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Research Article

PREDICTION ANALYSIS OF PHARMACOKINETIC PARAMETERS OF SEVERAL ORAL SYSTEMIC DRUGS USING *IN SILICO* METHOD

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ABSTRACT

Objective: This research aims to observe the pharmacokinetic parameters that can be predicted using a software, discover the best software to predict pharmacokinetic properties, and analyze the correlation between pharmacokinetic parameters used as descriptors with absorption percentage (%ABS) from references.

Methods: This research was conducted using Molinspiration, QikProp, admetSAR, SwissADME, Chemicalize, and pkCSM software. This research analyzed 34 oral systemic drug compounds for absorption rate and six descriptors comprising molecular weight (MW), logP, hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), polar surface area (PSA), and pKa.

Results: SwissADME showed the most accurate prediction of MW, logP, and HBD. Chemicalize showed the most accurate prediction of HBA, PSA, and pKa. Further, admetSAR showed the most accurate prediction of Caco-2 permeability. The highest R value was obtained from the correlation between %ABS with Caco-2 permeability on 34 drug compounds (R=0.8211).

Conclusion: The highest R value was obtained from the correlation between %ABS with Caco2 permeability on 34 drug compounds (R=0.8211), which showed a significant relationship (*p<0.001). This indicates that oral systemic drugs are affected by Caco-2 permeability. Moreover, the result of this research can be considered for the development of oral systemic drugs.

Keywords: Absorption percentage, Absorption, distribution, metabolism, and excretion prediction, *In silico*, Oral systemic drugs, Physicochemical parameters, Pharmacokinetic parameters.

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INTRODUCTION

Oral administration is the most commonly used route for drug administration due to its convenience, high level of patient safety, and the relatively low production cost. For efficiency, drugs designed to be systemically active must be absorbed from the site of administration [1]. The effectiveness of oral systemic drugs is affected by pharmacokinetic properties, involving absorption, distribution, metabolism, and excretion.

The major steps occurring during the absorption of oral drugs are the dissolution of the drug from the dosage form, the solubility of the drug, the drug's effective permeability to the intestinal mucosa, and the drug's pre-systemic metabolism [2]. Dissolution is the process by which a solid drug substance dissolves in a solvent over time [3]. Solubility is the mass of solute that dissolves in a specific mass or volume of solvent at a given temperature. Thus, the solubility test may be used to predict bioavailability.

Noyes–Whitney equation reveals that dissolution may be affected by the physicochemical characteristics of the drug, formulation, and solvent [4]. The permeation of drug across the gut wall (a model lipid membrane) is affected by the ability of the drug to diffuse (*D*) and partition between the lipid membranes. Further, the aqueous solubility of the drug can be estimated by aqueous environments, depending on the ionization of the tested drug [5].

Furthermore, most drugs are weakly acidic or weakly basic compounds [6]. Weakly acidic and weakly basic compounds cannot completely ionize in aqueous media, which are appropriate because unionized drugs, as opposed to ionized drugs, tend to exhibit considerably greater lipid solubility. In addition to their effect on dissolution kinetics, the physicochemical properties of the drug such as pKa and pH profile, particle size, polymorphism, hygroscopicity, and partition coefficient are important properties in drug designing [3].

This study analyzed the absorption of drugs in the body using *in silico* method. The solubility and permeability of the intestine toward the drug are considered the two most important determinants of the bioavailability of oral drugs. Moreover, the bioavailability of the drug may be reduced by efflux mechanism or first-pass metabolism in the intestine and/or liver. This study aimed to observe the pharmacokinetic parameters that can be predicted using software, discover the best software to predict pharmacokinetic properties, and analyze the correlation between pharmacokinetic parameters used as descriptors with absorption percentage (%ABS) from reference.

METHODS

Hardware and software

Two computers with the following specifications were used. The first computer had a Quad-Core Processor CPU Q9400 @ 2.67 GHz (Intel® Core TM, America), system type 64-bit operating system, and Windows operating system. The second computer had an Intel® Core™ i5-4210U CPU @ 1.70GHz (4 CPUs), ~2.4GHz, 8192MB RAM, and Windows 10 Home 64-bit (10.0, Build 16299).

The software used was admetSAR (Shanghai Key Laboratory of New Drug Design, China) [7], SwissADME (Swiss Institute of Bioinformatics, Swiss) [8], QikProp (Schrodinger, LLC, New York, United States of America)[9], Chemicalize (ChemAxon Ltd., Budapest,

Hungary) [10], pkCSM (Biosig Lab, University of Melbourne, Australia) [11], Molinspiration (Molinspiration Cheminformatics, Slovak Republic) [12], and Microsoft Excel.

Drug compounds

The drug compounds used in this research were two-dimensional structures of aminopyrine, cimetidine, ciprofloxacin, cromolyn sodium, cyclosporin, dexamethasone, doxorubicin, famotidine, fenoterol, hydrocortisone, ibuprofen, indomethacin, isoxicam, ketorolac, lansoprazole, lornoxicam, meloxicam, metaproterenol, methotrexate, methylprednisolone, naproxen, nizatidine, omeprazole, oxatomide, piroxicam, prednisolone, ranitidine, salicylic acid, sulindac, sumatriptan, tenidap, tenoxicam, terbutaline, and theophylline. The two-dimensional structures of the 34 drug compounds were downloaded from PubChem.

Preparation of two-dimensional drug compounds

The preparation of the structures of the drug compounds includes searching, selecting, downloading, and converting the structures from two-dimensional to three-dimensional; further, these drug compound structures were prepared using the information obtained from the database and bioinformatics website PubChem and MarvinSketch.

Preparation of experimental pharmacokinetic parameters

The pharmacokinetic parameters that were evaluated were %ABS, molecular weight (MW), logP, hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), polar surface area (PSA), pKa, and Caco-2 permeability. The data were collected from Zhao *et al*. [13] and previous researches [14-33].

Validation of predicted pharmacokinetic parameters

Validation was performed to predict the pharmacokinetic parameters (MW, logP, HBA, HBD, PSA, pKa, and Caco-2 permeability) of the 34 drug compounds using Molinspiration, admetSAR, SwissADME, QikProp, Chemicalize, and pkCSM.

Optimization of predicted pharmacokinetic parameters

By comparing experimental data from the reference with the software-predicted data from multiple software, optimization was performed to determine the software that showed the most accurate prediction of the pharmacokinetic parameters used in this research.

Analysis predicted descriptors for oral systemic drugs

The experimental %ABS was correlated with the predicted pharmacokinetic parameters and analyzed using Microsoft Excel. The resulting scatter plot showed the correlation coefficient (R) between the experimental %ABS with the descriptors of oral systemic drugs. Furthermore, SPSS was used to calculate significant values (*p). If *p-value was <0.05, the result was considered statistically significant.

RESULTS AND DISCUSSION

Preparation of experimental pharmacokinetic parameters

Experimental pharmacokinetic parameters were obtained from the study by Zhao *et al*. and previous studies (Table 1).

Validation of predicted pharmacokinetic parameters

MW, logP, HBA, HBD, and PSA can be predicted using QikProp, SwissADME, Molinspiration, and Chemicalize. Further, pKa can be predicted using Chemicalize. Caco2 permeability can be predicted using QikProp, admetSAR, and pkCSM.

Optimization of predicted pharmacokinetic parameters

SwissADME is the most accurate software in predicting MW, logP, and HBD. Chemicalize is the most accurate software in predicting HBA,

Table 1: Reference prediction pharmacokinetic parameters

Drugs	% ABS (g/mol)[a]	MW[b]	logP[c]	HBA[d]	HBD[e]	LR5[f]	PSA (Å^2)[g]	pKa[h]	Caco2 permeability (10^{-6} cm/s)[i]
Aminopyrine	100	231	1	4	0	✓	25	5.00	−4.44
Cromolyn sodium	0.4	468	1.92	11	3	✓	167	-	−6.89
Ibuprofen	95	206	3.5	2	1	✓	40	4.60	−4.58
Indomethacin	100	358	4.27	5	1	✓	68	4.50	−4.89
Isoxicam	100	335	2.83	8	2	✓	116	-	−5.61
Ketorolac	90	225	1.62	4	1	✓	62	4.47	-
Lornoxicam	100	372	3.15	7	2	✓	100	4.70	-
Meloxicam	90	351	3.01	7	2	✓	101	4.20	−4.71
Naproxen	99	230	3.34	3	1	✓	51	4.27	−4.66
Oxatomide	100	426	5.41	5	1	✓	44	-	-
Piroxicam	100	331	1.98	7	2	✓	99	5.28	−4.33
Salicylic acid	100	138	2.26	3	2	✓	55	2.85	−4.82
Sulindac	90	356	2.81	3	1	✓	58	4.70	-
Tenidap	89	321	0.63	5	3	✓	77	4.50	−4.57
Tenoxicam	100	337	2.42	7	2	✓	100	4.42	-
Theophylline	100	180	−0.02	6	1	✓	64	8.51	−4.61
Ciprofloxacin	69	331	−1.08	6	2	✓	77	6.16	−5.9
Doxorubicin	12	543	0.1	12	7	alert	204	8.20	−6.48
Cyclosporine	28	1202	3.8	23	5	alert	324	-	−6.05
Methotrexate	70	454	−0.3	13	7	alert	211	3.30	−6.1
Lansoprazole	85	369	3.07	5	1	✓	65	3.83	-
Omeprazole	80	345	2.23	6	1	✓	72	4.25	-
Dexamethasone	80	392	2.01	5	3	✓	90	6.00	−4.91
Hydrocortisone	91	362	1.61	5	3	✓	96	-	−4.82
Methylprednisolone	82	374	1.96	5	3	✓	95	-	−4.93
Prednisolone	99	360	1.62	5	3	✓	97	-	−4.72
Cimetidine	64	252	0.4	6	3	✓	84	6.93	−5.9
Famotidine	38	337	−0.57	9	8	✓	182	6.74	−6.16
Nizatidine	90	331	0.5	7	2	✓	83	13.23	-
Ranitidine	64	314	0.27	7	2	✓	82	13.26	−6.31
Metaproterenol	44	211	0.08	4	4	✓	81	4.30	−6.42
Terbutaline	62	225	0.08	4	4	✓	80	8.79	−6.16

[a]Absorption data were taken from Reference [13], [b]molecular weight data were taken from reference [13], [c]logP data were taken from Reference [13], [d]hydrogen bond acceptor (HBA) data were taken from reference [13], [e]hydrogen bond donor (HBD) data were taken from reference [13], [f]Lipinski's rule of five (RO5) data were taken from Reference [13]. Checkmark (✓) means the compound fulfilled the rule, [g]polar surface area (PSA) data were taken from reference [13], [h]pKa data were taken from reference [14-33], [i]Caco2 permeability data were taken from reference [34,35], -No data, ABS: Absorption

PSA, and pKa. Furthermore, admetSAR is the most accurate software in predicting Caco2 permeability. Fig. 1 shows the correlation between experimental data and predicted data.

The correlation between reference MW and predicted MW showed R=0.9985; the correlation between reference logP and predicted logP showed R=0.8694; the correlation between reference HBA and predicted HBA showed R=0.8716; the correlation between reference HBD and predicted HBD showed R=0.9253; the correlation between reference PSA and predicted PSA showed R=0.9916; the correlation between reference pKa and predicted pKa showed R=0.6463; and the correlation between reference Caco-2 permeability and predicted Caco-2 permeability showed R=0.8593.

Analysis predicted descriptors for oral systemic drugs

The correlation between %ABS and predicted pharmacokinetic parameters was analyzed using Microsoft Excel. The correlation between %ABS and predicted MW showed R=−0.4773; the correlation %ABS percentage and predicted logP showed R=0.3534; the correlation between %ABS and predicted HBA showed R=−0.7205; the correlation between %ABS and predicted HBD showed R=−0.7046; the correlation between %ABS and predicted PSA showed R=−0.6627; the correlation between %ABS and predicted pKa showed R=−0.5453; and the correlation between %ABS and predicted Caco-2 permeability showed R=0.8211 (Fig. 2).

Table 2 indicates the two absorption multiple regression models obtained in this research. Model 1 was created with all compounds with complete parameters and model 2 was created with all compounds with complete parameters but without 100% absorption. From the data, multiple regressions derived better R^2 value were obtained from model 2 than from model 1 (0.792948 and 0.750249, respectively). However, because the standard errors for the models were similar (17.22067 and 17.57382, respectively), the differences were not statistically significant. Further, the weightages of several parameters in model 2 were larger than those in model 1 and LogP, Caco2, and pKa were noticeably larger than the others. Absorption multiple regression results are listed in Table 2.

DISCUSSION

The correlation between reference MW and predicted MW; reference logP and predicted logP; reference HBA and predicted HBA; reference HBD and predicted HBD; reference PSA and predicted PSA; and reference Caco-2 permeability and predicted Caco-2 permeability showed strong correlations with R=0.9985, 0.8694, 0.8716, 0.9253, 0.9916, and 0.8593, respectively; however, the correlation between reference pKa and predicted pKa showed medium correlation with R=0.6463. Therefore, predicted pKa showing R value (<0.7) is the only parameter that exhibits a moderate positive relationship [36]. Several researches mention the accuracy problem of pKa prediction and state that pKa prediction is highly dependent on the dataset [37]. The simplification of the software calculation may also be a limitation of pKa prediction [38]. To improve the algorithm, drug type clustering based on its pKa level should be considered because the algorithm may show different results for acidic and basic drugs. The pKa range of clusterization should be optimized in further research. In addition, the dataset in this experiment contains various compounds that may act as obstacles in accurate pKa prediction for all structures. In this study, pKa of several compounds, such as aminopyrine with anti-inflammatory action; hydrocortisone, methylprednisolone, and prednisolone, which are corticosteroid agents; and nizatidine and ranitidine from H2 receptor antagonist group, could not be accurately predicted. The R value is suggested to reach >0.9 to be considered as accurate prediction.

From this research, we found that the various software programs provided different parameter prediction results. None of the software served as the most accurate prediction tool for all parameters. However, out of seven parameters, Chemicalize and SwissADME accurately predicted three complimentary parameters each. Moreover, Caco2 prediction only can be accurately done using admetSAR.

Analysis descriptors for the 34 oral systemic drugs resulting in the highest R value were the significant correlation between %ABS and Caco-2 permeability (R=0.8211; *p<0.001) (Fig. 2).

The absorption multiple regression models were derived from these data by including the compounds with 100% absorption (model 1) or excluding it (model 2) to observe how the nonlinear function part affects the correlation. Better R^2 values were obtained from model 2 than from model 1; however, the difference was not significant. Further, the weightages of several parameters in model 2 were larger than those in model 1, with LogP, Caco2, and pKa being noticeably larger than the others. This suggests that these three parameters, as opposed to MW and PSA, have higher tendencies to affect absorption.

In general, a model is acceptable if it has R^2>0.6 [39]. In addition, in this case, good model fitness was observed in both models. This study is limited by its small dataset and usually good prediction is statistically derived from large datasets; therefore, further considerations need to be undertaken such as to selectively include various drugs and also to try several other software programs not included in this study. Nevertheless, from the experiment, both models are acceptable to be used as early *in silico* tools to assist the prediction of the absorption of systemic oral drugs.

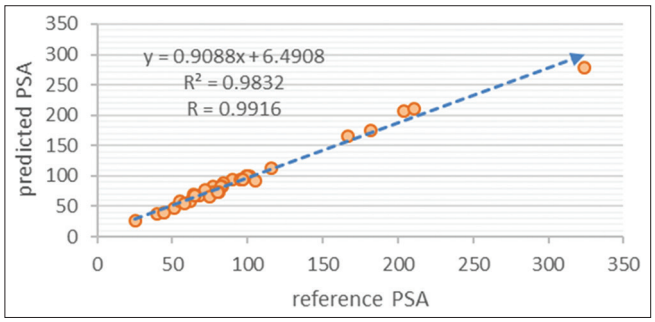

Fig. 1: Scatter plot reference polar surface area (PSA) [4] versus predicted PSA

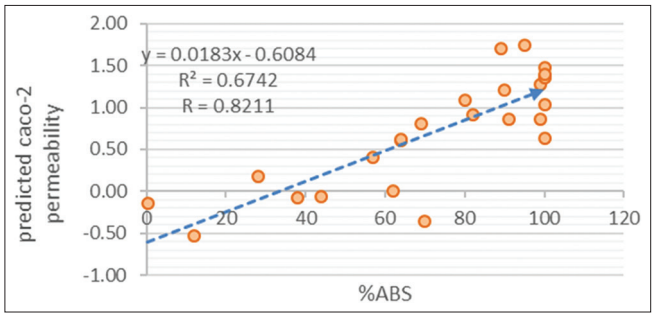

Fig. 2: Scatter plot absorption percentage versus predicted Caco-2 permeability

Table 2: Multiple regression model of absorption made from calculated parameters

No.	Model	R^2	n	SE
1	%ABS=0.002556 MW–1.61419 LogP–7.67912 HBA–3.92035 HBD+0.187031 PSA–1.38116 pKa+13.23259 Caco2+108.3029	0.750249	26	17.22067
2	%ABS=0.00649 MW–5.56972 LogP–8.45619 HBA+2.141478 HBD+0.205398 PSA–2.33053 pKa+25.98339 Caco2+93.12721	0.792948	18	17.57382

MW: Molecular weight, HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor, PSA: Polar surface area, ABS: Absorption

CONCLUSION

Parameter prediction was successfully performed in this research. SwissADME was the most accurate software in predicting MW, logP, and HBD; Chemicalize was the most accurate software in predicting HBA, PSA, and pKa; and admetSAR was the most accurate software in predicting Caco2 permeability. The highest R value was obtained from the significant correlation between %ABS and Caco-2 permeability of 34 drug compounds (R=0.8211; *p<0.001). These results indicate that the %ABS of oral systemic drugs is affected by Caco-2 permeability.

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CONFLICTS OF INTEREST

All authors have none to declare.

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