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IN VITRO AND IN SILICO APPROACHES FOR SCREENING INTESTINAL PERMEABILITY AND ABSORPTION OF DRUGS

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Because the oral route of drug delivery is incomparable, screening of intestinal permeability and absorption of drug candidates is a critical stage before clinical trials for time and cost reasons. Permeability assessment of drugs after oral administration has been investigated using different in-vitro approaches. Fast, reliable, and non-invasive in-vitro techniques are crucial in the early stages of the drug discovery process as primary screening tools to assess the intestinal permeability of lead compounds. In-vitro techniques are either experimental-based or computer-assisted (in-silico) methods. Experimental methods to predict the intestinal permeability of drugs are mainly partitioning-based physicochemical models and direct measurement-based models that depend on using laborious techniques of isolated human/animal cells or tissues. In this work, partitioning-based physicochemical models that can predict a compound/drug permeability potential across intestinal membranes will be elaborated. In addition, in silico models that could be of value in scaling up feasible hit compounds and throwing away possible losers will also be overviewed.

Keywords: *Intestinal permeability screening, In vitro approaches, In silico models*

INTRODUCTION

The efficacy of a given drug is dictated by its pharmacological activity and pharmacokinetic properties such as its access to the site of activity[1]. The oral route is preferred for drug administration, therefore, in the drug discovery process, once sufficient pharmacological activity has been attained, the next crucial need for a candidate drug is to achieve high permeability after oral administration. Numerous in-vivo and in-vitro models that are descriptive of drug absorption in vivo have been used for such purposes. In-vivo models based on using humans or animals have been used for a long time. These models have been subjected to many critics either related to their efficiency as a suitable model for high throughput screening (HTS) or ethical reasons. In-vitro approaches have been used parallel to the in-vivo methods and have gained wide acceptance in the last several decades as an alternative to human or animal models. These in-vitro approaches are either experimental or computer-based. Experimental approaches can be classified into 1) partitioning based physicochemical models and, 2) direct measurement based models. Partitioning-based physicochemical models relate the physicochemical properties of a drug candidate to its ability to cross the intestinal membrane. These models are useful to assess

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parameters that contribute to the oral absorption of compounds/drugs. Three major partitioning systems have been used for evaluating drug intestinal permeability as lipophilicity measurements using simple organic/aqueous solvents partitioning system[2], chromatographic partitioning and partitioning into liposomes[3]. Other partitioning-based physicochemical models are parallel artificial membrane permeation assay (PAMPA)[4], absorption potential[5], and other miscellaneous physiochemical descriptors. Partitioning-based physicochemical models are fast, facile, reliable, non-invasive and of value in predicting the intestinal permeability of lead compounds. On the other hand, direct drug measurement-based models employ laborious work of isolating and preparing human/animal cells or tissues in the permeability and absorption studies of drugs. These models may include isolated intestinal cells[6], cultured cells[7], isolated intestinal segments[8-11] or in-situ intestinal perfusion techniques[12]. This heavy part of direct measurement-based models, which is out of the scope of this article, can be used in the late stages of the drug discovery process once lead compounds have been identified.

As a result of advanced biotechnology and combinatorial chemistry, many drug leads can be synthesized in a short period, therefore, intestinal permeability evaluation needs to be fast and reliable. Various in-silico models[13,14] to predict intestinal permeability in the early discovery setting of drugs have been developed. In this study, experimental partitioning-based physicochemical models that have been used in screening intestinal permeability of drugs will be discussed along with current in-silico models.

Partitioning Based Physicochemical Models

When a drug molecule is present in the gastrointestinal (GI) lumen, it must transport across or permeate through the GI membrane to be able to reach the systemic circulation. Drug transporting across a membrane or permeability (P_m) is a function of the following equation[15]:

$$P_m = D_m K_m / L \qquad (1)$$

Where D_m is the membrane diffusion coefficient of the drug, K_m is the membrane partition coefficient and L is the membrane thickness. Having a constant value of L for a given membrane, D_m and K_m are of great importance in evaluating drug permeability. Since D_m is a measure of the rate by which a drug moves through a membrane, K_m is a key parameter in evaluating drug permeability and subsequent absorption. In fact, in-vivo measuring of drug partitioning is difficult to occur, therefore, in-vitro methods that measure K_m utilizing models that simulate biological membranes have been developed and will be discussed herein. Part of this section is being considered for publication in another periodical. However, it is detailed and more elaborate in this study.

Organic/Aqueous Solvent Partitioning

It has become evident that the partitioning of a drug substance between simple organic/aqueous solvent mixture parallels well with its biological activity since the pioneering work of Meyer[16] and Overton[17]. They found that the biological activities of drugs parallel the drugs' oil/water partition coefficients. Since then, the logarithm of the partition coefficient (log P) of a compound between nonpolar and polar solvents has been used as a lipophilicity index that indicates the degree of biological availability and activity of drug substances. In other words, log P has become an accepted model for lipophilicity in quantitative structure activity relationships[18, 19]. In these studies, the polar phase is always water while many organic solvents have been used as nonpolar such as octanol, chloroform, hexanes, and others, however, octanol is the most common choice[20]. In fact, the choice of a nonpolar solvent is debatable. Garst and Wilson[21] have reported that there is nothing unique about biological correlations using octanol/water as opposed to another non-polar solvent/water system. El Tayar et al.[22] have proposed the use of four critical non-polar solvents for modeling biological membranes. These solvents are octanol, chloroform, cyclohexane, and propylene glycol dipelargonate. They found that log P values measured in these different solvents show differences principally due to hydrogen bonding effects. Octanol can donate and accept hydrogen bonds whereas cyclohexane is inert. Chloroform can donate hydrogen bonds

whereas glycol dipelargonate can only accept them. Among them, octanol is common and was chosen as a simple model of phospholipid membrane[23]. However, it was reported that nonpolar/polar partitioning systems are good models only when the polar group interactions between the solute and the phospholipid bilayer are minimal or absent[24]. In another meaning, partitioning through such systems correlates well with drug partitioning into fluid membranes for hydrophobic compounds; however, for polar compounds, the correlations are not satisfactory[25]. Because of such shortcoming of using some nonpolar solvents, Hansch and Dunn[18] suggested that octanol is a rational model solvent because it models polar molecule interactions between solutes and membranes. Therefore, it is not surprising that log P determined using other solvents rather than octanol exhibits poor correlation since these solvents do not model the subtle polar and non-polar molecule interactions between solutes and membranes as octanol does[18]. It is well known that drugs cross the intestinal membrane by the following pathways: 1) passive transport, 2) active mediated transport, and 3) others of minor importance in the overall absorption processes such as endocytosis. Simple passive transport is the main absorption pathway for most drugs and is based on the lipid solubility of the drug molecule or generally, its lipophilicity. The importance of log P is its usefulness to estimate the lipophilicity of drug molecules. Although it is well recognized that there is a direct correlation between lipophilicity and log P, it should be taken into consideration that the relationship between log P and bioavailability as a percent of fraction absorbed after oral administration is not always linear as observed in **Table 1**. Plotting of the data in **Table 1** gives a poor correlation (r^2 = 0.4268) as depicted by **Fig. 1**.

Table 1: Relationship between log P and reported percentage of human fraction absorbed (%FA) of structurally diverse 18 compounds[26].

No.	Compound	Log P	% FA
1	Atenolol	0.01	50
2	Atomoxetine	4.21	100
3	Benzydamine	4.39	100
4	Caffeine	0.95	100
5	Cotinine	1.02	90
6	Dexamethasone	2.63	90
7	Diclofenac	4.14	82
8	Lenalidomide	-1.03	90
9	Lucifer yellow	-4.80	0
10	Metoprolol	2.2	98
11	Midazolam	4.54	60
12	Nicotine	2.07	100
13	Nifedipine	2.21	100
14	Pomalidomide	-0.03	73
15	Propranolol	3.07	90
16	Quetiapine	2.61	73
17	Tolbutamide	2.58	88
18	Warfarin	2.33	98

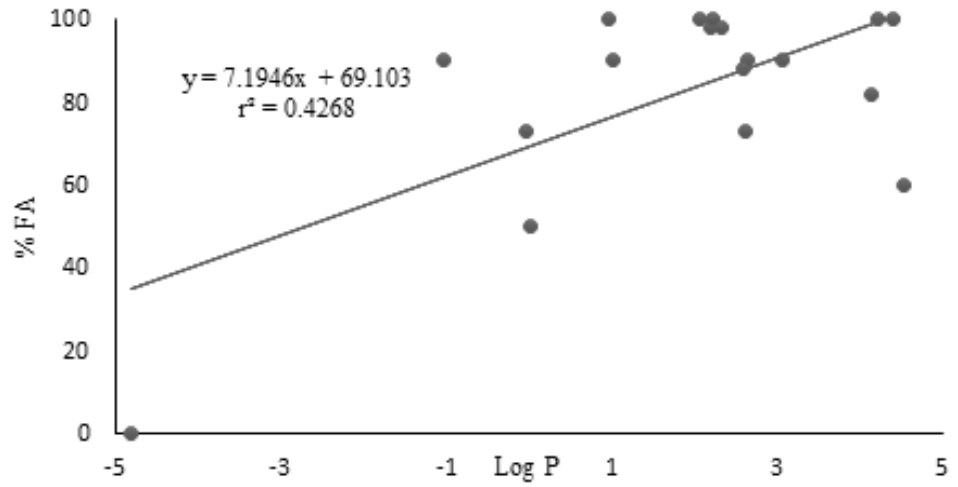

Fig. 1: Relationship between log P and reported percentage of human fraction absorbed (%FA) of structurally diverse 18 compounds listed in Table 1.

It can be stated that compounds having a log P value outside the range of -1 to 4 may have poor intestinal permeability and absorption. Drugs of log P value below –1 are highly hydrophilic and have minimal partitioning towards the lipoidal membranes whereas those of log P higher than 4 are highly lipophilic and have poor solubility/dissolution rate in the aqueous GI lumen prior to partitioning into the GI membrane[27]. Generally, drugs displaying log P values close to 2 are predicted to be completely absorbed in human[27]. Determination of log P using such a system is based on dissolving the solute under investigation in one phase then shaking both phases together until equilibrium is achieved, followed by measuring the equilibrium ratio of the solute in one or both phases. Although some difficulties are associated with such a procedure, for example, time and chemical consuming, very pure solutes and solvents should be used, possible instability of the solute in the solvent system and emulsion formation, which may hinder the separation and analysis, the technique is still of value for its simplicity and applicability for wide range of log P values determination.

Liposomes Partitioning

Structurally, liposomes are spherical or multilayered spherical vesicles made by the self-assembly of diacyl-chain phospholipids (lipid bilayer) in aqueous solutions[28]. The bilayer phospholipid membrane has a hydrophobic tail and a hydrophilic head[29] that leads to the formation of an amphiphilic structure. Liposomes can be made from both natural and synthetic phospholipids[30]. Since their discovery by Bangham et al.[31] liposomes have been used in drug delivery, a pharmaceutical carrier/delivery systems[32,33], partitioning-QSAR of drug molecules[34] and solute partitioning as a model of biological membranes[35]. Niosome drug delivery systems are structurally like liposomes; however, they are prepared from non-ionic surfactants[36]. Katz and Diamond[37] first demonstrated and established that a drug partition coefficient through phospholipid bilayer of liposomes into their aqueous vesicles was like the partition coefficients measured in endogenous membranes. The reason for using partitioning into liposomes to study and predict permeability and drug absorption is that they can model both polar and nonpolar solute-membrane binding interactions[37] since the lipidic nature of liposomes mainly constitutes biological membranes. After the preparation of liposomes, solute is added to the medium containing the liposome vesicles for partitioning until equilibration is attained. The amount entrapped into the aqueous vesicles of the liposomes is then analyzed for quantitation. Different procedures can be used in

partitioning study of solutes through liposomes, for example, equilibrium dialysis[38], pH-titration method[39], immobilization in the pores of gel beads by avidin-biotin binding[40] or by freeze-thawing technique[41] and the partitioning coefficients determined from retention data. As previously mentioned, liposomes are made from phospholipids or their analogs, which resemble the cellular membrane nature, therefore, they are a good model for studying compound partitioning, and hence, permeability gives reliable data. However, the technique as an in-vitro model for permeability screening is time-consuming and laborious. Therefore, it is not suitable for high throughput screening. The cost and stability of liposomes have also raised some drawbacks of this system.

Chromatographic Partitioning

Permeability prediction of solutes has also been extensively investigated in chromatographic systems as models that simulate solute partitioning in endogenous membranes[42], as paper chromatography[43], and thin layer chromatography (TLC)[43,44] using supports impregnated with nonpolar phase as octanol or silicon solutions were first used. The partition parameter, R_m, determined from reserved phase-TLC is defined[43] according to the following equation:

$$R_m = \log (1/R_f - 1) \qquad (2)$$

where R_f is the retention factor, which is used as a lipophilicity index that correlates well with the biological activity of drug substances[44]. R_f is also used to calculate the log P of compounds using the following equations[43, 45]:

$$\text{Log P} = \log K + \log (1/R_f - 1) \qquad (3)$$

$$\text{Log P} = b\, R_m + a \qquad (4)$$

where K, b and a are constants for a given system. At the beginning of using Liposomes Partitioning to study the lipophilicity or to determine log P of solutes, TLC was preferred for the following reasons: 1) simple to use, 2) reproducible, 3) does not need quantitative analysis, 4) small quantity of the solute is used, and 5) high purity of the compound is not necessary[46]. TLC has also expanded the range of log P values that could be determined[47]. However, after the discovery of high performance liquid chromatography (HPLC), partitioning on reserve-phase HPLC has been investigated as a means for determining the lipophilicity of compounds based on their retention on solid stationary phase as first established by McCall[48] and Henry et al[49]. The established retention parameters were retention time expressed by a term, k' and retention volume expressed by a term, V_R which are defined respectively as:

$$k' = [(t_r - t_0)/t_0] \qquad (5)$$

$$V_R = [(t_r - t_0)\ (\text{flow rate})] \qquad (6)$$

with t_r as the retention time of the compound and t_0 is the retention time of a solvent front. The logarithm of retention time, log k', and retention volume, log V_R, are used as lipophilicity indices that linearly correlate with log P, R_m and biological availability and activity of compounds[49]. Normally, the stationary phase used in HPLC studies to determine these parameters are columns packed with porous silica gel bonded chemically with octadecyl (ODS) chain[48, 49]. In addition to the advantages of TLC, clarity, fastness, selectivity, accuracy, and simplicity are other advantages of HPLC method for log P determination. However, the technique does not perfectly model the biological membrane due to its hydrophobic surface; therefore, HPLC is only a good system for hydrophobic compounds[25]. HPLC also inherits the most serious limitation of the octanol/aqueous system in that it lacks structural similarities to biological membranes[25]. Different from octanol which contains a polar OH group and a nonpolar hydrocarbon chain, ODS only contains hydrocarbon chain[25]. In the early nineties, phospholipid covalently bonded to silica gel packed columns namely, immobilized artificial membranes (IAM) were developed by Pidgeon and co-workers[50]. IAM columns are solid phases typically used as a chromatographic stationary phase, monolayers of phospholipid molecules covalently bonded to the surface of silica particles[51]. IAM surface emulates the lipid surface in liposomes and cell membranes[51, 52]. These columns were first used

to purify membrane proteins[53], immobilize enzymes[54], and obtain enzyme-ligand binding constants for drugs[54], and to study the hydrophobicity of drugs by another working group[55]. Later IAM columns were prepared from a mix of phospholipid and phosphatidylcholine (PC) and gained the abbreviation IAM.PC, which are mixed lipid-liposome columns[25]. Drug interaction with the column surface is like the interaction between the drug and liposomes as can be seen in **Fig. 2 (A-B)**. As HPLC, partitioning or binding of solutes to IAM.PC columns is used to predict permeability based on retention time parameter[25, 56], expressed as capacity factor, k'_{IAM} and as depicted in **Fig. 2-C.**

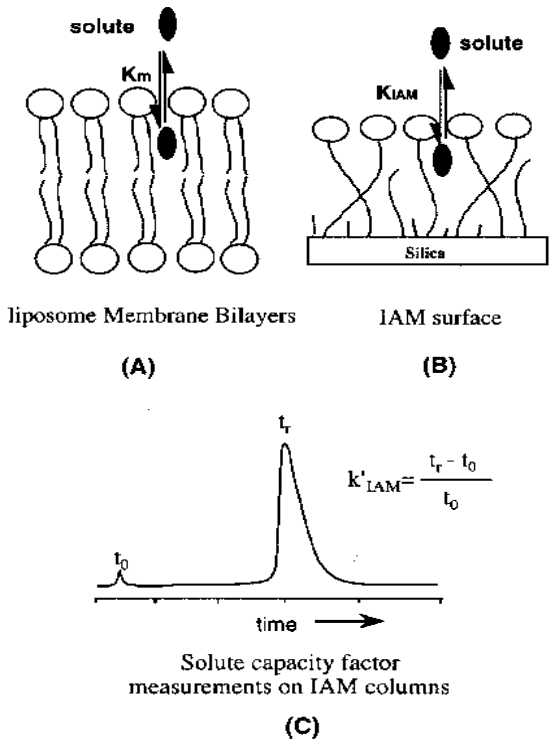

Fig. 2: (A) and (B) show the similarity of molecule interaction with liposome membrane and IAM surface, (C) shows measuring of the capacity factor from retention time on IAM columns [25].

Log k'_{IAM}, is used to evaluate lipophilicity of drug substances and predict their absorption. Moreover, it was found to significantly correlate with the log P, R_m, log k' [56], and the membrane partitioning coefficients into liposome[35]. It is also reported that log k'_{IAM} correlates well with logarithm of the apparent permeability coefficients through caco-2 cells[57], passive permeability coefficients through everted or non-everted gut sacs[58], log % of the intestinal absorption using perfused rat small intestine, and log % of oral absorption in mice[57]. IAM.PC columns are also used to predict drug permeability in skin tissues[57, 59]. These studies show that IAM.PC columns can be used to predict permeability through various biological membranes due to structure similarity with natural membranes[25]. These columns are made from phospholipids analogs, which are the main part of the cellular membrane that encounters drugs before absorption[56]. Based on that fact, IAM.PC columns are considered a good model for predicting drug permeability for their simplicity where large volume screening of experimental compounds for absorption can be achieved in a timely fashion.

Parallel Artificial Membrane Permeation Assay

PAMPA is based on a 96-well microtiter plate technology as originally developed by Kansy et al[60]. In this system, the wells are filled with a buffer and then covered, in a sort of sandwich construction, with a hydrophobic microtiter filter plate pre-impregnated with a solution of phospholipid dissolved in an inert organic solvent. A solution of the compound under investigation is applied on the top of the filter plate and the flux into the buffer is measured spectrophotometrically against reference solution defining the equilibrium. The plot of flux data obtained from PAMPA vs. % of human absorption of a diverse set of drug substances showed a similarity to a plot of permeability data in caco-2 cells vs. % of human absorption for the same set[61]. The technique was a little modified to closely mimic the intestinal membrane by Sugano et al[62]. They changed the composition of the lipid solution used in the original method, which was used to make a lipid membrane on the filter support, by changing the chain length of the organic solvent which resulted in the addition of a negative charge to the membrane. In general, the PAMPA technique is simple, less laborious and can be used to screen the intestinal permeability of large compound libraries.

Absorption Potential (AP)

An index proposed by Dressman et al[63] can be used to estimate the intestinal permeability of compounds. It is based upon using some physicochemical characteristics of the compound under investigation such as its log P, fraction of the compound un-ionized at pH 6.5 (F_{un}), and the aqueous solubility of the unionized specious (S_{un}) as follows:

Absorption potential (AP) =

$$\log [P. F_{un} (S_{un}. V_L/X_0)] \quad (8)$$

with V_L is the luminal volume (approximately 250 mL) and X_0 is the dose of the compound. Like other partitioning based physicochemical models, it is used to estimate the permeability of compounds passively transported only. Data showing the correlation between AP and fraction absorbed in humans for 7 diverse well-established drugs are presented in **Table 2**[63]. A good correlation was obtained when data plotted as shown in **Fig. 3.**

However, to validate such a model it needs to be applied to a large set of compounds so that it can be widely applicable. In addition, it may be time consuming if the parameters included in the model need to be experimentally determined.

Table 2: Correlation between absorption potential and fraction absorbed for 7 structurally diverse established drugs [63].

No.	Drug	Absorption potential	Fraction absorbed
1	Acyclovir	-1.5	17
2	Chlorothiazide	-0.89	25
3	Digoxin	3.13	90
4	Griseofulvin	0.36	43
5	Hydrochlorothiazide	0.7	67
6	Phenytoin	1.0	90
7	Prednisolone	1.9	99

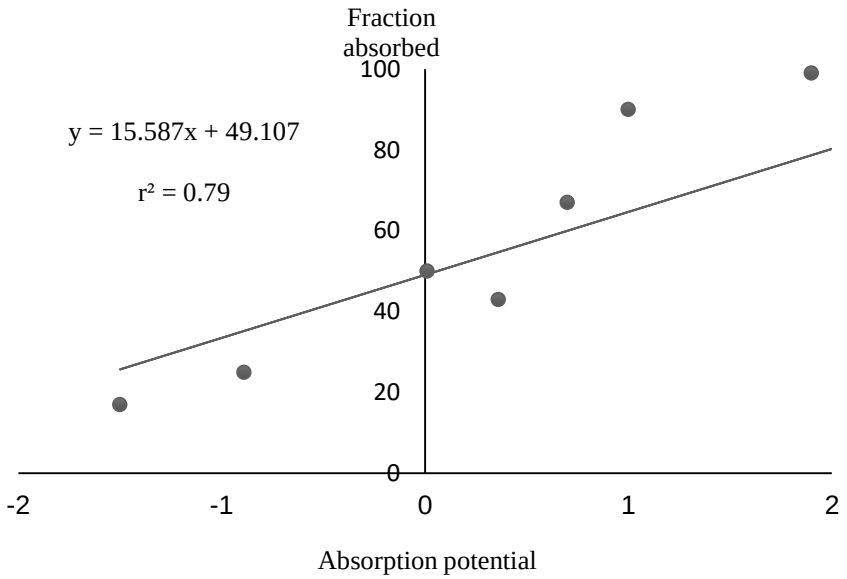

Fig. 3: Relationship between Absorption potential and fraction absorbed in human for drugs given in **Table 2**.

Miscellaneous Physicochemical Descriptors

In addition to the above mentioned physicochemical based models that can used to screen permeability and intestinal absorption, some other physicochemical properties, for example, molecular weight (MW), aqueous solubility, ionization constant, and hydrogen bonding ability, among others are also important descriptors. MW is one of the four physicochemical parameters that constitute Lipinski's rule of [64-65] that is if there are more than two of these parameters in a molecule it will show a poor absorption profile. Lipinski identified four physicochemical parameters, i.e., MW, the number of H-bond donors, the number of H-bond acceptors, and log P that contribute to a compound's ability to cross endogenous membranes. The rule states that poor absorption or permeation is expected when MW>500, the number of H-bond donors >5, the number of H-bond acceptors >10 or log P>5. MW of 500 is indicated as a limit above which permeability after oral administration is more likely to decrease. In a deconstructed analysis study[66], it was found that highly absorbed drugs (>80%) have MW values less than 500. Nevertheless, the lipid nature of the biological membranes and the need of drug candidates to partition and permeate through them, aqueous solubility is an important issue in intestinal absorption especially for a suspension or solid dosage form drug. Dissolution in the aqueous GI fluid is required before partitioning into the GI cell membrane takes place. In addition, partitioning through the aqueous part of the membrane or leaving it to the interstitial fluid is also necessary for the completion of the absorption process. Based on that, the aqueous solubility of compounds is of value in the overall permeability process. It was reported that if the drug is poorly soluble it will not only show a slow rate of partitioning from the membrane to the extracellular fluid, but also protein binding in the extracellular submucosal tissues may influence drug permeability[67]. Aqueous solubility of less than 100 μg/mL is reported to indicate poor dissolution, which limits the intestinal absorption[68].

Permeability and absorption of compounds having ionizable group(s) depend upon their pKa values. Higher absorption takes place at gastrointestinal pH close to pKa of the drug. However, changing the permeability of a compound based upon modifying the pKa is a chemistry trend, which is out of the scope of this text.

In summary, most of the partitioning based physicochemical models are simple and of value for evaluating the intestinal permeability of drugs or new chemical entities. However, the main disadvantage of these systems is that they lack the architecture similarity to the intestinal membrane and oversimplify the complex gastrointestinal absorption process. In addition, they are only used to estimate the intestinal permeability of compounds that are passively transported; therefore, they underestimate candidates that could be transported by active mechanisms.

In Silico Models

The cost of research and development for a new medicine is estimated at 1.1 billion euro[69]. However, after such expenses and times, a failure may occur during the development stage of the drug discovery process. Such failure may be related to a lack of therapeutic effect in humans, unexpected side effects and the inability of the prospective drug to be delivered into its site of action due to its inability to be absorbed from the GI tract[70]. Given these estimations and expectations in discovering and developing a new drug, it is important, and interesting, to the chemist to design a molecule and screen its potential for intestinal permeability or its pharmacokinetics at the same time. Such design and search rely on using different molecular descriptors that correlate with intestinal permeability for example MW, lipophilicity, polar surface area, molecular charge, and others. Thing that means that time, money, resources, and effort can be minimized and directed to synthesize compounds that have physicochemical properties that favor its absorption. Computational screening methods use many physicochemical descriptors to evaluate the intestinal permeability of drug candidates in seconds. Computational techniques to screen the permeability of designed, already synthesized compounds, or well-established drugs have been emerged and applied in pharmaceutical industry for few decades. Within the in silico assessment area[71, 72], there have been two major various models;

first, the simple and easy-to-compute "rule of 5" model developed by Lipinski et al[65]. The rule proposes poor absorption or permeability is likely to happen for compounds if it has > 5 H-bond donors, > 10 H-bond acceptors, MW > 500 and log P > 5. However, poor permeability is highly considered if two of these 4 parameters are exceeded. Since computational model is always based on experimental data, a large number of training sets of diverse structures should be used for wide range applicability of the model and not be confined to compounds that are structurally related to those used to develop the model as the case with the rule of 5. Second, the effect of H-bonding ability of compounds on their permeability using what is called polar surface area (PSA) was studied by many groups[73, 74]. PSA is defined as the sum of surface contributions of polar atoms (usually oxygen, nitrogen and attached hydrogen atoms) in a molecule, and has been shown to predict well drug transport properties, such as Caco-2 cells permeability[75] and oral fraction absorbed[76, 77]. It is either calculated using one single conformer of the drug molecule[73,74] or the Boltzmann-weighted average PSA of the low energy conformers[77, 78] obtained by a detailed conformational search bringing a measure termed dynamic polar surface area (PSA_d). Palm et al[77] studied the relationship of the absorbed fraction after oral administration to humans and PSA_d of twenty structurally diverse model drugs, which displayed diversity in their physicochemical properties such as lipophilicity, hydrogen bonding potential, molecular size and ranging from 0.3 to 100% oral absorption in human. An excellent sigmoidal relationship was established (r^2 = 0.94) which indicated the usefulness of the model in predicting the intestinal permeability of drugs[73].

Drugs that are completely absorbed, (FA > 90%) had a $PSA_d \leq 60$ Å^2 while drugs that are < 10% absorbed had a $PSA_d \geq 140$ Å^2. Remko et al[79] also found an inverse relationship between the calculated % absorbed (% ABS) for 10 centrally acting antihypertensive drugs and their PSA as seen in **Table 3**.

Table 3: Relationship between PSA and calculated % ABS of some antihypertensive drugs[79].

No.	Drug	PSA	% ABS
1	Agmatine	87.93	79
2	Amiloride	156.80	55
3	Aminopyrroline	24.05	100
4	Amoinothiazoline	24.39	100
5	Clonidine	36.42	96
6	Efaroxan	33.62	97
7	Harmane	28.68	99
8	Idazoxan	42.86	94
9	Moxonidine	71.44	84
10	Rilmenidine	33.63	97

An excellent inverse correlation between PSA and % ABS of the plotted data in **Table 3** is seen **Fig. 4,** which indicates the effectiveness of the model to predict intestinal permeability of drugs.

Calculation of PSA or PSA_d requires the generation of three-dimensional shapes of the molecule and surface calculation. Another methodology for calculating PSA is termed topological PSA (TPSA) developed by Ertl et al[80]. The method is based on the summation of tabulated surface contributions of polar fragments including not only oxygen and nitrogen but also sulfur and phosphorus. Data obtained had excellent correlation with PSA and PSA_d for the same set of drug molecules studied by Palm et al[77] and Clark[73]. The method does not require generating three-dimensional structures of the molecule or surface calculation, which means PSA calculation can be done in seconds. In general, PSA as an approach to predict drug permeability and intestinal absorption is simple, time and cost-effective and has been proven as an effective virtual model.

Rule of 5 and PSA are successful predictors of intestinal permeability. However, Veber et al[81] have used combined molecular descriptors such as MW, PSA, and molecular flexibility, as measured by number of the rotatable bonds, and the total hydrogen bond count (donors and acceptors). They defined a rotatable bond as any single bond, not in a ring, bound to a nonterminal heavy (i.e., non-hydrogen) atom. Excluded from the count were amide C-N bonds because of their high rotational energy barrier. They found that the commonly applied MW cutoff at 500 does not significantly discriminate between poor and acceptable or good permeability compounds. This also can be a weak point of the rule of 5 where many drugs of MW higher than 500 are reported to be highly bioavailable. Therefore, MW was excluded from Veber and co-workers' rule, which states that: a compound that has rotatable bond ≤10 and PSA ≤ 140 $Å^2$ (or H-bond donors and acceptors ≤ 12) will be highly permeable after oral administration in rats. The study was based on a data set of 1100 drug-like compounds whose oral bioavailability in rats was studied.

As previously mentioned, the in silico model should be based upon large sets of compounds for reliability purposes. Although that is the case for the rule of 5, many already established drugs have violated the rule[82]. The reason is that, as reported by Renche[83], the in-suitability of treatment of multivariate data using univariate statistical methods, may be misleading. Univariate statistical models, such as the rule of 5, do not consider interactions between the molecular descriptors[84]. Thus, many researchers have done various studies using combined physicochemical descriptors of drug molecules in different ways to generate models ranging from simple to more sophisticated ones that can be used to predict intestinal absorption based on multivariate statistics[85-87].

The above-mentioned methods indicate the usefulness of in silico models as a preliminary screening tool to predict intestinal permeability early in the drug discovery setting to help scale up possible hits and throw away possible losers.

At the end of this study, it is reasonable to present a summary of the main approaches currently used in predicting the intestinal permeability of compounds/drugs with their major characteristics, **Table 4**. These approaches include organic/aqueous solvent partitioning, liposome partitioning, chromatographic partitioning, and in silico models.

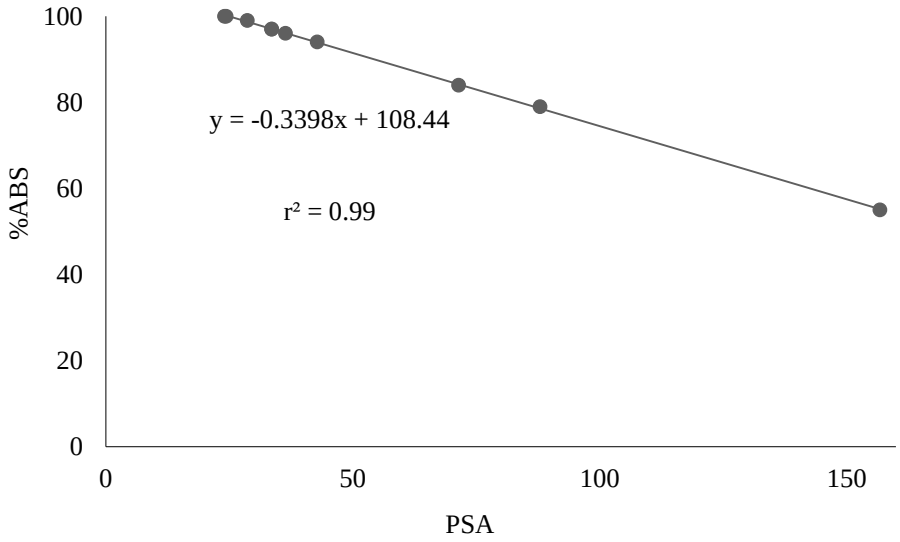

Fig. 4: Relationship between PSA and calculated % ABS of some antihypertensive drugs reported in **Table 3**.

Table 4: Main approaches for predicting intestinal permeability of drugs and their characteristics.

Approach	Characteristics
Organic/aqueous solvents partitioning	The approach is simple and applicable for a wide range of log P values determination. However, it is time and chemical-consuming, high purity of investigated compounds and used solvents are required, and possible instability of solutes in the solvent system and emulsion formation may obstruct the separation and analysis processes.
Liposomes partitioning	A rational model for predicting the permeability of drugs for its structural similarity with endogenous membrane. However, the processes of preparation and partitioning study are time-consuming and laborious. Not suitable for HTS. The cost and stability issues of liposomes are also disadvantages of this system.
Chromatographic partitioning	It is considered a good model for predicting drug permeability since it simulates solute partitioning in endogenous membranes. Simple, suitable for HTS, reproducible, no need for quantitative analysis, small quantity of the solute is used, and high purity of investigated compounds is not necessary.
In silico	The models are easy, time cost-effective and useful as preliminary screening tools to decide on scaling up possible lead compounds and throwing away feasible losers.

Conclusion

Due to advanced biotechnology and combinatorial chemistry, the synthesizing of compounds has not become a bottleneck in the drug discovery process. Thousands of compounds can be synthesized in a short period. On the other side, failure of a drug candidate to reach the market, although clinically proven, has been recognized to happen very often during the development process because inability of the candidate to cross the intestinal membrane after oral administration. Therefore, it is necessary to use effective intestinal absorption methods that can screen the permeability of lead compounds in a timely and cost-effective manner. Partitioning-based physicochemical models are facile, straightforward, and less laborious to use for screening the intestinal permeability of drug candidates. Although it is easy to use a single physicochemical molecular descriptor to screen permeability, it is preferred to use more than one descriptor to judge the intestinal permeability of compounds. In silico models

are efficient and useful for the mass screening of candidate compounds. However, the cornerstone for in-silico models is to produce reliable results so the chemist can feel restful when throwing away compounds from further progressing.

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الأساليب المختبرية والمحاكاة الحاسوبية لفحص نفاذية وامتصاص الأمعاء للأدوية بحث مرجعي

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نظرًا لأن الطريق الفموي لتوصيل الدواء لا مثيل له، فإن فحص نفاذية وامتصاص الأمعاء للأدوية يعد مرحلة حرجة قبل التجارب السريرية لأسباب تتعلق بالوقت والتكلفة. تم دراسة تقييم نفاذية الأدوية بعد تناولها عن طريق الفم باستخدام أساليب مختلفة في المختبر. تعتبر التقنيات المختبرية السريعة والموثوقة والغير اجتياحيه حاسمة في المراحل المبكرة من عملية اكتشاف الدواء كأدوات فحص أولية لتقييم نفاذية الأمعاء للمركبات والدواء. التقنيات المختبرية هي إما طرق تجريبية أو تعتمد على مساعدة الحاسوب (المحاكاة الحاسوبية). تتمثل الطرق التجريبية للتنبؤ بنفاذية الأدوية المعوية بشكل أساسي في نماذج تجزا الدواء معتمدا على خواصه الفيز وكيميائية او التنبؤ معتمدا على القياس المباشر لنفاذية للدواء في الخلايا أو الأنسجة البشرية او الحيوانية المعزولة.

في هذا العمل، سيتم دراسة نماذج تجزا الدواء معتمدا على خواصه الفيز وكيميائية والتي يمكن التنبؤ بها بإمكانية نفاذية المركب/الدواء عبر الغشاء المعوي بالإضافة الي نماذج المحاكاة الحاسوبية التي يمكن أن تكون ذات قيمة في تصعيد المركبات النافذة والتخلص من المركبات الخاسرة.