this must be added to the errors associated with calculating the S/S_0 values; (ii) the phase-solubility diagrams, at high concentrations of cyclodextrin, often show positive (Higuchi–Connors' A_P-type) (Higuchi and Connors, 1965) or negative (A_N-type) deviation from linearity (A_L-type); (iii) formation of insoluble complexes (B-type phase solubility diagrams) can occur even at moderate cyclodextrin level; (iv) drug/cyclodextrin complexes can self-associate to form water-soluble aggregates or micelles, which can further contribute to solubilize the drug through non-inclusion complexation (Loftsson et al., 2002). For the majority of the drugs examined an A_L type profile had been observed. However, the training set also included cholesterol showing a phase-solubility diagram with a positive deviation from linearity (i.e., a slight upward

Table 6
Observed and predicted log S/S_0 values for compounds in the validation set[a]

No.	Drugs	log S/S_0 observed[b]	log S/S_0 predicted (Eq. (1))
1	Chlorthalidone	1.81	1.93
2	Etizolam	1.46[c]	2.35
3	Isorbide dinitrate	1.60	1.58
4	Linalool	1.54	2.42
5	Propofol	2.33[c]	2.24
6	Zolpidem	1.71[c]	2.80
7	Carbamazepine	3.41	2.25
8	Dexamethasone	3.60	2.50
9	Estradiol	3.69	2.16

[a] The validation set is represented by entries (1–6). Entries (7–9) are drugs with log S/S_0 beyond the upper limit (3.18) selected for the training set.

[b] Unless otherwise stated, the observed values were deduced from Szente and Strattan (1991).

[c] Experimental values measured by us using HP-β-CD (from Roquette, Italy) with a degree of substitution of 5.88 (calculated by means of ^{1}H NMR). For experimental details on the solubilization of propofol with HP-β-CD see Trapani et al. (1998). For experimental details on the solubilization of zolpidem with HP-β-CD see Trapani et al. (2000). The experimental details about the solubilization of etizolam with HP-β-CD are similar to those employed for zolpidem.

curvature and hence an A_P-type system) (Rajewski et al., 1995; Loftsson et al., 2002). Thus, the log S/S_0 value of cholesterol should be considered as roughly estimated at 45% (w/v) HP-β-CD concentration. Taking into account all the above, it can be stated that such a dataset composition could also significantly affect statistics and physicochemical meaning of the above reported MLR and PLS equations. A careful examination of Szente and Strattan's original dataset led us to rule out those data that presumably can be affected by large experimental errors. We therefore limited the regression analysis to a dataset of 25 compounds that meets the criteria reported in Section 2.1.

Distinct features of the models herein derived are that they involve easily calculated 1-D and 2-D descriptors only and do not rely on experimentally determined parameters. The models generated are validated within the property space defined by six physicochemical descriptors and the training set utilized in model development. A closer look at the literature data reveals that the S/S_0 ratio for most pharmaceutical agents upon complexation with HP-β-CD falls within four orders of magnitude (i.e., from 0 to 4 log units). As a consequence of the criterion adopted in data selection (i.e., to rule out compounds that show very high or very low solubility increases), the *y*-values (solubility enhancements) cover a narrow range (about 2.3 log units) and this could also affect the statistics and physicochemical meaning of the models generated. As shown in Table 6, compounds with an enhancement factor of over 3.18 log units (entries 7–9 in Table 6) are underestimated by the models. This is unsurprising especially in the light of the limitations mentioned above. On the other hand, it was found that compounds showing very low solubility increase (log $S/S_0 < 1$) are overestimated by the present models. This may be due to the fact that these compounds were not represented in the training set. In conclusion, the models can be used for predicting solubility increases but the predictive power could be improved using an expanded training set comprising accurate data both for compounds with log $S/S_0 < 1$ and log $S/S_0 > 3.18$. Given the currently available training set, we thought it more appropriate to use the models generated as rapid screening filters to estimate whether HP-β-CD is suitable for solubilizing a given poorly water-soluble drug. It could also allow formulation scientists to gain information on compounds at the limits of or even outside the structural space of model validation, as discussed in detail in the next section.

As for the physico-chemical meaning, from the results of the MLR and PLS analyses, Eqs. (1) and (2) prove that log S/S_0 mainly correlates with descriptors that encode chemical features governing the dissolution process of a substance, such as bulkiness (MW, MV and CMR), lipophilicity ($C\log P$), hydrogen bonding (TPSA) and cohesive force (δ_{tot}). Moreover, properties such as lipophilicity, total polar surface area and cohesive force are negatively correlated with log S/S_0, while molar refractivity contributes positively to this ratio. To get a clearer insight in this regard, it must be taken into account that the total aqueous solubility of drug in the presence of HP-β-CD (S) is essentially the sum of the inherent solubility of the drug (S_0) and that of the drug-CD complexed species. Thus, the influence of the above mentioned properties on log S/S_0 will be a resultant of the two single terms, namely the effect on S_0 and that on the solubility of drug-CD complexed species. MR encodes for molecular volume and polarizability of a molecule. It can be regarded as a measure of how important the dispersion forces are for the complexation process (Klein et al., 2000), and the positive sign for its regression coefficient may be interpreted as a favorable influence of the dispersion forces in the host-guest complexation, but not the aqueous solubility of the free drug. Lipophilicity (log P) is negatively correlated with the aqueous solubility of the free drug. The role of hydrogen bonding (TPSA) and cohesive force (δ_{tot}) descriptors is more difficult to interpret because their effects on the complexation and water solubility of the free drug still remain to be fully elucidated. In this regard, indeed, it is reported that the increase in solubility is related to hydrogen-bonding effects, even though intermolecular hydrogen-bond interactions will lead to an increase in MP and hence to a decrease in solubility (Jorgensen and Duffy, 2002; Abraham and Le, 1999; Bergström et al., 2003). As for the effect of hydrogen bonding and cohesive forces on the solubility of drug-CD complexed species, it seems very complicated and difficult to understand.

4.2. Application of the models developed

It is generally accepted that a pharmaceutical formulation for oral or parenteral administration should contain a drug concentration of at least 10 mg/ml. An

Table 7
Predicted log S/S_0 values for some drugs and their application for solubilization with HP-β-CD

No.	Compound	MW (g/mol)	MV (cm^3)	$C\log P$	TPSA ($Å^2$)	log S/S_0 predicted (Eq. (2))	S_0[a] (mg/ml)	Time-fold increase	Calculated S (mg/ml) at 45% (w/v) of HP-β-CD	Note[b]
1	Acetylsalicylic acid	180.2	139.5	1.02	63.60	2.08	3.198[c]	120	384	Y
2	Cimetidine	252.3	198.2	0.35	65.10	2.55	6.046[c]	355	2145	Y
3	Epristeride (SKF 105657)	399.6	352.0	5.04	66.40	2.83	<0.001[c]	676	<0.676	N
4	Griseofulvin	352.8	255.1	1.75	71.08	2.45	0.0052[c]	282	1.47	N
5	Hydrochlorthiazide	297.7	175.8	−0.40	118.36	1.88	0.595[c]	76	45.14	Y
6	Miconazole	416.1	296.0	5.81	27.06	2.14	0.04[d]	138	5.52	N
7	Midazolam	325.8	239.8	3.22	30.19	2.36	<0.001[e]	229	<0.23	N
8	Prazosin	383.4	283.4	1.10	106.96	2.56	0.0032[c]	363	1.16	N
9	Probenecid	285.4	233.5	3.37	74.68	2.21	0.0036[c]	162	0.58	N
10	Propanidid	337.41	310.1	2.78	65.08	3.04	5.00[f]	1096	5500	Y
11	Propranolol	259.4	237.1	2.75	41.49	2.68	0.031[c]	479	14.84	N
12	Thiazolobenzimidazole	288.3	195.8	3.54	17.83	2.02	0.011[g]	105	1.15	N
13	Acyclovir	225.2	127.1	−2.52	119.06	2.03	1.213[c]	107	130	Y
14	Acetazolamide	222.3	127.3	−1.25	115.05	1.85	0.70[d]	71	49.56	Y
15	Taxol	853.9	610.5	4.95	221.31	2.84	0.00034[h]	692	0.235	N
16	Itraconazole	705.6	502.0	6.50	104.72	2.63	0.001[i]	427	0.427	N

[a] S_0 values reported in the literature.
[b] HP-β-CD may be (Y) or not (N) the excipient of choice for efficient solubilization of this drug without the use of a cosolvent or hydrophilic polymer or pH adjustment.
[c] Data from Bergström et al. (2002).
[d] Data from Veiga et al. (1998).
[e] Data from Loftsson (2002).
[f] Data from MacKenzie et al. (1997).
[g] Data from Tinvalla et al. (1993).
[h] Data from Loftsson and Brewster (1996).
[i] Data from Peters et al. (2002).

additional requirement when cyclodextrins are considered for solubilization purposes is that the amount of cyclodextrin in the formulation should be as small as possible. Although liquid dosage forms containing 40% (w/v) HP-β-CD are commercially available, the choice of such a concentration is not suitable because these solutions are viscous and potentially dangerous. The models herein developed should allow the log S/S_0 ratio to be evaluated and consequently an estimate of the behaviour at more appropriate and realistic HP-β-CD concentrations (e.g., 20%, w/v) to be obtained. In detail, once the predicted log S/S_0 value is available through Eqs. (1) or (2), and the intrinsic solubility S_0 is known, the solubility S at 45% (w/v) of HP-β-CD can be quickly calculated. When S is greater than 20 mg/ml, then an appropriate solubilization (10 mg/ml) may be provided by a 20% (w/v) HP-β-CD solution. By contrast, when S is less than 20 mg/ml, the solubilization capacity of a 20% (w/v) HP-β-CD solution may not be enough for an appropriate oral or parenteral formulation. The concentration of 20 mg/ml is arbitrarily assumed and should be regarded as a minimum value for successful formulation. It is also immediately argued that higher than 20 mg/ml the S value, greater the feasibility of the use of HP-β-CD as solubilization enhancer. Table 7 shows the increase in solubility calculated by Eq. (2) of a number of drugs possessing different physicochemical properties. Thus, from the calculated log S/S_0 value a satisfactory solubilization in HP-β-CD at 20% (w/v) solution can be deduced for acetylsalicylic acid, cimetidine, hydrochlorthiazide, and propanidid and assessment of the feasibility warrants experimentation. In contrast, the analysis of the results concerning epristeride, griseofulvin, miconazole, midazolam, prazosin, probenecid, propranolol, and thiazolobenzimidazole shows that an appropriate solubilization of these drugs in a HP-β-CD solution at 20% (w/v) cannot be achieved. All these analyses are in good agreement with the available experimental data (Loftsson and Brewster, 1996; Lofts-

son et al., 1991, 1994; Veiga et al., 1998; Zia et al., 2001; Loftsson, 2002; MacKenzie et al., 1997; Tinvalla et al., 1993). In fact, a 50 mg/ml solution of propanidid in 42% (w/v) HP-β-CD has been evaluated for intravenous anesthesia and found to be an alternative to the drug formerly marketed for clinical use which employed the non ionic surfactant Cremofor EL (MacKenzie et al., 1997). Again, it has been found that the amount of thiazolobenzimidazole solubilized by a 40% (w/v) of HP-β-CD solution in neutral conditions was 2.79 mg/ml, very close to that shown in Table 7 at 45% cyclodextrin. Moreover, appropriate solubilization of this drug in a HP-β-CD solution at 20% (w/v) cannot be achieved without pH adjustment (Tinvalla et al., 1993). In Table 7 four additional examples (entries 13–16) are provided to show the application of Eq. (2) to drugs with physicochemical properties different from those of the training set. It seems that HP-β-CD at 20% (w/v) might be useful to solubilize the hydrophilic drugs acyclovir and acetazolamide at the desired concentration of 10 mg/ml, whereas solubilization of taxol and itraconazole in HP-β-CD at 20% (w/v) is unlikely. In these latter cases, a combination of several approaches (use of cosolvents or water-soluble polymers or pH adjustment and complexation with HP-β-CD) could be useful. Actually itraconazole, an orally active antifungal agent which is particularly insoluble in water at physiological pH, was recently formulated as a 40% (w/v) HP-β-CD aqueous solution containing propylene glycol for pH adjustment to 4.5 (Sporanox®) (Peters et al., 2002).

Finally, the question of determining if cyclodextrins can be used in the formulation of poorly water-soluble drugs has been recently addressed by Rao and Stella (2003) who introduced the dimensionless cyclodextrin utility number, U_{CD}, which is defined by the following equation:

$$U_{CD} = \frac{K_c S_0 m_{CD} MW_D}{1 + K_c S_0 m_D MW_{CD}}$$

where K_c is the binding constant, m_D and m_{CD} the drug dose and workable amount of CD in mg, respectively, MW_D and MW_{CD} the molecular weights of D and CD, respectively. If U_{CD} is greater or equal to one, solubilization is adequately provided by CD complexation. As outlined by the authors, this number serves as a guide but not as a predictive tool that the formulator can follow. The method presented herein for addressing the same point is a predictive one and interestingly, an estimation of the binding constant value of drug:HP-β-CD complexes may also be performed provided that the molar solubilities of the drug in concentrated aqueous solution of CD and in water (S and S_0, respectively) are known, and that an A_L-type profile of the corresponding phase-solubility diagram is assumed (Higuchi and Connors, 1965). K_c, indeed, can be easily estimated according to the following Eq. (3) (Higuchi and Connors, 1965) employing S (mol/l) and S_0 (mol/l) values obtained as above discussed, and the total CD concentration L (0.2922 mol/l). Then, by applying the Rao and Stella (2003) relationship, the U_{CD} can be calculated

$$K_c = \frac{S - S_0}{S_0(L - (S - S_0))} \quad (3)$$

We believe that both Rao and Stella's approach and the one herein presented are useful tools for determining the potential of HP-β-CD complexation for solubilization purposes.

In conclusion, the computational models developed in this study can predict the solubility increase of poorly water-soluble compounds by using a concentrated (45%, w/v) aqueous solution of HP-β-CD with a reasonable degree of accuracy. These models work quite well both for liquid and solid drugs, and can serve as a tool for supporting the formulation scientist's early efforts for a rapid estimation of the suitable use of HP-β-CD.

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