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Comparison of Two In-Silico Modeling Programs, ADMET Predictor® and Percepta® to Predict Intrinsic Solubility and pKa of Poorly Soluble Drugs

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PURPOSE

Aqueous solubility is a prerequisite for oral absorption of a drug and the pH-dependence of aqueous solubility is critical information to guide formulation development strategies. The purpose of this study was to evaluate the physical property modules in two commercially available in-silico modelling programs in predicting the pH-solubility profiles as described by the ionization constant (pKa) and the intrinsic solubility of the unionized form.

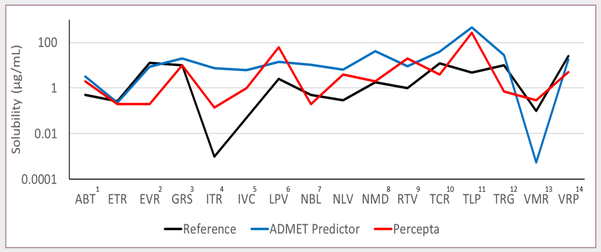
METHOD(S)

The drugs studied were: abiraterone acetate (ABR), etravirine (ETR), everolimus (EVR), griseofulvin (GRS), itraconazole (ITR), ivacaftor (IVC), lopinavir (LPV), nabilone (NBL), nilvadipine (NLV), nimodipine (NMD), ritonavir (RTV), tacrolimus (TCR), telaprevir (TLP), troglitazone (TRG), vemurafenib (VMR), and verapamil (VRP). The two in-silico modeling programs evaluated were ADMET Predictor® (Simulations Plus, V 9.0) and Percepta® (Advanced Chemistry Development, Inc., V14.2) using the Classic and GALAS algorithms. Definitive literature reference values were used to evaluate the accuracy of the predictions. Where literature data was not available, experimental measurements were made: pKa was measured for ETR, GRS, ITR, IVC, LPV, NLV, NMD, TLP, and VMR using a Sirius T3 and solubility was measured for NLV and ETR at a pH appropriate for intrinsic solubility of the unionized form (shaker method; room temp; 2 days equilibration time).

RESULT(S)

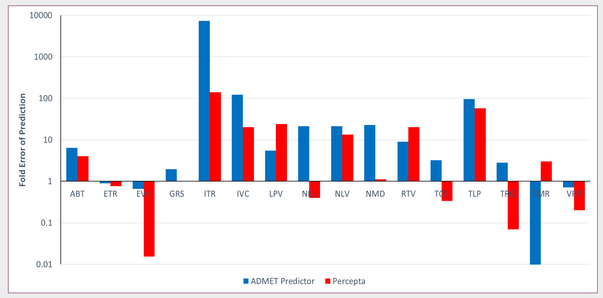
The 16 drugs studied were selected primarily from examples of drugs that have been commercialized as amorphous solid dispersions. As such, these are challenging poorly soluble drugs with a range of intrinsic solubilities from 1 ng/mL (ITR) to 25 µg/mL (VRP); eight have an intrinsic solubility at or lower than 1 µg/mL. Percepta Classic and GALAS predictions were essentially indistinguishable. Generally ADMET Predictor and Percepta programs both over predicted intrinsic solubility, with Percepta tracking the reference data slightly closer (Figure 1). ETR solubility prediction was most accurate with both programs closely matching the measured intrinsic solubility of 0.26 µg/mL. ITR and TLP predictions were least accurate with both programs significantly over-estimating (>50 fold) the intrinsic solubility (Figure 2). Measurement error and uncertainty in the range of literature values was considered in evaluating the accuracy of the predictions

Figure 1. Reference intrinsic solubility compared to solubility predicted by ADMET Predictor and Percepta Classic



Predicted pKa from ADMET Predictor and Percepta (Classic and GALAS) were compared to reference pKa values obtained from both direct measurements and/or literature. Each ionizable group or compound, was classified as basic, acidic or neutral (Table 1). The two Percepta algorithms did yield significant differences in the predicted pKa for ETR, ITR, IVC, NMD and RTV.

Figure 2. Fold prediction error for predicted intrinsic solubility by ADMET Predictor and Percepta Classic



Predicted and reference pKa's are shown in Table 1. Note that only the strongest calculated acidic or basic pKa is compared with the reference (measured) pKa. Figure 3A compares acidic reference pKa for 5 compounds to predicted pKa obtained from ADMET Predictor and Percepta (Classic and GALAS). Predictive ability was scored as within or outside of 1 pH unit from the reference pKa. IVC, which has a single acidic reference pKa of 9.3 also had basic pKa's predicted by the two Percepta algorithms but these are not included in the figures. Overall, 2, 2, and 3 out of 5 acidic reference pKa were correctly predicted by ADMET Predictor, Percepta Classic, and Percepta GALAS, respectively.

Figure 3B compares basic reference pKa for 6 compounds to predicted pKa's. For RTV, which possesses two basic reference pKa's, the lower predicted pKa was compared to the lower reference pKa and the higher predicted pKa to the higher reference pKa. For compounds where more than one pKa was predicted but there was only a single reference pKa (ITR) only the strongest calculated basic pKa is compared. 4, 5 and 4 out of 7 basic reference pKa were correctly predicted by ADMET Predictor, Percepta Classic, and Percepta GALAS, respectively.

Table 1. Reference and predicted pKa from ADMET Predictor, Percepta Classic, and Percepta GALAS (blue text refers to basic pKa and red text acidic pKa)

Drug Name	Reference pKa	Class	Predicted pKa		
			ADMET Predictor	Percepta Classic	Percepta GALAS
ABT[15]	5.19	Base	4.64	5.3	5.7
ETR	0.52	Base	2.77	0.5	4
EVR[16]	8.5	Acid	No pKa	10.4	10.4
GRS	No pKa	Neutral	No pKa	No pKa	No pKa
ITR	3.7	Base	4.57 [1.28, 2.93, 3.69]	6.5 [3.3, 3.6]	5.5 [0.5, 2.3]
IVC	9.3	Acid	9.8	11.1 [0.6, 1.2]	9.3 [1.7]
LPV	No pKa	Neutral	No pKa	No pKa	No pKa
NBL[14]	No pKa	Neutral	9.93	9.7	9.6
NLV	No pKa	Neutral	No pKa	No pKa	2.2
NMD	No pKa	Neutral	0.83	2.8	1.8
RTV[9]	1.8	Base	2.47	2	2.9
	2.6	Base	4.46	2.5	3.5
TCR[17]	9.96	Acid	No pKa	10	10.1
TLP	No pKa	Neutral	1.88	No pKa	No pKa
TRG[18]	6.1	Acid	7.77	6.3	6.3
VMR*	1.6	Base	3.25	3	2.5
	7.93	Acid	8.45 [9.72]	6.6	6.4
VRP[19]	8.72	Base	8.46	9	8.7

Compounds were considered neutral if pKa was outside the physiological range i.e. acidic pKa >10 or basic pKa <0.5. If predicted pKa was outside of the physiological range but reference pKa was located inside the range the strongest pKa was used for comparison (EVR, IVC and TCR).
**Square brackets denote additional predicted pKa's not used in comparisons*

Six of the 16 drugs were classified as neutral based on reference pKa data (GRS, LPV, NBL, NLV, NMD and TLP). Three of the six (GRS, LPV and NBL) were predicted as essentially neutral by the software programs (a weakly acidic pKa of between 9.5 and 10.0 was predicted by all three for NBL). NLV, NMD and TLR all had weakly basic pKa's predicted by at least one of the algorithms (for NMD all 3 predicted a weakly basic pKa (Table 1)). ITR and IVC also had additional pKa's predicted by more than one of the software programs. Overall, 3, 4, and 3 compounds were correctly predicted as neutral by ADMET Predictor, Percepta Classic, and Percepta GALAS, respectively.

As solubility across the physiological pH range is important for oral drugs, it was of interest to explore predicted solubility across the pH range. Figure 4 shows generated pH solubility profiles from ADMET Predictor and Percepta Classic for a well predicted drug (VRP) and a less well predicted drug (IVC). In general, the shape and curve position with respect to the X-axis is more reliable than the Y-axis position (which reflects the lower reliability of the intrinsic solubility prediction).

Figure 3. Comparison of reference pKa and predicted pKa from ADMET Predictor and Percepta algorithms for acids (A) and bases (B)

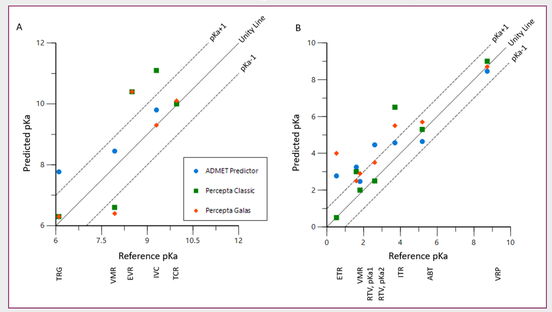
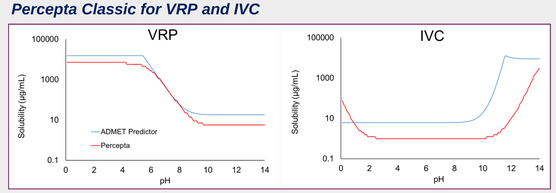


Figure 4. Predicted pH solubility profiles from ADMET Predictor and Percepta Classic for VRP and IVC



For this small subset of compounds Percepta Classic performed best with Percepta GALAS and ADMET Predictor performing slightly less well. Other analyses have shown ADMET Predictor and Percepta software packages to perform well over large diverse groups of compounds, thus this small subset may not be representative of larger more diverse datasets.

CONCLUSION(S)

- The best pKa predictions were associated with mid-range pKa; basic pKa were predicted more accurately.
- The two Percepta algorithms generated similar solubility predictions but yielded notable differences in predicted pKa.
- Generally, intrinsic solubility was overpredicted with sufficient prediction error to reinforce the continued need for experimental data for critical decision making.
- The output from these programs can be very insightful in understanding the ionization nature of drug molecules and guiding subsequent experiments.

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