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Novel high/low solubility classification methods for new molecular entities

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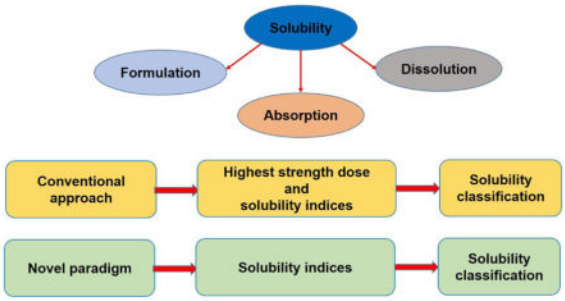
Abstract

This research describes a rapid solubility classification approach that could be used in the discovery and development of new molecular entities. Compounds (N = 635) were divided into two groups based on information available in the literature: high solubility (BDDCS/BCS 1/3) and low solubility (BDDCS/BCS 2/4). We established decision rules for determining solubility classes using measured log solubility in molar units ($MLogS_M$) or measured solubility (MSol) in mg/ml units. ROC curve analysis was applied to determine statistically significant threshold values of MSol and $MLogS_M$. Results indicated that NMEs with $MLogS_M$ >−3.05 or MSol >0.30 mg/mL will have ≥85% probability of being highly soluble and new molecular entities with $MLogS_M$ ≤ −3.05 or MSol ≤0.30 mg/mL will have ≥85% probability of being poorly soluble. When comparing solubility classification using the threshold values of $MLogS_M$ or MSol with BDDCS, we were able to correctly classify 85% of compounds. We also evaluated solubility classification of an independent set of 108 orally administered drugs using MSol (0.3 mg/mL) and our method correctly classified 81% and 95% of compounds into high and low solubility classes, respectively. The high/low solubility classification using $MLogS_M$ or MSol is novel and independent of traditionally used dose number criteria.

Graphical Abstract



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Keywords

Solubility; High throughput technologies; Analytical chemistry; Computational ADME; *In silico* modeling; Computer aided drug design; ROC curve analysis

1. Introduction

The solubility of compounds impacts formulation, dissolution, and absorption from the gastrointestinal tract. Extensive research has been conducted to develop *in silico* quantitative structure pharmacokinetic relationships and *in vitro* assays to predict the solubility of compounds in the early phases of the drug discovery process (Balakin *et al.*, 2006; Dearden, 2006; Hughes *et al.*, 2008; Kerns *et al.*, 2008). The Biopharmaceutics Classification System (BCS) and Biopharmaceutics Drug Disposition Classification System (BDDCS) have classified compounds according to their extent of solubility (high or low) using the rate and the extent of dissolution (Amidon *et al.*, 1995; Yu *et al.*, 2002) and/or dose number (Benet *et al.*, 2011; Dahan *et al.*, 2013). Dose number (D_0) is defined as (Amidon *et al.*, 1995; Benet *et al.*, 2011):

$$D_0 = \frac{Highest\ Strength\ Dose\,(mg)}{250\,mL\ water \times Solubility\,(mg/mL)}$$

where compounds with $D_0 \leq 1$ and $D_0 > 1$ are considered to have high and low solubility.

About 10% and 90% of new molecular entities have been proposed to have high and low solubility, respectively (Benet *et al.*, 2011). An *in silico/in vitro* method for the determination of solubility for classification by BCS and BDDCS was recently reported (Dahan *et al.*, 2013). This method predicted the dose number of 185 orally administered compounds by first using the reference solubility reported in the literature or by several regression models for predicting *in silico* solubility and then determining D_0, as described above (Dahan *et al.*, 2013). Benet *et al.,* (2011) also predicted the BDDCS solubility classes of over 900 compounds using the dose number criteria (Benet *et al.*, 2011). However, these *in silico* approaches require the knowledge of the highest strength dose of compounds, which is available only at the later phases of the drug development process. In this research, we propose a method for the rapid determination of the solubility class of compounds in early drug discovery and development, with statistically significant threshold values determined using Receiver Operating Characteristic (ROC) curve analysis.

ROC curve analysis is a robust and reliable statistical method that is highly sensitive and specific, and minimizes the probability of false positive and false negative predictions. ROC curve analysis was originally developed to accurately differentiate signal from noise in radar technology (Lusted, 1971). Owing to its accuracy, several clinical areas routinely use ROC curve analysis in screening and diagnostic tests (Zou *et al.*, 2007), including laboratory testing (Campbell, 1994), radiology (Obuchowski, 2003; Omalley *et al.*, 2001), bioinformatics (Lasko *et al.*, 2005), and diagnosis of several disease states such as Sjogren Syndrome (Vitali *et al.*, 2002) and insulin resistance (Keskin *et al.*, 2005). In brief, given two

predefined categories of response variables, ROC curve analysis computes potential threshold (cut-off) values (TV) with certain degree of sensitivity and specificity. The threshold value with the highest sensitivity and specificity can then be used to differentiate between the two response variables with significant statistical accuracy. Usefulness and unique advantages of ROC curve analysis have been extensively reported (Hajian-Tilaki, 2013; Park *et al.*, 2004; Zou *et al.*, 2007). ROC curve analysis (1) is not a single point analysis method, but utilizes all data to compute a wide range of potential threshold values, (2) is independent of the frequency of the observations in the two response variables with unique values of sensitivity and specificity, and (3) can be used for data with covariance and non-normal distribution unlike the conventional parametric methods. Our laboratory has previously demonstrated the use of ROC curve analysis to determine a quantitative molecular weight threshold for compounds undergoing biliary excretion in rats, dogs, and humans (Yang *et al.*, 2009; Yang *et al.*, 2010).

The overall objective of the present study is to determine a threshold value of $MLogS_M$ and MSol using ROC curve analysis to accurately classify compounds into high/low solubility classes. We also compared the performance of this method with BCS and BDDCS solubility classification of compounds available in the literature.

2. Materials and Methods

2.1 Acquisition and processing of data

Using the data from Benet *et al.,* (2011), we obtained the BDDCS classification of 635 compounds and associated available solubility data (water as media) on measured solubility (MSol) (N = 635) at pH 7.4 and measured Log_{10} solubility in molar units ($MLogS_M$) (N=634). We also obtained the data available for ALOGPS 2.1 $Log_{10}S$ (cLogS), and minimum $Log_{10}S$ (cLogS) between pH values of 3 – 7.5 calculated using VolSurf+ (minVSLgS 3–7.5).

Binning of compounds #1—For analysis of all solubility indices (cLogS, MSol, $MLogS_M$, and minVSLgS 3–7.5), data for compounds in BDDCS classes 0, 1 and 3 (high solubility) were combined and those in BDDCS classes 2 and 4 (low solubility), were combined. The resulting two groups were (1) $BDDCS_{HS}$ and (2) $BDDCS_{LS}$, respectively. pDose ($-Log_{10}$ highest strength dose in molar units) data was obtained (Benet *et al.*, 2011) for the compounds in these groups. The highest strength dose values were obtained either from the product label or from the reported values in literature (Benet *et al.*, 2011).

2.2 Receiver operating characteristic (ROC) curve analysis

ROC curve analysis was used to determine a statistically significant threshold value for all solubility related parameters that would distinguish the compounds in the $BDDCS_{HS}$ group from those in the $BDDCS_{LS}$ group, using the ROC curve toolbox in SigmaPlot 11.0 (Systat Software, San Jose, CA). ROC curve analysis is a statistical method that computes a sensitivity and a specificity value for each potential TV where sensitivity is defined as the ratio of positives selected by the test for the true positives and specificity is defined as the ratio of negatives selected by the test for the true negatives (Bewick *et al.*, 2004). The ROC

curve is a plot of all potential threshold values where sensitivity values are plotted against the respective values of 1 – specificity (Hanley and McNeil, 1982). If the area under the curve (AUC) of the ROC curve is 1, then there is 100% sensitivity and specificity, whereas AUC < 0.5 is considered as the result of chance and statistical randomness. The generally accepted criteria for the selection of a statistically significant TV is when sensitivity, specificity, and AUC values are greater than 0.8 (Galley, 2004; Yang *et al.*, 2009; Yang *et al.*, 2010). The most optimal TV is the one closest to the top left corner of the ROC curve, which has the highest sensitivity and specificity values.

For the purpose of the present study, the $BDDCS_{HS}$ group represented the true positives (P+) and the $BDDCS_{LS}$ group represented the true negatives (P−). Positives according to the test (T+) refer to the compounds having a value greater than a certain threshold value for the test parameter, whereas negatives according to the test (T−) refer to compounds having a certain parameter value less than a certain threshold value for the test parameter.

$$\text{Sensitivity (true positive fraction, TPF)} = \text{P}(\text{T}+|\text{P}+)$$
$$\text{Specificity (true negative fraction, TNF)} = \text{P}(\text{T}-|\text{P}-)$$

For a given TV, sensitivity, specificity, and AUC values greater than 0.8 implies that a probability for the occurrence of true positives is greater than 80 % and a probability for the occurrence of false positives and false negatives is less than 20 %. Thus, in 80 % of cases true positives will be distinguished from the true negatives (Yang *et al.*, 2009; Yang *et al.*, 2010). Standard error of the test and 95 % confidence interval about sensitivity, specificity, and AUC values were also computed.

2.3 Comparison of the proposed methods with BDDCS and BCS

Binning of compounds #2—Once the TV of $MLogS_M$ and MSol were determined using ROC analysis for the compounds in the $BDDCS_{HS}$ and $BDDCS_{LS}$ groups, four new groups were created:

1. Compounds with $MLogS_M > TV$ ($MLogS_{M\_HS}$)
2. Compounds with $MLogS_M \leq TV$ ($MLogS_{M\_LS}$)
3. Compounds with MSol > TV ($MSol_{\_HS}$)
4. Compounds with MSol ≤ TV ($MSol_{\_LS}$)

Percent of correctly classified compounds in all four groups were determined by comparing the results with $BDDCS_{HS}$ and $BDDCS_{LS}$ classification data to determine the performance of our proposed methods, namely:

1. Percent of correctly classified compounds in $MLogS_{M\_HS}$ compared with $BDDCS_{HS}$
2. Percent of correctly classified compounds in $MLogS_{M\_LS}$ compared with $BDDCS_{LS}$

3. Percent of correctly classified compounds in $MSol_{\_HS}$ compared with $BDDCS_{HS}$
4. Percent of correctly classified compounds in $MSol_{\_LS}$ compared with $BDDCS_{LS}$

2.4 External Validation of Methods

We obtained a second database of 185 orally administered drugs from the literature (Dahan *et al.*, 2013). We excluded 77 compounds that were present in both datasets and used an independent set of 108 compounds for external validation of our method. In their study, Dahan *et al.* had predicted solubility (mg/mL) values using several regression models consisting of *in silico* and/or *in vitro* properties such as cLogP and melting point (Dahan *et al.*, 2013). Moreover, the BCS solubility classification was then carried out using the dose number criteria (dose number equation) (Dahan *et al.*, 2013) similar to the BDDCS method (Benet *et al.*, 2011). Of all *in silico* methods evaluated, solubility classification using cLogP (calculated using BioLoom 5.0), experimental melting point, and reported highest strength dose (in silico method, ISM) was in closest agreement with the solubility classification using the reference solubility (RFS) (Dahan *et al.*, 2013).

Binning of compounds #3—For external validation of our method (MSol), 108 compounds were divided into following groups:

1. Compounds with high solubility according to reference solubility (RFS_{HS})
2. Compounds with low solubility according to reference solubility (RFS_{LS})
3. Compounds with high solubility according to *in silico* method (ISM_{HS})
4. Compounds with low solubility according to *in silico* method (ISM_{LS})

Binning of compounds #4—108 compounds were divided into two groups:

(1) Compounds with MSol > threshold value – Validation $MSol_{\_HS}$

(2) Compounds with MSol ≤ threshold value – Validation $MSol_{\_LS}$

The following comparisons were also made to evaluate the performance for our method:

(5) Percent of correctly classified compounds in ISM_{HS} compared with RFS_{HS}

(6) Percent of correctly classified compounds in ISM_{LS} compared with RFS_{LS}

(7) Percent of correctly classified compounds in Validation $MSol_{\_HS}$ compared with RFS_{HS}

(8) Percent of correctly classified compounds in Validation $MSol_{\_LS}$ compared with RFS_{LS}

Hypothesis testing: We further computed descriptive statistics for pDose, $MLogS_M$, and MSol of compounds in groups $BDDCS_{HS}$ and $BDDCS_{LS}$. We compared means and medians using a two-sample t-test and Mann-Whitney rank test for medians, respectively, to test the hypothesis that the respective means and medians of $BDDCS_{HS}$ are statistically significantly

greater than $BDDCS_{LS}$ using in Minitab® 16 Statistical Software (Minitab Inc., State College, PA).

3. Results

3.1 Receiver operating characteristic (ROC) curve analysis

Using ROC curve analysis, we determined statistically significant threshold values for $MLogS_M$ and MSol to distinguish compounds with high solubility ($BDDCS_{HS}$; N_{MLogSM} = 433 and N_{MSol} = 433) from compounds with low solubility ($BDDCS_{LS}$; N_{MLogSM} = 201 and N_{MSol} = 202). The threshold values of $MLogS_M$ and MSol with highest values of sensitivity and specificity are: −3.05 (SE = 0.008; P–value < 0.0001) and 0.3 mg/mL (SE = 0.008 and p–value < 0.0001), respectively. The ROC curve of $MLogS_M$ exhibited a threshold value of −3.05 (Figure 1A), sensitivity = 0.86 (95% CI = 0.83 – 0.89), specificity = 0.84 (95 % CI = 0.81 – 0.87), and AUC = 0.93 (95 % CI = 0.89 – 0.97). ROC curve analysis of MSol provided a threshold value of 0.3 mg/ml (Figure 1B) with a sensitivity = 0.86 (95 % CI = 0.83 – 0.89), specificity = 0.84 (95 % CI = 0.81 – 0.87), and AUC = 0.93 (95 % CI = 0.89 – 0.97). Using ROC curve analysis, statistically significant threshold values for minVSLgS 3–7.5 and cLogS could not be determined (not shown). MSol was also log-transformed (MLogS), but unlike $MLogS_M$, a statistically significant threshold value could not be computed for MLogS.

3.2 Comparison of the proposed methods with BDDCS and BCS

Using the $MLogS_M$ threshold value of −3.05 for the solubility classification and comparing the results with the reported $BDDCS_{HS}$ and $BDDCS_{LS}$ solubility classes of compounds, it was found that 86% of compounds were correctly classified in $MLogS_{M\_HS}$ (N = 408) and $MLogS_{M\_LS}$ (N = 226) groups. Similarly, using the MSol threshold value of 0.3 mg/mL, 86% and 84% of compounds were correctly classified in $MSol_{\_HS}$ (N = 401) and $MSol_{\_LS}$ (N = 234) groups, respectively. Table 1 lists results of all 635 compounds. Moreover, TV of $MLogS_M$ and MSol predicted solubility classes of 617 (97.4%) compounds identically (Table 1). Seventeen compounds for which the predicted solubility classes by the two methods were different are listed in table 2. Of these, 10 and 7 compounds, respectively, were predicted correctly by threshold values of MSol and $MLogS_M$. Potential reasons for this differences can be attributed to (1) poor correlation between MSol and $MLogS_M$ (Pearson's correlation coefficient, r = 0.3) and (2) absence of correlation between molecular weight and solubility of compounds. These results indicate that both solubility indices ($MLogS_M$ or MSol) have equally strong prediction power and either can be used for solubility classification of new molecular entities.

Table 3 lists results of comparison of solubility classes with the two BCS solubility classification methods: (1) BCS according to literature reference solubility and (2) BCS using *in silico* solubility obtained from cLogP and experimental melting point, and reported highest strength dose of compounds (*in silico* approach). For 108 compounds that were evaluated, it was found that Dahan et al, (2013) had correctly classified 73% and 63% of compounds in ISM_{HS} and ISM_{LS} groups compared with the RFS_{HS} and RFS_{LS} groups. Using MSol of 0.3 mg/mL, we were able to correctly classify 81% and 95% of compounds

in the validation $MSol_{\_HS}$ and validation $MSol_{\_LS}$ groups, respectively, when comparing with RFS_{HS} and RFS_{LS} groups. Moreover, our method was independent of the traditionally used dose number criteria.

3.3 Hypothesis testing

Descriptive statistics and the summary of hypothesis testing ($BDDCS_{HS}$, high solubility > $BDDCS_{LS}$, low solubility) of means and medians of $MLogS_M$, MSol, and pDose are presented in table 4 and the boxplots for the three parameters are illustrated in figure 2 to aid visual comparison. There are three important findings to note: (1) hypothesis testing of $MLogS_M$ and MSol indicated the means and medians of $BDDCS_{HS}$ are statistically significantly greater than those of $BDDCS_{LS}$ (Table 4), (2) despite a slight overlap in the ranges of $MLogS_M$ (Figure 2A) and MSol (Figure 2B), for $BDDCS_{HS}$ and $BDDCS_{LS}$ groups, 85% of compounds were correctly classified in $MLogS_{M\_HS}$/ $MSol_{\_HS}$ and $MLogS_{M\_LS}$/ $MSol_{\_LS}$ groups using the TV from the ROC curve analysis (Table 1), and (3) although means and medians of pDose values in $BDDCS_{HS}$ are significantly greater than those in $BDDCS_{LS}$ (Table 4), a significant overlap in ranges of pDose between the two groups is observed (Figure 2C), indicating that the highest dose strength of compounds with high and low solubility fell within a similar range.

4. Discussion

In the present study, we evaluated $MLogS_M$ and MSol as indices of solubility using ROC curve analysis. On average, the results show 85% statistical confidence that compounds with $MLogS_M > -3.05$ or MSol > 0.3 mg/mL will have high solubility and compounds with $MLogS_M \leq -3.05$ or MSol ≤ 0.3 mg/mL will have low solubility. Although the values of $MLogS_M$ or MSol for compounds were not significantly correlated, ~97% of compounds were classified identically by these two methods, indicating that either method can be used to classify new molecular entities. The application of our findings in the determination of the extent of solubility is illustrated in figure 3. ROC curve analysis has also been used for the qualitative prediction of human oral bioavailability from animal data, although in that analysis solubility was determined by the D_0 equation (Olivares-Morales *et al.*, 2014). Solubility is only one of the determinants of oral bioavailability of compounds and the present study focused on the rapid determination of solubility classes of compounds, which is applicable in early drug discovery.

FDA and EMA guidelines recommend the use of minimum Log solubility (cLogS) between pH of 1–7.5 for solubility determination of new molecular entities (CDER/FDA, 2000; EMA, 2010); however, we could not determine a statistically significant threshold value for minVSLgS 3–7.5 parameter as discussed above. Varma *et al.,* have reported pH-dependent solubility and permeability criteria for provisional biopharmaceutics classification (BCS and BDDCS) where pH dependent solubility was evaluated for a set of 49 compounds (Varma *et al.*, 2012). For the measured solubility (MSol), a threshold value of 0.2 mg/mL with 93 % sensitivity and 86 % specificity was reported to classify compounds according to BCS and BDDCS (Varma *et al.*, 2012). In our analysis, MSol value of 0.2 mg/mL had the sensitivity and specificity values of 0.88 (95 % CI = 0.84 – 0.91) and 0.79 (95 % CI = 0.75 – 0.85);

therefore, specificity was not statistically significant based on generally accepted criterion, albeit the value is close to being statistically significant. Broccatell *et al.,* (2012) developed a model using 17 VolSurf+ descriptors to predict extent of metabolism and FDA solubility with >75 % accuracy on average using a training set of 300 oral drugs and a test set of 379 oral drugs (Broccatelli *et al.*, 2012). Although, this model had fair predictive power, it required the calculation of 17 physicochemical descriptors, making its application less parsimonious (Broccatelli *et al.*, 2012). Dahan *et al.,* (2013) reported *in silico/ in vitro* methods to classify 185 compounds into BCS and BDDCS solubility classes by first using cLogP, KLogP (molecule contribution to LogP), ALogP (atomic contribution to LogP), and melting point of compounds to predict their solubility (Dahan *et al.*, 2013). The authors then used the dose number equation (ratio of the highest strength dose and the predicted solubility) for their classification (Dahan *et al.*, 2013). Utilizing this dataset as a validation dataset after excluding all compounds present in our experimental dataset, for an independent set of 108 compounds that we evaluated for external validation, we were able to correctly classify 81% and 95% of these compounds in high and low solubility groups, compared with respective RFS groups.

As discussed previously, the highest strength dose of new molecular entities is not available until the later phases of the drug development making the D_0 approach less feasible for implementation in the early drug discovery process. Benet *et al.* (2011) observed that values of pDose were highest for BDDCS class 1 compared to other classes and the converse was true for BDDCS class 4, whereas BDDCS classes 2 and 3 were in the intermediate range (Benet *et al.,* 2011). In terms of means and medians, our evaluation of pDose for compounds with high ($BDDCS_{HS}$) and low ($BDDCS_{LS}$) solubility demonstrated significant overlap (figure 2C); whereas, the ranges of both groups have minimal overlap for $MLogS_M$ (figure 2A) and MSol (figure 2B). This clearly illustrates that solubility class determination depends predominantly on the actual solubility indices (i.e. $MLogS_M$ or MSol) and not on the highest strength dose as these are very similar for both groups of compounds. Additionally, solubility classification can be determined based on our proposed methods without knowledge of highest strength dose. One limitation and consideration for using this approach is the knowledge of solubility value of a NME at physiological pH in water (media). It is important to note that solubility of compounds is sensitive to pH and media, which could potentially be a source of variability in the reported experimental solubility values. For example, solubility of alvimopan between pH 3–9 is <1 mg/mL (in water), 1–5 mg/mL at pH 1.2 (in water), and 10–25 mg/mL in aqueous 0.1 N sodium hydroxide (ENTEREG®, alvimopan FDA label).

5. Conclusion

In conclusion, we propose the use of statistically significant threshold values for two *in vitro* parameters, $MLogS_M$ (−3.05) and MSol (0.3 mg/ml), where either can be used to distinguish between new molecular entities with high and low solubility with ≥85% statistical confidence. This method has the advantages of not requiring knowledge of the highest strength dose and has high throughput screening capacity.

Acknowledgments

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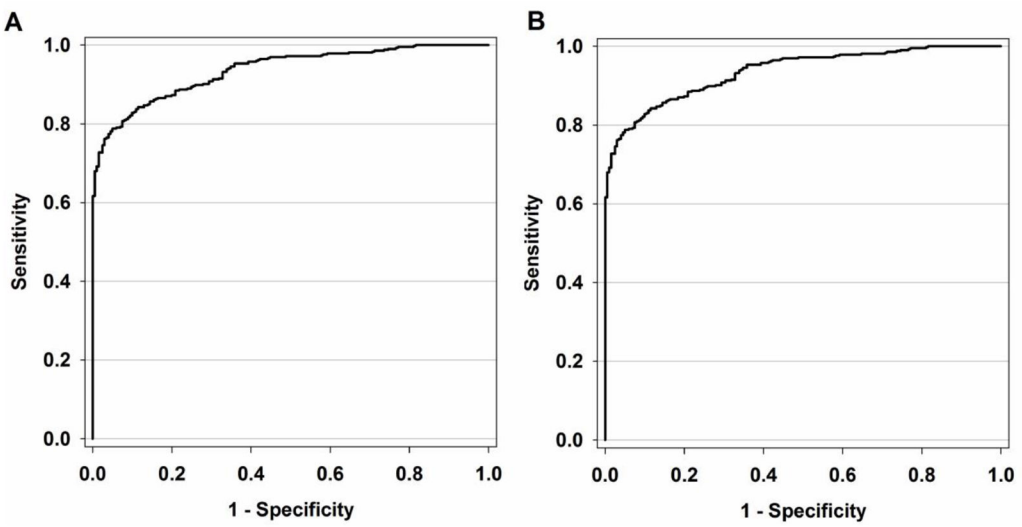

Figure 1.

Receiver operating characteristic (ROC) curve (Sensitivity vs. 1 – Specificity) of potential threshold values of (A) $MLogS_M$ [AUC = 0.93, sensitivity = 0.86, specificity = 0.84, P–value < 0.0001] and (B) MSol [AUC = 0.93, sensitivity = 0.86, specificity = 0.84, P–value < 0.0001].

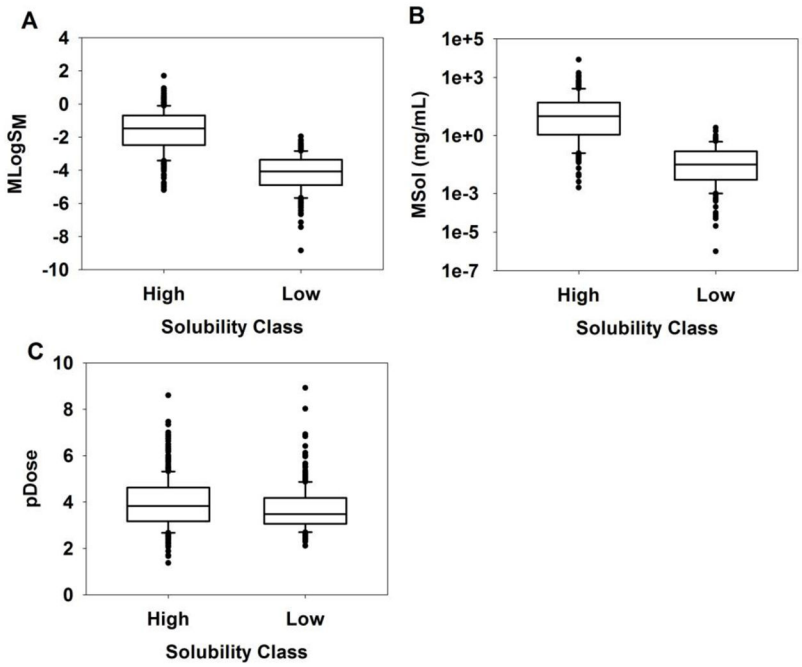

Figure 2.

Boxplot of compounds in $BDDCS_{HS}$ (high solubility) and $BDDCS_{LS}$ (low solubility): (A) $MLogS_M$, (B) MSol, and (C) pDose; the box itself (from top-to-bottom) represents 75^{th}-, median, 25^{th}-percentiles, the whiskers are 10^{th} and 90^{th} percentiles, and close black circles are outliers.

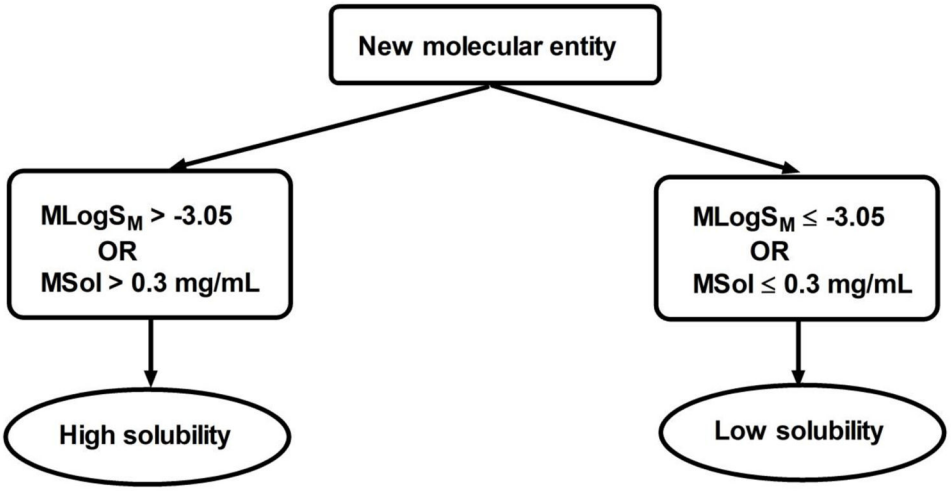

Figure 3.
Decision tree for the determination of the extent of solubility in humans

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Table 1

Solubility classification of compounds according to BDDCS ($BDDCS_{HS}/BDDCS_{LS}$) (from Benet et al, 2011) and ROC curve threshold values (TV) of MSol and $MLogS_M$. (H is high solubility and L is low solubility)

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
10-Hydroxy-Carbamazepine	L	0.045	L	−3.75	L
Abacavir Sulfate	H	77	H	−0.57	H
Acecainide; N-Acetyl Procainamide	H	50	H	−0.74	H
Acetaminophen; Paracetamol	H	23.7	H	−0.80	H
Acetazolamide	L	0.64	H	−2.54	H
Acetohexamide	H	3.43	H	−1.98	H
Acetylsalicylic Acid; Aspirin	H	10	H	−1.26	H
Acrivastine	H	0.7	H	−2.70	H
Acyclovir	L	2.5	H	−1.95	H
Adefovir Dipivoxil	H	0.4	H	−2.92	H
Adenosine	H	5	H	−1.73	H
Aliskiren	H	350	H	−0.20	H
Allopurinol	L	0.569	H	−2.38	H
Alosetron	H	61	H	−0.68	H
Alprazolam	H	0.073	L	−3.63	L
Alprenolol	H	50	H	−0.70	H
Alvimopan	H	0.1	L	−3.63	L
Amantadine	H	50	H	−0.48	H
Ambrisentan	H	0.06	L	−3.80	L
Ambroxol	H	10.9	H	−1.52	H
Amiloride	H	50	H	−0.66	H
Aminocaproic Acid	H	333	H	0.40	H
Aminophenazone; Aminopyrine	H	55.55	H	−0.62	H
Amiodarone Hydrochloride	L	0.7	H	−2.96	H
Amitriptyline Hydrochloride	H	1000	H	0.50	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Amoxicillin	H	3.5	H	−2.02	H
Amphetamine Sulfate	H	30	H	−0.65	H
Amphotericin B	L	0.1	L	−3.97	L
Ampicillin	H	7.8	H	−1.65	H
Amprenavir	L	0.04	L	−4.10	L
Anastrozole	H	0.5	H	−2.77	H
Anhydrovinblastine; Anhydrovincaleukoblastine	H	10	H	−1.90	H
Anidulafungin	L	0.05	L	−4.36	L
Antipyrine; Phenazone	H	1700	H	0.96	H
Apomorphine	H	20	H	−1.13	H
Aripiprazole	L	0.0001	L	−6.65	L
Atenolol	H	24.8	H	−1.03	H
Atomoxetine	H	27.8	H	−0.96	H
Atorvastatin Calcium	L	0.0000204	L	−7.44	L
Atropine (DL)	H	0.002	L	−5.16	L
Azacitidine	H	89	H	−0.44	H
Azapropazone; Apazone	L	0.0615	L	−3.69	L
Azathioprine	H	10	H	−1.44	H
Azithromycin	H	39	H	−1.28	H
Azlocillin	H	50	H	−0.97	H
Aztreonam	H	10	H	−1.64	H
Baclofen	H	2.1	H	−2.01	H
Bambuterol	H	33	H	−1.05	H
Benazepril	H	78	H	−0.74	H
Bendroflumethiazide	H	0.108	L	−3.59	L
Benidipine	H	1.9	H	−2.45	H
Benznidazole	H	0.4	H	−2.81	H
Bepridil	H	5	H	−1.87	H
Beraprost	H	19	H	−1.32	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Betamethasone	H	0.066	L	−3.77	L
Betaxolol	H	0.451	H	−2.83	H
Bevantolol	L	0.1843	L	−3.27	L
Bicalutamide	L	0.005	L	−4.93	L
Bimatoprost	H	0.8	H	−2.72	H
Biotin	H	0.22	L	−3.05	L
Biperiden	H	1	H	−2.49	H
Bleomycin A2	H	20	H	−1.85	H
Bopindolol	H	3.3	H	−2.06	H
Bortezomib	H	3.3	H	−2.07	H
Bosentan	L	0.001	L	−5.74	L
Bretylium	H	50	H	−0.69	H
Brimonidine	H	1.5	H	−2.29	H
Bromazepam	H	0.17	L	−3.27	L
Bromocriptine	H	0.8	H	−2.91	H
Bromperidol	H	0.09	L	−3.67	L
Budesonide	H	0.02	L	−4.33	L
Bumetanide	H	0.1	L	−3.56	L
Bupivacaine	H	0.17	L	−3.23	L
Buprenorphine Hydrochloride	H	17	H	−1.47	H
Bupropion	H	312	H	0.11	H
Buspirone	L	0.0214	L	−4.26	L
Busulfan (Busulphan)	H	0.1	L	−3.39	L
Butorphanol	H	2	H	−2.21	H
Cadralazine	H	1.3	H	−2.34	H
Caffeine	H	21.5	H	−0.96	H
Candesartan Cilexetil	L	0.05	L	−4.09	L
Capecitabine	H	26	H	−1.14	H
Capsaicin	L	0.06	L	−3.71	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	MLogS$_M$ [a]	ROC TV (−3.05)
Captopril	H	160	H	−0.13	H
Carbamazepine	L	0.256	L	−2.97	H
Carbamazepine 10,11Epoxide	L	0.1	L	−3.40	L
Carbenicillin	H	50	H	−0.88	H
Carbidopa	H	2.5	H	−1.96	H
Carboplatin	H	14	H	−1.42	H
Carmustine	H	3.8	H	−1.75	H
Carvedilol	L	0.01	L	−4.61	L
Cefaclor	H	8.59	H	−1.63	H
Cefadroxil	H	14.2	H	−1.41	H
Cefamandole	H	333	H	−0.14	H
Cefazolin	H	33	H	−1.14	H
Cefditoren Pivoxil	L	0.08	L	−3.89	L
Cefixime	L	0.05511	L	−3.92	L
Cefmetazole Sodium	H	0.0942	L	−3.70	L
Cefodizime	H	270	H	−0.34	H
Cefoxitin	H	1000	H	0.37	H
Cefpodoxime Proxetil	L	0.3	L	−3.27	L
Cefprozil	L	0.055	L	−3.85	L
Cefsulodin	H	50	H	−1.03	H
Ceftazidime	H	5	H	−2.04	H
Ceftibuten	L	0.08	L	−3.71	L
Ceftriaxone	H	400	H	−0.14	H
Cefuroxime	H	200	H	−0.33	H
Celecoxib	L	0.005	L	−4.88	L
Celiprolol	H	151	H	−0.40	H
Cephalexin	H	12	H	−1.46	H
Cephalothin Sodium	H	50	H	−0.92	H
Cephradine	H	26	H	−1.13	H

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Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Cerivastatin	H	195	H	−0.37	H
Cetirizine	H	0.101	L	−3.59	L
Cetrorelix	H	8	H	−2.25	H
Chloral Hydrate	H	8300	H	1.70	H
Chlorambucil	H	12	H	−1.40	H
Chloramphenicol	H	2.5	H	−2.11	H
Chlordiazepoxide	H	2	H	−2.18	H
Chlormethiazole; Clomethiazole	H	10	H	−1.21	H
Chloroquine	H	100	H	−0.50	H
Chlorothiazide	L	0.52	H	−2.75	H
Chlorpromazine	H	400	H	0.10	H
Chlorpropamide	H	2.2	H	−2.10	H
Chlorthalidone	L	0.27	L	−3.10	L
Chlorzoxazone	L	0.25	L	−2.83	H
Ciclesonide	L	0.0002	L	−6.43	L
Cidofovir	H	170	H	−0.22	H
Cilastatin	H	25	H	−1.16	H
Cilazapril	H	1	H	−2.62	H
Cilostazol	L	0.003	L	−5.09	L
Cimetidine	H	6.2	H	−1.61	H
Cinacalcet	L	0.1	L	−3.55	L
Ciprofloxacin	L	0.15	L	−3.34	L
Cisapride	L	0.0027	L	−5.24	L
Cisplatin	H	2.53	H	−2.07	H
Citalopram	L	0.031	L	−4.02	L
Clarithromycin	H	2	H	−2.57	H
Clemastine	H	2.3	H	−2.17	H
Clindamycin Hydrochloride Hydrate	H	40	H	−1.08	H
Clobazam	H	0.188	L	−3.20	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	MLogS$_M$ [a]	ROC TV (−3.05)
Clodronic Acid	L	0.395	H	−2.79	H
Clofarabine	H	1	H	−2.48	H
Clofazimine	L	0.001	L	−5.68	L
Clofibric Acid	H	45	H	−0.68	H
Clomiphene Citrate	H	1.11	H	−2.73	H
Clonazepam	H	0.1	L	−3.50	L
Clopidogrel Bisulfate	L	0.05078	L	−3.80	L
Clotrimazole	L	0.003	L	−5.06	L
Cloxacillin	L	0.0139	L	−4.50	L
Clozapine	L	0.0118	L	−4.44	L
Cocaine	H	1.6	H	−2.28	H
Codeine Monohydrate	H	435	H	0.14	H
Colchicine	H	45	H	−0.95	H
Conivaptan Hydrochloride	L	0.15	L	−3.55	L
Cortisone	H	0.28	L	−3.11	L
Cromolyn	H	210	H	−0.35	H
Cyanocobalamin (Vitamin B12)	H	12.5	H	−2.04	H
Cyclizine	H	8.7	H	−1.49	H
Cyclobenzaprine	H	200	H	−0.14	H
Cyclophosphamide	H	40	H	−0.81	H
Cycloserine	H	100	H	−0.01	H
Cyclosporine	L	0.008	L	−5.18	L
Cyproheptadine	H	3.636	H	−1.90	H
Cyproterone Acetate	L	0.0021	L	−5.30	L
Dabigatran Etexilate	H	1.8	H	−2.54	H
Dacarbazine	H	4.2	H	−1.64	H
Dactinomycin (Actinomycin D)	H	0.5	H	−3.40	L
Danazol	L	0.0009	L	−5.57	L
Dantrolene	H	2	H	−2.20	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Dapsone	L	0.2	L	−3.09	L
Daptomycin	H	1000	H	−0.21	H
Darunavir	L	0.15	L	−3.56	L
Daunorubicin	L	0.0392	L	−4.13	L
Debrisoquine	H	29	H	−0.78	H
Delavirdine	L	0.00081	L	−5.75	L
Demeclocycline	H	1.5	H	−2.49	H
Desloratadine	L	0.000077	L	−6.61	L
Desmethyldiazepam (Nordazepam)	H	0.057	L	−3.68	L
Desogestrel	H	0.32	H	−2.99	H
Desvenlafaxine	H	572	H	0.34	H
Dexamethasone	H	0.092	L	−3.63	L
Dexrazoxane	H	11	H	−1.39	H
Dextroamphetamine	H	1	H	−2.13	H
Dextromethorphan Hydrobromide	H	15	H	−1.26	H
Dezocine	H	20	H	−1.09	H
Diazepam	H	0.057	L	−3.70	L
Diazoxide	L	0.15	L	−3.19	L
Diclofenac	H	9	H	−1.52	H
Dicoumarol	L	0.128	L	−3.42	L
Didanosine	H	27.3	H	−0.94	H
Diethylcarbamazine Citrate	H	63.7	H	−0.50	H
Digitoxin	H	0.01	L	−4.88	L
Digoxin	H	0.986	H	−2.90	H
Dihydroquinidine; Hydroquinidine	H	11.1	H	−1.51	H
Dilevalol	H	16	H	−1.31	H
Diphenhydramine	H	1000	H	0.59	H
Dipyridamole	L	0.007	L	−4.86	L
Disopyramide	H	1	H	−2.53	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Disulfiram	L	0.2	L	−3.17	L
Docetaxel	L	0.0065	L	−5.09	L
Domperidone	L	0.006	L	−4.85	L
Donepezil	L	0.0029	L	−5.12	L
Dorzolamide Hydrochloride	H	3.9	H	−1.92	H
Dosulepin; Dothiepin	H	500	H	0.23	H
Doxorubicin	H	10	H	−1.74	H
Dronedarone	L	0.5	H	−3.05	L
Edetate Calcium Disodium	H	91	H	−0.51	H
Efavirenz	L	0.005	L	−4.80	L
Eletriptan Hydrobromide	H	4	H	−1.98	H
Emtricitabine	H	112	H	−0.34	H
Enalapril	H	25	H	−1.18	H
Enfuvirtide	H	1000	H	−0.65	H
Enoxacin	L	0.6	H	−2.73	H
Entacapone	L	0.0166	L	−4.26	L
Entecavir	H	2.4	H	−2.06	H
Eprosartan	L	0.08	L	−3.72	L
Eptifibatide	H	65	H	−1.11	H
Ergonovine; Ergometrine	H	10	H	−1.51	H
Ergotamine Tartrate	H	2	H	−2.82	H
Erlotinib Hydrochloride	L	0.4	H	−2.99	H
Erythromycin (Base)	H	2.1	H	−2.54	H
Erythromycin Lactobionate	H	20	H	−1.73	H
Erythromycin Stearate	L	0.33	H	−3.49	L
Esmolol	H	20	H	−1.17	H
Esomeprazole Magnesium	H	0.5	H	−2.84	H
Estazolam	L	0.0015	L	−5.29	L
Estradiol	H	0.09	L	−3.48	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Ethosuximide	H	39.2	H	−0.56	H
Etodolac	L	0.01	L	−4.46	L
Etomidate	L	0.045	L	−3.73	L
Etonogestrel	H	0.51	H	−2.80	H
Etoposide	H	0.22	L	−3.43	L
Etoricoxib; Arcoxia	L	0.14	L	−3.41	L
Everolimus	H	0.01	L	−4.98	L
Exenatide	H	25	H	−2.22	H
Famciclovir	H	250	H	−0.11	H
Febuxostat	L	0.013	L	−4.39	L
Felbamate	L	0.7	H	−2.53	H
Felodipine	L	0.001	L	−5.58	L
Fenofibrate	L	0.0008	L	−5.65	L
Fentanyl	H	25	H	−1.13	H
Ferrous Sulfate	H	570	H	0.57	H
Fesoterodine	H	256	H	−0.21	H
Finasteride	H	0.043	L	−3.94	L
Flecainide	H	48.4	H	−0.93	H
Fleroxacin	L	0.87	H	−2.63	H
Fluconazole	H	1	H	−2.49	H
Flucytosine	H	15	H	−0.93	H
Fludarabine 5′-Monophosphate	H	3.53	H	−2.01	H
Fludrocortisone Acetate	H	0.14	L	−3.48	L
Flufenamic Acid	L	0.0265	L	−4.03	L
Flumazenil	H	0.128	L	−3.37	L
Flunarizine	L	0.0165	L	−4.39	L
Flunitrazepam	H	0.004	L	−4.89	L
Fluorouracil	H	12.2	H	−1.03	H
Fluoxetine	H	15.2	H	−1.31	H

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Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Fluphenazine Hydrochloride	L	0.031	L	−4.22	L
Flurazepam	H	500	H	0.11	H
Flutamide	L	0.0095	L	−4.46	L
Fluticasone Propionate	L	0.00051	L	−5.99	L
Fluvastatin Sodium	H	50	H	−0.92	H
Fluvoxamine	H	14.869	H	−1.33	H
Folic Acid	L	0.0016	L	−5.44	L
Formoterol Fumarate	H	0.66	H	−2.72	H
Fosamprenavir Calcium	L	0.31	H	−3.28	L
Fosfomycin Tromethamine	H	50	H	−0.44	H
Fosinopril	L	0.022	L	−4.41	L
Fosinoprilat	L	0.01	L	−4.64	L
Fulvestrant	L	0.001	L	−5.78	L
Gabapentin	H	10	H	−1.23	H
Galantamine	H	10	H	−1.46	H
Ganciclovir Sodium	H	6	H	−1.66	H
Gefitinib	L	0.0017	L	−5.42	L
Gemcitabine Hydrochloride	H	15	H	−1.24	H
Gemfibrozil	L	0.019	L	−4.12	L
Gentamicin C1 Sulfate	H	50	H	−0.98	H
Glibornuride	H	0.2	L	−3.26	L
Gliclazide	L	0.0039	L	−4.92	L
Glimepiride	L	0.0012	L	−5.61	L
Glyburide (Glibenclamide)	L	0.004	L	−5.09	L
Granisetron	H	100	H	−0.49	H
Guanabenz	H	11	H	−1.32	H
Guanfacine Hydrochloride	H	1	H	−2.39	H
Haloperidol	L	0.037	L	−4.01	L
Heparin; Enoxaparin	H	50	H	−1.36	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Hexobarbital	H	640	H	0.43	H
Hydralazine Hydrochloride	H	44.2	H	−0.65	H
Hydrochlorothiazide	H	0.6	H	−2.70	H
Hydrocodone	H	62.5	H	−0.68	H
Hydrocortisone; Cortisol	H	0.42	H	−2.94	H
Hydroflumethiazide	H	0.3	L	−3.04	H
Hydromorphone	H	10	H	−1.46	H
Hydroxychloroquine Sulfate	H	200	H	−0.23	H
Hydroxyurea	H	50	H	−0.18	H
Hydroxyzine	H	700	H	0.27	H
Hyoscyamine; L-Atropine	H	3.56	H	−1.91	H
Ibuprofen	L	0.038	L	−3.73	L
Ibutilide	H	100	H	−0.58	H
Ifosfamide	H	100	H	−0.42	H
Iloperidone	L	0.03	L	−4.15	L
Iloprost	H	1	H	−2.56	H
Imatinib Mesylate	L	1	H	−2.69	H
Imipenem	H	10	H	−1.48	H
Imiquimod	H	0.6	H	−2.60	H
Inamrinone; Amrinone Lactate	H	0.9	H	−2.49	H
Indapamide	H	0.59	H	−2.79	H
Indinavir Sulfate	L	0.015	L	−4.61	L
Indomethacin	L	0.0025	L	−5.16	L
Iopanoic Acid; Iodopanoic Acid	L	0.015	L	−4.58	L
Irbesartan	L	0.08	L	−3.73	L
Irinotecan	H	10	H	−1.77	H
Isoniazid	H	153	H	0.05	H
Isosorbide 2-Mononitrate	H	1.1	H	−2.24	H
Isosorbide 5-Mononitrate	H	1.1	H	−2.24	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Isosorbide Dinitrate	H	1.089	H	−2.34	H
Isradipine	L	0.008	L	−4.67	L
Itraconazole	L	0.000001	L	−8.85	L
Ivermectin	H	4	H	−2.34	H
Ketamine	H	200	H	−0.08	H
Ketanserin	L	0.05	L	−3.90	L
Ketoconazole	L	0.0069	L	−4.89	L
Ketoprofen	L	0.18	L	−3.15	L
Ketorolac	H	200	H	−0.11	H
Labetalol	H	16	H	−1.31	H
Lacosamide; Erlosamide	H	2	H	−2.10	H
Lamivudine	H	70	H	−0.52	H
Lamotrigine	L	0.17	L	−3.18	L
Lansoprazole	L	0.00097	L	−5.58	L
Lapatinib Ditosylate	L	0.001	L	−5.76	L
Latamoxef; Moxalactam	H	50	H	−1.02	H
Latanoprost	L	0.05	L	−3.94	L
Leflunomide	L	0.023	L	−4.07	L
Lenalidomide	L	0.00045	L	−5.76	L
Letrozole	H	0.041	L	−3.84	L
Leucovorin; Folinic Acid	H	500	H	0.02	H
Leuprolide	H	250	H	−0.68	H
Levalbuterol	H	180	H	−0.12	H
Levetiracetam	H	1040	H	0.79	H
Levobupivacaine	H	0.17	L	−3.23	L
Levocetirizine	H	0.101	L	−3.59	L
Levodopa	H	1.65	H	−2.08	H
Levofloxacin	H	50	H	−0.86	H
Levonorgestrel	L	0.0014	L	−5.35	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	MLogS$_M$ [a]	ROC TV (−3.05)
Lidocaine	H	3.58	H	−1.82	H
Lincomycin	H	50	H	−0.91	H
Linezolid	H	8	H	−1.62	H
Lisinopril	H	97	H	−0.62	H
Lithium Carbonate	H	13	H	−0.75	H
Lomefloxacin	H	1.64	H	−2.33	H
Loperamide	H	1.4	H	−2.53	H
Loracarbef	H	41	H	−0.93	H
Loratadine	L	0.005	L	−4.88	L
Lorazepam	H	0.08	L	−3.60	L
Lorcainide Hydrochloride	H	2.4	H	−2.19	H
Losartan Potassium	L	0.048	L	−3.98	L
Lovastatin	L	0.0004	L	−6.00	L
Maprotiline	H	3.134	H	−1.95	H
Mecamylamine	H	212	H	0.10	H
Medroxyprogesterone Acetate	L	0.022	L	−4.24	L
Mefenamic Acid	L	0.08	L	−3.48	L
Megestrol Acetate	L	0.002	L	−5.28	L
Melatonin	H	0.1	L	−3.37	L
Meloxicam	L	0.012	L	−4.47	L
Melphalan	H	0.1	L	−3.48	L
Meperidine; Pethidine	H	3.22	H	−1.89	H
Mepivacaine	H	2.4	H	−2.01	H
Meprobamate	H	3.4	H	−1.81	H
Mesalamine; Mesalazine	L	1	H	−2.19	H
Metaxalone	L	0.3	L	−2.87	H
Methadone	H	120	H	−0.41	H
Methamphetamine	H	1000	H	0.83	H
Methaqualone	L	0.3	L	−2.92	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Methazolamide	H	0.704	H	−2.53	H
Methicillin	H	300	H	−0.10	H
Methohexital	H	100	H	−0.42	H
Methotrexate	H	0.45	H	−3.00	H
Methyldopa	H	10	H	−1.32	H
Methylprednisolone	H	0.3236	H	−3.06	L
Metoclopramide	H	0.2	L	−3.18	L
Metocurine Iodide	H	3	H	−2.34	H
Metoprolol	H	1000	H	0.57	H
Metronidazole	H	10	H	−1.23	H
Mianserin	H	3.4	H	−1.89	H
Miconazole	L	0.89	H	−2.67	H
Midazolam Hydrochloride	H	10.3	H	−1.55	H
Miglustat	H	1000	H	0.66	H
Milrinone	H	1	H	−2.32	H
Minocycline Hydrochloride	H	50	H	−0.96	H
Minoxidil	H	2.2	H	−1.98	H
Mirtazapine	H	0.5	H	−2.72	H
Mitoxantrone	H	7.5	H	−1.77	H
Mizolastine	L	0.013	L	−4.52	L
Morphine 6-Glucuronide	H	1000	H	0.34	H
Morphine hydrochloride	H	57.14	H	−0.75	H
Moxifloxacin Hydrochloride	H	27.5	H	−1.20	H
Mycophenolate Mofetil	L	0.043	L	−4.00	L
Nabumetone	L	0.015	L	−4.18	L
Nadolol	H	30.4	H	−1.01	H
Nafarelin	H	1	H	−3.12	L
Nalbuphine Hydrochloride	H	35.5	H	−1.00	H
Nalidixic Acid	L	0.054	L	−3.63	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Nalmefene Hydrochloride	H	124	H	−0.44	H
Naltrexone	H	100	H	−0.53	H
Naproxen	L	0.115	L	−3.30	L
Naratriptan	H	35	H	−0.98	H
Nateglinide	L	0.322	H	−2.99	H
Nefopam	H	34	H	−0.87	H
Nelarabine	L	1	H	−2.47	H
Neomycin B Sulfate	H	6.3	H	−2.05	H
Neostigmine	H	100	H	−0.35	H
Nevirapine	L	0.1	L	−3.43	L
Niacin; Nicotinic Acid	H	16.66	H	−0.87	H
Niacinamide; Nicotinamide	H	1000	H	0.91	H
Nicardipine	H	7.9	H	−1.78	H
Niclosamide	L	0.013	L	−4.40	L
Nicorandil	H	4.2	H	−1.70	H
Nifedipine	L	0.006	L	−4.76	L
Nilvadipine	L	0.0013	L	−5.47	L
Nimesulide	L	0.014	L	−4.34	L
Nimodipine	L	0.0025	L	−5.22	L
Nitrazepam	L	0.0254	L	−4.04	L
Nitrendipine	L	0.0022	L	−5.21	L
Nitrofurantoin	L	0.19	L	−3.10	L
Nitroglycerin	H	0.8	H	−2.45	H
Nizatidine	H	21.65	H	−1.18	H
Norethindrone	H	0.01	L	−4.47	L
Norethindrone Acetate	L	0.005	L	−4.83	L
Norfloxacin	L	0.75	H	−2.63	H
Norgestimate	H	0.02	L	−4.27	L
Norgestrel	H	0.002	L	−5.19	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Nystatin	H	4	H	−2.36	H
Ofloxacin	H	3.54	H	−2.01	H
Olanzapine	L	0.01	L	−4.49	L
Olmesartan Medoxomil	H	2	H	−2.45	H
Olopatadine Hydrochloride	H	2	H	−2.23	H
Omeprazole	H	0.5	H	−2.84	H
Ondansetron	H	5.7	H	−1.71	H
Orphenadrine	H	10	H	−1.43	H
Oxaliplatin	H	6	H	−1.82	H
Oxaprozin	L	1.7	H	−2.24	H
Oxatomide	L	0.043	L	−4.00	L
Oxazepam	L	0.045	L	−3.80	L
Oxcarbazepine	L	0.085	L	−3.47	L
Oxprenolol	H	30.86	H	−0.93	H
Oxybutynin Hydrochloride	H	0.8	H	−2.69	H
Oxycodone	H	100	H	−0.50	H
Oxymorphone	H	24	H	−1.10	H
Paliperidone	L	0.01125	L	−4.58	L
P-Aminosalicylic Acid (PAS)	H	142.85	H	−0.03	H
Paroxetine	H	5.4	H	−1.79	H
Pefloxacin	H	11.4	H	−1.47	H
Pemetrexed Disodium	H	90	H	−0.68	H
Penciclovir	H	170	H	−0.17	H
Penicillin V; Phenoxymethylpenicillin	L	0.25	L	−3.15	L
Pentamidine	H	100	H	−0.53	H
Pentazocine	L	0.0449	L	−3.80	L
Pentostatin	H	30	H	−0.95	H
Pentoxifylline	H	191	H	−0.16	H
Perhexiline	L	0.00006	L	−6.67	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Phenacetin	L	0.73	H	−2.39	H
Phenmetrazine	H	2.5	H	−1.85	H
Phenobarbital	H	1	H	−2.37	H
Phenylbutazone	H	0.7	H	−2.64	H
Phenytoin Sodium	L	0.02	L	−4.14	L
Pimozide	H	0.008	L	−4.76	L
Pindolol	H	7.9	H	−1.50	H
Piperacillin	H	714.3	H	0.14	H
Piperazine	H	260	H	0.48	H
Pirenzepine	H	50	H	−0.85	H
Piroxicam	L	0.0073	L	−4.66	L
Plerixafor	H	10	H	−1.70	H
Posaconazole	L	0.00005	L	−7.15	L
Potassium Chloride	H	333.3	H	0.65	H
Pramipexole	H	0.2	L	−3.02	H
Pravastatin	H	300	H	−0.15	H
Prazepam	L	0.004	L	−4.91	L
Praziquantel	L	0.4	H	−2.89	H
Prazosin	H	1.4	H	−2.44	H
Prednisolone	H	0.38	H	−2.98	H
Prednisone	L	0.133	L	−3.43	L
Pregabalin	H	33	H	−0.68	H
Primidone	L	0.6	H	−2.56	H
Procainamide	H	4	H	−1.77	H
Prochlorperazine	H	0.1	L	−3.57	L
Progesterone	L	0.007	L	−4.65	L
Proguanil	H	9.09	H	−1.45	H
Promazine	H	333.33	H	0.07	H
Propafenone Hydrochloride	L	0.093	L	−3.56	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Propantheline Bromide	H	50	H	−0.87	H
Propofol	L	0.164	L	−3.04	H
Propoxyphene Napsylate	L	0.0196	L	−4.27	L
Propranolol Hydrochloride	H	50	H	−0.71	H
Propylthiouracil	H	1.2	H	−2.15	H
Protriptyline	H	50	H	−0.72	H
Pyrantel Pamoate	L	0.5	H	−2.62	H
Pyrazinamide	H	15	H	−0.91	H
Pyridostigmine	H	100	H	−0.26	H
Pyrimethamine	H	0.121	L	−3.31	L
Quetiapine Fumarate	H	94	H	−0.97	H
Quinacrine; Mepacrine	H	28.57	H	−1.15	H
Quinapril	L	0.001	L	−5.64	L
Quinidine Sulfate Dihydrate	H	11.1	H	−1.85	H
Quinine Bisulfate Heptahydrate	H	111.1	H	−0.69	H
Raloxifene; Keoxifene	L	0.013	L	−4.56	L
Ranitidine	H	555	H	0.25	H
Reboxetine	H	8	H	−1.59	H
Regadenoson	H	0.05	L	−3.89	L
Reserpine	H	0.01	L	−4.78	L
Ribavirin	H	142	H	−0.24	H
Ridogrel	H	0.02	L	−4.26	L
Rifabutin	L	0.19	L	−3.65	L
Rifaximin	L	0.001	L	−5.90	L
Rimantadine Hydrochloride	H	50	H	−0.55	H
Risperidone	H	0.25	L	−3.22	L
Rizatriptan	H	42	H	−0.81	H
Rofecoxib	L	0.1	L	−3.50	L
Rolitetracycline	H	1250	H	0.37	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	$MLogS_M$ [a]	ROC TV (−3.05)
Ropinirole	H	133	H	−0.29	H
Ropivacaine	H	53.8	H	−0.71	H
Rosiglitazone Maleate	H	0.04	L	−3.95	L
Rotigotine	H	5.6	H	−1.75	H
Roxithromycin	L	0.1	L	−3.92	L
Rufinamide	L	0.059	L	−3.61	L
Salicylic Acid	H	2.51	H	−1.74	H
Saquinavir Methanesulfonate	L	0.08	L	−3.98	L
Saxagliptin	H	17.6	H	−1.25	H
Scopolamine	H	666.67	H	0.34	H
Secobarbital (Quinalbarbitone)	H	1.1	H	−2.34	H
Sertraline Hydrochloride	H	3.8	H	−1.91	H
Sibutramine	H	2.9	H	−1.98	H
Sildenafil	H	3.5	H	−2.13	H
Simvastatin	L	0.03	L	−4.14	L
Sotalol	H	137	H	−0.30	H
Sparfloxacin	H	1.1	H	−2.55	H
Spectinomycin	H	7.5	H	−1.65	H
Spironolactone	L	0.022	L	−4.28	L
Stavudine	H	83	H	−0.43	H
Streptomycin	H	20	H	−1.46	H
Sulfadiazine	L	0.13	L	−3.28	L
Sulfamethizole	L	0.25	L	−3.03	H
Sulfamethoxazole	L	0.392	H	−2.81	H
Sulfasalazine	L	0.0024	L	−5.22	L
Sulfinpyrazone	L	0.031	L	−4.12	L
Sulfisoxazole	L	0.13	L	−3.31	L
Sulindac	L	0.0028	L	−5.10	L
Sulindac Sulfide	L	0.0028	L	−5.08	L

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	MLogS$_M$ [a]	ROC TV (−3.05)
Sulpiride	H	2.28	H	−2.18	H
Sumatriptan Succinate	H	21.4	H	−1.14	H
Sunitinib Malate	H	25	H	−1.20	H
Tacrolimus	L	0.008	L	−5.00	L
Talinolol	H	1.23	H	−2.47	H
Tamoxifen	H	0.5	H	−2.87	H
Tazobactam Sodium	H	50	H	−0.78	H
Telithromycin	L	0.8	H	−3.01	H
Temazepam	H	0.604	H	−2.70	H
Temsirolimus	H	0.01	L	−5.01	L
Teniposide	L	0.025	L	−4.42	L
Tenofovir Disoproxil	H	13.4	H	−1.59	H
Tenoxicam	H	0.803	H	−2.62	H
Terazosin	H	24.2	H	−1.20	H
Terbutaline	H	213	H	−0.02	H
Terfenadine	L	0.006	L	−4.90	L
Testolactone	L	0.027	L	−4.05	L
Testosterone	L	0.0234	L	−4.09	L
Tetracycline	H	1.7	H	−2.42	H
Tetracycline Hydrochloride	H	10.9	H	−1.64	H
Thalidomide	L	0.0525	L	−3.69	L
Theophylline	H	8.3	H	−1.34	H
Thiabendazole	L	0.05	L	−3.60	L
Thioguanine	H	0.2	L	−2.92	H
Thiopental	H	50	H	−0.69	H
Thioridazine	H	1	H	−2.57	H
Thyroxine; Levothyroxine	L	0.000585	L	−6.12	L
Tiagabine Hydrochloride	L	0.03	L	−4.10	L
Ticarcillin	H	1000	H	0.42	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	MLogS$_M$ [a]	ROC TV (−3.05)
Tigecycline	H	295	H	−0.29	H
Timolol	H	2.74	H	−2.06	H
Tinidazole	H	20	H	−1.09	H
Tobramycin	H	1000	H	0.33	H
Tocainide	H	10	H	−1.28	H
Tolazamide	L	0.278	L	−3.05	L
Tolbutamide	L	0.109	L	−3.39	L
Tolmetin	L	0.22	L	−3.07	L
Tolterodine	H	12	H	−1.43	H
Tolvaptan	L	0.0005	L	−5.95	L
Topiramate	H	9.8	H	−1.54	H
Topotecan	H	1	H	−2.62	H
Toremifene	H	0.38	H	−3.03	H
Torsemide; torasemide	L	0.16	L		
Tranylcypromine Sulfate	H	48	H	−0.44	H
Trazodone	L	0.2	L	−3.27	L
Triamcinolone	H	0.08	L	−3.69	L
Triamcinolone Acetonide	H	0.114	L	−3.58	L
Triamterene	L	0.029	L	−3.94	L
Triazolam	H	0.045	L	−3.88	L
Triclabendazole	L	0.0002	L	−6.25	L
Trifluoperazine	H	50	H	−0.91	H
Trihexyphenidyl (Benzhexol)	H	10	H	−1.48	H
Trimethoprim	H	1.37	H	−2.33	H
Trimetrexate Glucuronate	H	50	H	−0.87	H
Tropisetron	H	11	H	−1.41	H
Trospium Chloride	H	500	H	0.11	H
Tubocurarine	H	50	H	−1.09	H
Urapidil	H	19	H	−1.31	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	MLogS$_M$ [a]	ROC TV (−3.05)
Valacyclovir	H	174	H	−0.27	H
Valganciclovir; Valcyte	H	70	H	−0.70	H
Valproic Acid	H	1.3	H	−2.05	H
Valsartan	L	0.18	L	−3.38	L
Vancomycin	H	50	H	−1.46	H
Vardenafil	H	0.11	L	−3.65	L
Varenicline Tartrate	H	0.2	L	−3.02	H
Vasopressin	H	0.1	L	−4.04	L
Venlafaxine Hydrochloride	H	572	H	0.31	H
Verapamil Hydrochloride	H	0.75	H	−3.05	L
Vinblastine	H	10	H	−1.91	H
Vincristine	H	10	H	−1.92	H
Vinorelbine Tartrate	H	1000	H	0.11	H
Vitamin A (Retinol)	L	0.044	L	−3.81	L
Vitamin B1 (Thiamine)	H	27	H	−0.99	H
Vitamin B2 (Riboflavin)	L	0.11	L	−3.53	L
Vitamin B6 (Pyridoxine)	H	222	H	0.12	H
Vitamin C; Ascorbic Acid	H	333	H	0.28	H
Vitamin D3	H	0.1	L	−3.59	L
Voriconazole	L	0.39	H	−2.95	H
Warfarin	L	0.018	L	−4.23	L
Zalcitabine	H	76.4	H	−0.44	H
Zanamivir	H	18	H	−1.27	H
Zidovudine	H	25	H	−1.03	H
Zileuton	L	0.5	H	−2.67	H
Ziprasidone Hydrochloride	L	0.00043	L	−5.98	L
Zolmitriptan	H	20	H	−1.16	H
Zolpidem Tartrate	H	23	H	−1.13	H
Zonisamide	H	0.8	H	−2.42	H

Generic Name	BDDCS Solubility Class [a]	MSol [a] (mg/mL)	ROC TV (0.3 mg/mL)	MLogS$_M$ [a]	ROC TV (−3.05)
Zopiclone	H	0.12	L	−3.51	L

*Note:

[a]Data was obtained from Benet *et al.* (Benet *et al.*, 2011)

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Table 2

List of compounds with different solubility class when predicted by TV of MSol and $MLogS_M$ compared between the two proposed methods

Generic Name	BDDCS Solubility Classification [a]	ROC TV MSol	ROC TV $MLogS_M$
Carbamazepine	L	L	H
Chlorzoxazone	L	L	H
Dactinomycin	H	H	L
Dronedarone	L	H	L
Erythromycin Stearate	L	H	L
Fosamprenavir Calcium	L	H	L
Hydroflumethiazide	H	L	H
Metaxalone	L	L	H
Methaqualone	L	L	H
Methylprednisolone	H	H	L
Nafarelin	H	H	L
Pramipexole	H	L	H
Propofol	L	L	H
Sulfamethizole	L	L	H
Thioguanine	H	L	H
Varenicline Tartrate	H	L	H
Verapamil Hydrochloride	H	H	L

[*] Note: TV of MSol and $MLogS_M$ identically predicted the solubility class of the compounds that are not listed in this table and are listed in Table 1.

[a] Data was obtained from Benet *et al.*(Benet *et al.*, 2011).

Table 3

Solubility classifications of 108 orally administered compounds from Dahan et al, 2013 according to literature reference solubility (RFS_{HS}/ RFS_{LS}), *in silico* solubility prediction (ISM_{HS}/ ISM_{LS},utilizing cLogP, measured melting point, and highest strength dose), and ROC curve TV of MSol.

Generic Name	MSol (mg/mL)	RFS solubility prediction	*in Silico* Solubility prediction	ROC TV MSol
Aceclofenac	0.01	L	L	L
Acetaminophen	0.1	L	H	L
Albendazole	0.01	L	L	L
Alibendol	10	H	H	H
Amiloride hydrochloride	1	H	H	H
Atropine sulfate	1	H	H	H
Azithromycin hydrate	0.01	L	L	L
Azulene sulfonate	10	H	H	H
Benazepril hydrochloride	33	H	H	H
Biperiden hydrochloride	0.01	H	H	L
Bisacodyl	0.01	L	H	L
Brotizolam	0.01	H	H	L
Cabergoline	0.01	L	L	L
Cetirizine hydrochloride	33	H	H	H
Chloroquine phosphate	0.1	L	L	L
Clonidine hydrochloride	33	H	H	H
Codeine phosphate	1	H	H	H
Cyclosporin A	0.01	L	L	L
Dapsone	0.01	L	H	L
Diazepam	0.01	L	H	L
Diclofenac sodium	0.1	H	L	L
Diloxanide furoate	0.1	L	L	L
Domperidone maleate	0.1	H	L	L
Doxifluridine	33	H	H	H
Epalrestat	0.01	L	L	L
Epinastine hydrochloride	100	H	L	H
Eprosartan mesylate	0.01	L	L	L
Ergometrine maleate	1	H	H	H
Erythromycin ethylsuccinate	0.01	L	H	L
Ethambutol hydrochloride	10	H	H	H
Ethinyl estradiol	0.01	H	H	L
Etizolam	0.01	H	H	L
Ezetimibe	0.01	L	L	L
Famotidine	0.1	L	H	L
Fexofenadine hydrochloride	1	H	L	H

Generic Name	MSol (mg/mL)	RFS solubility prediction	*in Silico* Solubility prediction	ROC TV MSol
Flurbiprofen	0.01	L	L	L
Furosemide	0.01	L	L	L
Glipizide	0.01	L	H	L
Glyburide	0.01	L	L	L
Griseofulvin	0.01	L	L	L
Hydrochlorothiazide	0.01	L	H	L
Imidapril hydrochloride	33	H	H	H
Isotretinoin	0.01	L	L	L
Ketotifen fumarate	1	H	H	H
L-carbocysteine	0.1	L	H	L
Levamisole hydrochloride	33	H	H	H
Levodopa	1	L	H	H
Levosulpiride	0.01	L	H	L
Limaprost alfadex	100	H	H	H
Linezolid	1	L	H	H
Lopinavir	0.01	L	L	L
Lorazepam	0.08	H	H	L
Losartan potassium	100	H	L	H
Loxoprofen sodium	1000	H	H	H
Manidipine hydrochloride	0.01	L	L	L
Mebendazole (chewable)	0.01	L	L	L
Metoclopramide hydrochloride	0.01	L	H	L
Metronidazole	1	L	H	H
Modafinil	0.01	L	H	L
Morphine sulfate	33	H	H	H
Mosapride citrate	0.01	L	L	L
Nicergoline	0.01	L	L	L
Niclosamide (chewable)	0.01	L	L	L
Nicotinamide	100	H	H	H
Nifurtimox	33	H	H	H
Nilvadipine	0.01	L	H	L
Norethindrone (norethisterone)	0.01	H	H	L
Ondansetron hydrochloride	10	H	L	H
Orlistat	0.01	L	L	L
Oxycodone hydrochloride	0.01	L	H	L
Penicillamine	100	H	H	H
Pergolide mesylate	0.01	H	H	L
Phenobarbital	0.1	L	H	L
Phenytoin (chewable)	0.01	L	L	L

Generic Name	MSol (mg/mL)	RFS solubility prediction	*in Silico* Solubility prediction	ROC TV MSol
Pioglitazone hydrochloride	0.01	L	L	L
Pranlukast hydrate	0.01	L	L	L
Promethazine hydrochloride	100	H	L	H
Propranolol hydrochloride	33	H	L	H
Pseudoephedrine hydrochloride	10	H	H	H
Pyrantel embonate	0.01	L	L	L
Pyridostigmine bromide	100	H	H	H
Pyridoxine hydrochloride	100	H	H	H
Raloxifene hydrochloride	0.1	L	L	L
Ramipril	10	H	H	H
Ranitidine hydrochloride	100	H	H	H
Rizatriptan benzoate	33	H	H	H
Sildenafil citrate	1	H	L	H
Spironolactone	0.01	L	H	L
Sulfadiazine	0.01	L	L	L
Sultamicillin tosilate	0.1	L	L	L
Tacrolimus	0.01	L	L	L
Taltirelin hydrate	33	H	H	H
Tamoxifen citrate	0.01	L	L	L
Tegafur	10	H	H	H
Telmisartan	0.01	L	L	L
Temocapril hydrochloride	0.1	H	H	L
Tenofovir disoproxil fumarate	13.4	H	L	H
Terazosin hydrochloride	100	H	L	H
Terbinafine hydrochloride	1	H	L	H
Toremifene citrate	0.63	H	L	H
Triflusal	0.01	L	L	L
Trimebutin maleate	1	H	L	H
Trimethoprim	0.1	L	H	L
Tulobuterol hydrochloride	100	H	H	H
Ursodeoxycholic acid (ursodiol)	0.01	L	L	L
Voglibose	1000	H	H	H
Warfarin sodium	0.01	L	H	L
Zaltoprofen	0.01	L	L	L

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Table 4

Descriptive statistics of means and medians of $MLogS_M$, MSol (mg/mL), and pDose of compounds in $BDDCS_{HS}$ (high solubility, H) and $BDDCS_{LS}$ (low solubility, L).

Category	N	Mean ± SD	Summary[a]	Median	Summary[b]	Range
$MLogS_M$ (H)	433	−1.62 (1.25)	t-stat = 26 p-value < 0.0001	−1.47	W-stat = 175503 p-value < 0.0001	−5.19, 1.70
$MLogS_M$ (L)	201	−4.19 (1.11)		−4.07		−8.84, −1.95
MSol (H)	433	113 (454)	t-stat = 5.17 p-value < 0.0001	10	W-stat = 176234 p-value < 0.0001	0, 8300
MSol (L)	202	0.15 (0.29)		0.03		0, 2.5
pDose (H)	460	3.96 (1.07)	t-stat = 3.25 p-value = 0.001	3.83	W-stat = 180475 p-value < 0.0001	1.37, 8.60
pDose (L)	280	3.70 (0.96)		3.47		2.10, 8.90

[a] – Two-sample t-test for means (Testing mean of H > L)

[b] – Mann-Whitney rank test for medians (Testing median of H > L)