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Original Article

Towards a Correlation between Polar Surface Area of Drugs with *Ex-vivo* Transdermal Flux Variability

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Abstract

The aim of the present study was to investigate the relationship between the polar surface area and other molecular properties of the model drugs and their transdermal permeability across the rat skin. Few model drugs which are weakly acidic (ibuprofen, aceclofenac and glipizide) and weakly basic (olanzapine, telmisartan and sildenafil citrate) were selected for the study based on Polar surface area (PSA). Ex- vivo studies were carried out in franz diffusion cell. The skin permeation parameters of the model drugs were correlated to the physicochemical properties. The physicochemical properties considered for the study have shown to be synonymous with the pre-established ideal properties for the transdermal permeation. In acidic drugs, the order of correlation of the physicochemical properties to flux was mol. wt. > total no. of hydrogen bonds > M.P > PSA > Log P > Log D > solubility. In basic drugs, the order of correlation of the physicochemical properties to flux was mol. wt > PSA > solubility > log P > log D> total no. of hydrogen bonds> M.P. The property considered for the study PSA has acquired 4th rank in acidic drugs with R^2= 0.9465 and 2nd in basic drugs with R^2= 0.9477. The prime important factor for the study PSA, has shown a tortuous effect on the permeation of the selected drugs, whereas further study of PSA in relation to skin permeability parameters by considering larger drug data sets may impart a clearer image of its influence on transdermal permeation.

***Key words*:** ex-vivo skin permeation, log P, M.P, mol. wt., Polar surface area, transdermal flux.

1. Introduction

Pharmaceutical industries have been focusing on the relevant prediction of structural characteristics based on the transport of solutes in biological systems, specifically absorption across the intestinal membrane. The QSAR characteristics (known as quantitative structure–activity relationships), that is known to mimic solute membrane transport processes based on molecular structure–permeability

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relationships, is considered to be the ultimate time-saving method. These computational models have been vastly investigated for the applicability to intestinal drug permeability, as oral route is the most advantageous and preferred route for administration. The introduction of Lipinski's 'Rule of Five' that provided a guide to correlating physical properties such as lipophilicity, molecular weight and hydrogen bonding to successful drug development for orally administered compounds, has initiated a profound shift in the exemplar thinking of medicinal chemists.[1] Addressing the pharmacokinetic properties of the biologically active small molecules and drugs at early stage during lead optimisation became the priority in the drug discovery process.

The absorption computational field have also introduced several other structural descriptors, including surface properties and rotatable bonds. Polar surface area is one such surface property that encode the hydrogen bonding capacity, as both the descriptors have a strong correlation.[2] PSA (polar surface area) is defined as the sum of Vander Waals surface area of all nitrogen and oxygen atoms plus their attached hydrogen atoms. There are a number of approaches to calculating PSA, depending primarily on the kind of molecular surface area used (van der Waals being the most common) or which atoms are considered to be polar, with the use of nitrogen, oxygen (although sometimes also sulphur) and attached hydrogen atoms the most common. One of the first applications of PSA is a study of Van de Waterbeemd and Kansy to predict BBB penetration. Van de Waterbeemd *et al.* also used this parameter to predict the Caco - 2 permeability of drugs (in these papers the name "polar part of the surface" was still used).[3] PSA has been successfully used for the prediction of , intestinal and blood–brain barrier transport. The PSA ,for predicting oral bioavailability in rats, PSA of less than 140 $Å^2$ (or 12 or fewer hydrogen bonding groups) giving a high probability of good oral bioavailability in the rat.[4]

The priority of pharmaceutical research is for a substitute to the oral route of administration that overcomes its disadvantages, such as the hepatic metabolism or adverse effects. During the past few years, transdermal therapeutic systems (TTS) have been the best alternate method to oral delivery and the skin to be a suitable delivery route for delivery of drugs. This increasing interest has led to the growth of predictive methods for transdermal absorption. Previous solute physicochemical predictors of transdermal absorption potential have included lipophilicity (octanol : water partition coefficient), molecular weight (mol. wt.), various functional group contributions, hydrogen acceptor and donor ability, dipole properties and solubility parameters. The reporting of transdermal penetration in terms of either permeability coefficient (K_p, cm/s), the rate with which a solute can move through a membrane, or maximum flux (J_{max}, $mg/cm^2/hr$), the maximum amount of a solute that can be delivered through a membrane per unit time, has great bearing on the relative importance of the predictors mentioned above.

Our analysis of literature data for solutes applied to human epidermal membranes in aqueous solution or as pure liquids used J_{max} rather than K_p.[5] The maximum flux provides the more clinically relevant answer for the pharmaceutical industry, where the aim is to optimise solute penetration, and to the risk assessors, whose aim is to determine potential maximum exposure.

The aim of this study was to determine the relationship expressing solute permeability through rat skin as functions of PSA and the other molecular properties. We used some model drugs and applied to rat skin in vitro and performed correlations of this data with calculated PSA (using SMILES notation inputs with a Web-based molecular descriptors calculator (http://www.molinspiration.com) and other physicochemical parameters.

2. Materials and Methods

Ibuprofen, aceclofenac, glipizide, olanzapine and telmisartan as well as sildenafil citrate were gifted by Sri Krishna pharmaceuticals Ltd ,Hyd and SD Fine –Chem Pvt, Mumbai respectively. Sodium hydroxide and Potassium di hydrogen ortho phosphate were procured from SD Fine-Chem Pvt., Mumbai.

2.1. Selection of Drugs

Few model drugs which are weakly acidic and basic were selected for the study based on Polar surface area (PSA). Accordingly, drugs were categorized into weakly acidic and weakly basic group, each group containing 3 drugs with PSA range as 30 $Å^2$, 70 $Å^2$ and > 100 $Å^2$, they are ibuprofen (37.3 $Å^2$), aceclofenac (75.6 $Å^2$) and glipizide (130.15 $Å^2$) in weakly acidic group and olanzapine (30.87 $Å^2$), telmisartan (72.94 $Å^2$) and sildenafil citrate (109 $Å^2$).

2.2. Solubility Study [6]

Excess amount of drug (ibuprofen, aceclofenac, glipizide, olanzapine, telmisartan and sildenafil citrate) was added to 2 ml of distilled water in plastic cuvettes. The cuvettes were sonicated for 1 hr in a water bath at 37 °C and kept at 37 °C for up to 72 h. The solution was then centrifuged at 16,000 rpm for 5 min and aliquots were filtered through Whatman No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at their respective wavelengths.

2.3. Partition coefficient [7]

N-octanol was used to represent the bio membrane. The partition coefficients between n-octanol and water at 37ºC were determined by shake-flask method which was known in the literature has been slightly modified in order to determine the partition coefficient of the drug. N-octanol and water solution was co-saturated with each other for 24 hr. at 37ºC before use. To the pre-equilibrated water (10ml), specified amount of drug [ibuprofen (400mg), aceclofenac (500mg), glipizide (200mg), olanzapine (50mg), telmisartan (100mg) and sildenafil citrate (5 mg)], was dissolved in aqueous solution. 10ml of octanol was added to the equal volume of aqueous solution of drug and kept for intermittent

shaking for 3 hr. Concentration of drug in each phase was determined spectrophotometrically by measuring absorbance at their respective wavelengths in aqueous phase.

$$\text{LogP}_{\frac{\text{oct}}{\text{wat}}} = \log \left(\frac{[solute]_{octanol}}{[solute]_{water}}\right)$$

2.4. Ex-Vivo skin permeation studies [8]

The institutional animal ethical committee (IAEC) has approved the experimental protocol. The permeation study was performed using Male wistar rats (150‑180 g). The animal was sacrificed by excessive ether anaesthesia and abdominal hair was removed using an animal hair clipper. The abdominal skin section was excised and observed for presence of cuts and wounds. The fat attached to dermis was separated using scalpel and was washed under tap water. The skin was stored at −20°C and used within a 48 hrs.

For the permeation studies locally fabricated Franz diffusion cells with an area of 7.54 cm^2 and 25ml receptor volume were used. The receptor compartment was filled with 25ml of phosphate buffer solution of pH 7.4. The rat skin was mounted onto Franz diffusion cell such that the dermis side was in constant contact with receptor solution. 5ml of saturated drug solutions were poured onto the stratum corneum facing the donor compartment and the hydrodynamics in the receptor compartment were maintained by stirring on magnetic stirrer at 600 rpm. 2ml sample was withdrawn at predetermined time intervals for 6 h and drug content was analyzed by UV‑VIS double beam spectrophotometer at respective absorptive maximas of drugs.

Ex-vivo permeation rate studies such as percentage drug release, steady state transdermal flux (SSTF), permeability coefficient, across rat skin were estimated for the drugs.

2.5. Data Analysis

The cumulative amount permeated in 6 hrs (Q_6) was calculated from permeation studies. Flux (Jss) was calculated from slope of curve on plotting Q_6 Vs time. Flux divided by donor concentration resulted in apparent permeability coefficient (Kp). Mean and standard deviation were calculated using Microsoft Excel 2007. The experiments were performed in triplicate (n = 3).

3. Results and Discussion

The permeation profiles of the drugs through the rat skin are shown in figure 1. Ibuprofen has showed significantly higher permeation in comparison to other drugs that may be due to its self permeation enhancement nature as reported by S.M. Al-Saidan, *et al*.[9] In comparison to basic drugs acidic drugs have shown higher permeability that could be attributed to their higher solubility's at pH 7.4.

3.1. Relation between Skin Permeability and Physicochemical Properties of the Drugs

Solubilities and partition coefficient of the drugs are listed in Table 1 along with the other physicochemical properties that could be relevant for transdermal permeability as well

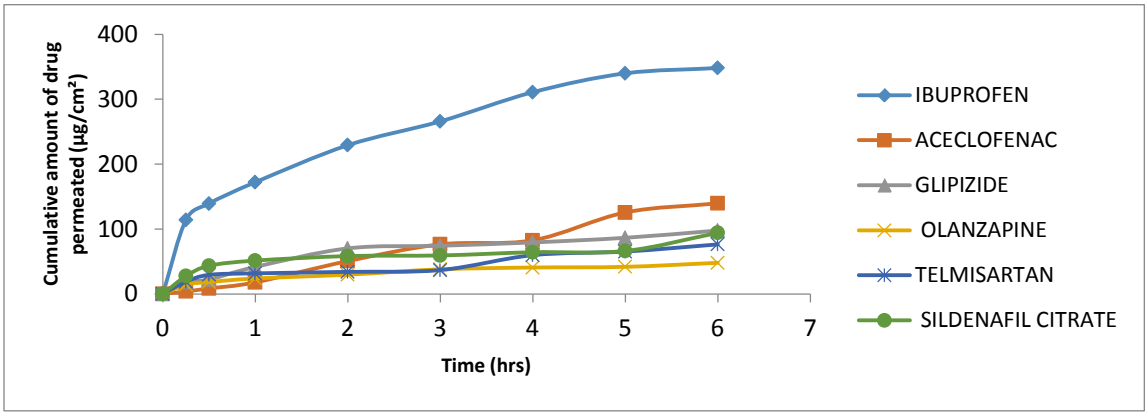

Figure 1. *Ex-vivo* release profile of the selected drugs.

as their obtained flux and permeability coefficients.

3.1.1. Effect of Molecular Weight on Transdermal Flux

The maximum flux for any given drug in a saturated solution or as a pure drug can be initially estimated by its mol.wt (molecular weight). The selected acidic and basic drugs have shown an increase in PSA with increase in molecular weight along with the flux when considered separately. From the figure 2.A, it can be noted that the increase in molecular weight showed decrease in the flux, with an exception of olanzapine (312.43 Da) showing less flux than other drugs that have higher molecular weight. Among olanzapine and aceclofenac having similar molecular weight of 312 Da and 354 Da respectively, maximum flux of 24.12 µg/cm^2/h has been shown for aceclofenac than olanzapine (flux 9.18 µg/cm^2/hr). It may be due to high log P (partition coefficient) 4.14 and low MP (149 °C) of aceclofenac than log P 1.2 and MP (195 °C) of olanzapine. The maximum flux for certain series of solutes with a similar MW has been reported to be associated with a log P of >2.5 and to be greatest for solutes with a low melting point. [5]

Acidic drugs have shown an inverse relation of mol.wt. with flux and PSA as shown in figure 2.B. Glipizide with high

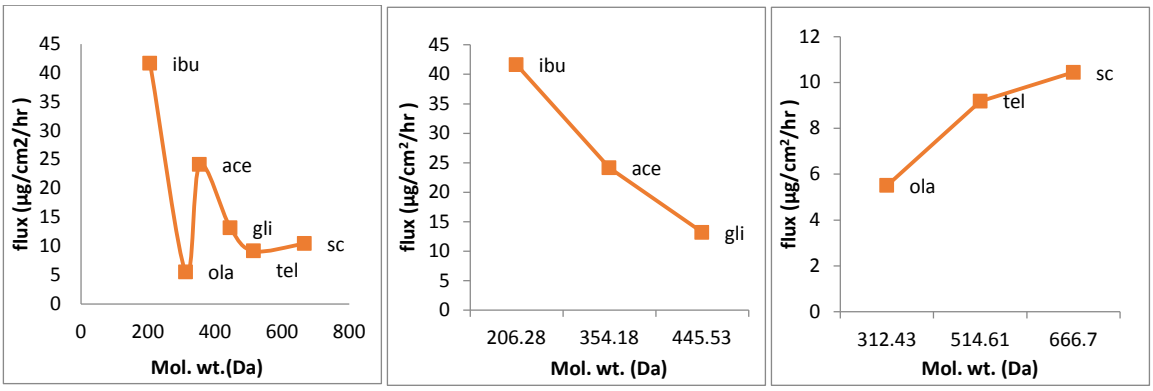

Figure 2. Relation of flux to Mol. wt. A) All the selected drugs B) Weakly acidic drugs C) Weakly basic drugs.

Table 1. The physicochemical properties of the drugs and their respective skin permeability parameters.

drug	**weakly acidic**			**weakly basic**		
Property	Ibuprofen	Aceclofenac	Glipizide	Olanzapine	Telmisartan	Sildenafil
Mol.wt	206.28	354.18	445.53	312.43	514.61	666.7
MP	76	149	208	195	261	202
log P	3.97	4.14	1.91	1.2	3.14	2.22
Aqueous solubility	0.75	0.65	0.09	0.43	0.02	5.01
log D	0.62	1.32	0.99	0.95	1.05	2.26
Pka	5.2	4.7	5.9	7.4	3.5	7.2
No. of HB	3	7	9	6	5	19
PSA	37.3	75.6	130.15	30.87	72.94	109
Solubility at pH 7.4	1.63	12.85	0.25	1.79	0.2	0.24
Flux ($\mu g/cm^2/hr$)	41.62	24.12	13.19	5.51	9.18	10.44
Permeability coefficient ($*10^{-3}$) (cm/hr)	25.53	1.88	52.76	3.08	45.91	43.50

mol.wt. 445.53 Da and high PSA 130.15 $Å^2$ have shown least flux of 13.19 $\mu g/cm^2/hr$, Concurrent with the results of Okumura, that showed least flux for higher molecular weight disodium cromoglycate, a water soluble compound. [10] Conversely, basic drugs have shown an increase in the flux with increase in the molecular weight as well as PSA as seen in figure 2.C. Sildenafil citrate with high mol.wt. 666.7 Da and high PSA 109 $Å^2$ have shown highest flux of 10.44 $\mu g/cm^2/hr$. A similar relation of flux to mol.wt was seen in case of narcotic analgesics, sufentanil with high mol. wt. among the selected analgesics has shown higher flux. [11]

The results lead into conclusion that the other determinants of permeability dominate the overall behaviour, with mol. wt. being secondary.

3.1.2. Effect of melting point on transdermal flux

The selected acidic drugs have shown an increase in M.P (melting point) with increase in mol. wt. and PSA. Whereas in basic drugs, the telmisartan with medial values of mol.wt.

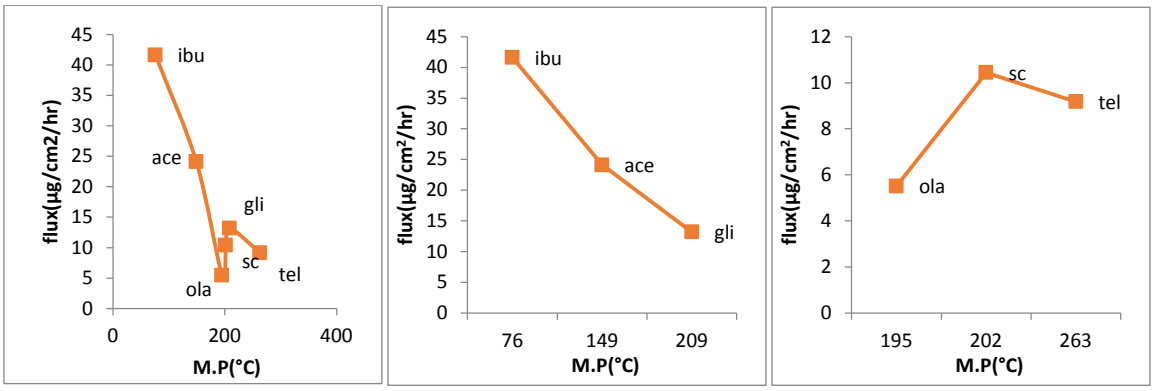

Figure 3. Relation of flux to M.P. A) All the selected drugs B) Weakly acidic drugs C) Weakly basic drugs.

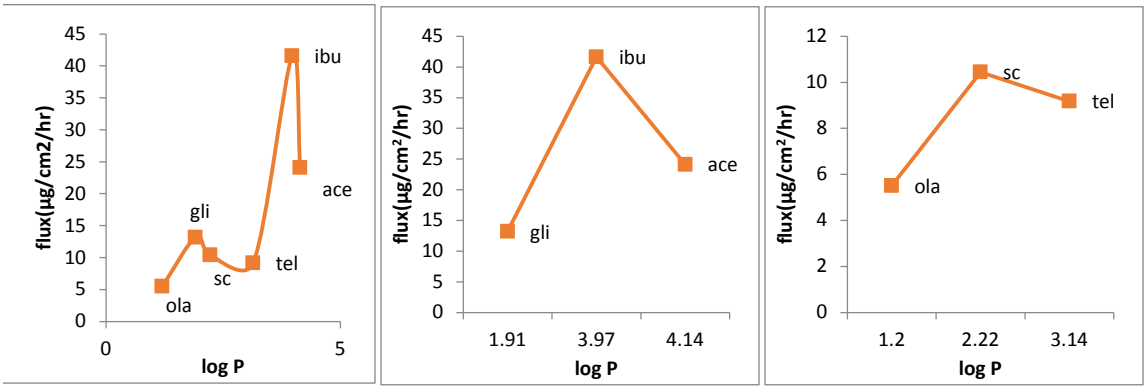

Figure 4. Relation of flux to log P. A) All the selected drugs B) Weakly acidic drugs C) Weakly basic drugs.

and PSA have shown the highest M.P.

As represented in the figure 3.A with the increase of melting point there has been a decrease in flux rate of the drugs. Concurrent with the results of Okumura *et al.*, Roy *et al.*, and Ghosh *et al.*[10,12,13] There has been a sharp decrease in flux with increase in melting point from 76 °C (ibuprofen) to 195 °C (olanzapine) further with small increase in melting point ranges there has been a variation in flux (in the range of 195,202,209 °C), though there has been a decrease in flux with increase in M.P 209 °C (glipizide) to 263 °C (telmisartan). Since M.P is a measure of the cohesive strength of the drug molecules, it appears that drugs, having low intermolecular attraction can move freely through the stratum corneum. [13]

Acidic drugs have shown a decreasing trend in flux with increase in M.P, Mol.wt. and PSA in the order of ibuprofen (76 °C) > aceclofenac (149 °C) > glipizide (209 °C) as represented in figure 3.B. Similar to the anti hypertensive's, where higher flux was noted for atenolol with low M.P (156 °C) and lowest flux was noted for prazocin with higher M.P (279 °C) by Ghosh *et al.*[13] In case of basic drugs from figure 3.C, sildenafil citrate with medial M.P 202 °C but with highest PSA 109 $Å^2$ and mol.wt. 666.7 Da have shown the highest flux 10.44 µg/cm^2/hr**,** that could be due to the higher solubility and olanzapine with lowest M.P 195°C, mol.wt. 312.43 Da and low PSA 30.87 $Å^2$ have shown least flux of 5.51 µg/cm^2/hr. Inverse to the reported values of narcotic analgesics by Roy *et al.*, where meperidine with higher M.P has shown higher flux.[12] That could be attributed to the higher influence log P that is ideal for sildenafil citrate (log P of 2.22).

3.1.3. Effect of partition coefficient (log P) on transdermal flux

Partition coefficient of drugs did not show a particular pattern with PSA in both acidic and basic drugs. But, both the acidic and basic drugs with PSA around 70 $Å^2$ i.e., 75.6 $Å^2$ (aceclofenac) and 72.94 $Å^2$ (telmisartan) have shown a highest log P values of 4.14 and 3.14 respectively. As represented in the figure 4.A the drugs ibuprofen (log P 3.97) and aceclofenac (log P 4.3) have shown higher flux rates. Olanzapine with log P 2 has shown least flux. Alike with the established conclusions

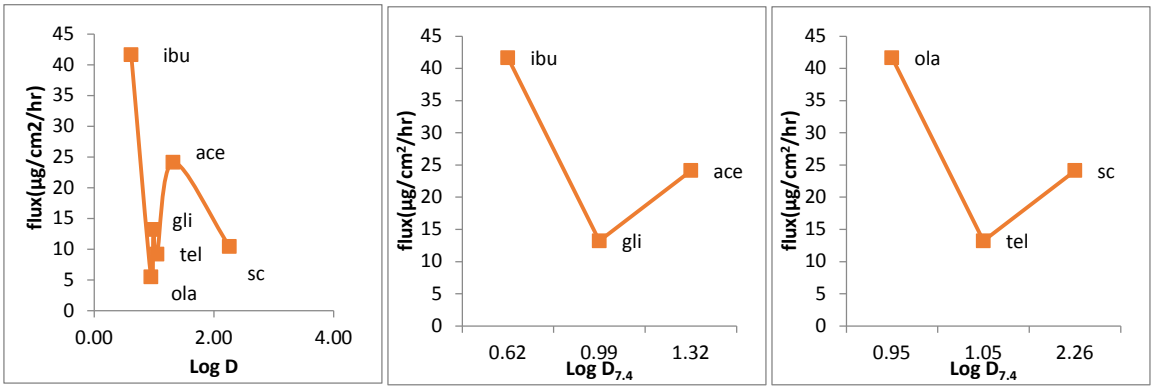

Figure 5. Relation of flux to log D. A) All the selected drugs B) Weakly acidic drugs C) Weakly basic drugs.

that compounds with high lipophilicites, are likely to be best permeants of skin.[12] Though a relative correlation cannot be drawn from the above figure 4.A with respect to log P and skin permeability parameters, a comparison of other physicochemical properties along with log P may draw some light in the pattern of permeability parameters.

From figure 4.B, in acidic drugs the highest flux of 41.62 µg/cm^2/hr was obtained for ibuprofen may due to its low mol.wt 206.28 Da, M.P 76 °C, PSA 37.3 Å^2 and optimal log P of 3.96, where as in basic drugs from figure 4.C, the highest flux of 10.44 µg/cm^2/hr was obtained for sildenafil citrate with highest mol.wt 666.7 Da, PSA 109 Å^2 and medial M.P 202 °C, log P 2.22. Telmisartan having log P 3.14 similar to ibuprofen has shown lower flux than sildenafil may be due to its higher M.P, low log D (diffusion coefficient) and least aqueous solubility. The above data has confirmed that log P values 2 to 4 to be ideal for transdermal transport.[14]

3.1.4. Effect of Distribution Coefficient (log D) on Transdermal Flux

The selected basic drugs have shown an interesting trend of increase in log D with increase in the other properties such as mol.wt. M.P. and PSA. In case of acidic drugs it did not follow any similar pattern, but lowest log $D_{7.4}$ value was shown by ibuprofen with low mol.wt., PSAand M.P. The drugs Ibuprofen (log $D_{7.4}$ 0.62) and aceclofenac (log $D_{7.4}$ 1.32) have shown higher flux rates (figure 5.A). Olanzapine with log $D_{7.4}$ 0.95 has shown least flux.

In acidic drugs (figure 5.B), the highest flux of 41.62 µg/cm^2/hr was obtained for ibuprofen with lowest log $D_{7.4}$ 0.62 and low mol.wt. 206.28 Da, M.P 76 °C, PSA 37.3 Å^2 and optimal log P of 3.96, conversely in basic drugs (figure 5.C) the highest flux of 10.44 µg/cm^2/hr was obtained for sildenafil citrate with high log $D_{7.4}$ 2.26 and highest mol.wt 666.7 Da, PSA 109 Å^2 and medial M.P 202 °C, log P 2.22. The above results have shown that log P are more predictive than log D values, that contradict with the report of Amit kokate *et al.*, that showed log D gave better correlation of permeability

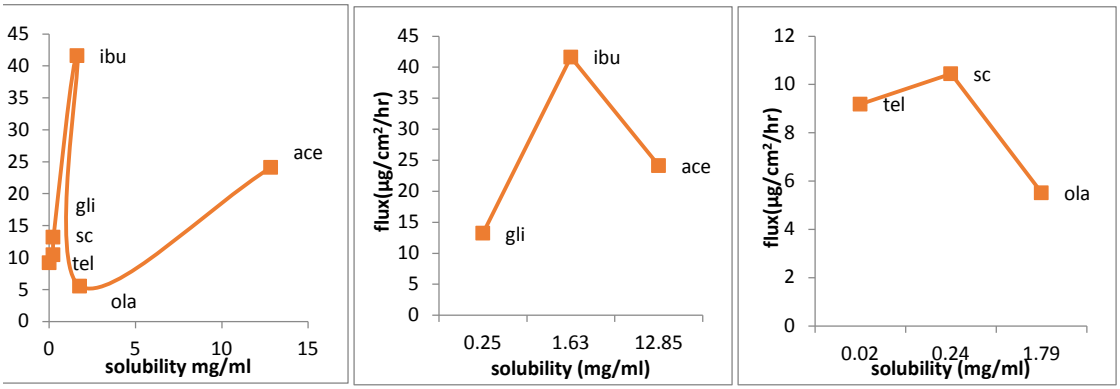

Figure 6. Relation of flux to solubility. A) All the selected drugs B) Weakly acidic drugs C) Weakly basic drugs.

than log P [15], may be due to the narrow log $D_{7.4}$ range (0.5 to 2.5) the predictability of optimal log D value to obtain better flux has been difficult.

3.1.5. Effect of solubility on transdermal flux

Overall, the solubility of drugs in 7.4 pH buffer did not show any correlation with other properties as seen in figure 6.A. But when acidic and basic drugs were compared separately, acidic drugs showed a direct proportion with the log P and basic drugs have shown an increase in solubility with decrease in both log P and M.P.

Although flux has a tendency to be proportional to the solubility, there was no efficient correlation. Ibuprofen (1.63 mg/ml) has shown highest flux, as the solubility > 1mg/ml considered to be ideal for better transdermal permeation.[14] The aceclofenac with solubility more than 1 mg/ml has shown higher flux. But olanzapine though having a good solubility of 1.79 mg/ml has shown least flux that may be due to its basic nature and lowest log P 1.2. A similar trend as shown in figure 6.A, has also been reported for anti hypertensive's by Ghosh *et al.*[13]

In acidic drugs (figure 6.B), the highest flux of 41.62 µg/cm^2/hr was obtained for ibuprofen with minimal solubility of 1.63mg/ml and low log $D_{7.4}$ 0.62, may be due to low mol.wt. 206.28 Da, M.P 76 °C, PSA 37.3 Å^2, and optimal log P of 3.96, incidentally in basic drugs the highest flux of 10.44 µg/cm^2/hr was obtained for sildenafil citrate with a low solubility of 0.24 mg/ml than ibuprofen, but with high log $D_{7.4}$ 2.26 and highest mol.wt 666.7 Da, PSA 109 Å^{2}and medial M.P 202 °C , log P 2.22, the reason may be due to its higher permeability at pH 7.4 where both ionised and unionised species contribute to its high flux. The basic drug olanzapine with a similar solubility of 1.79mg/ml as that ibuprofen and though having low mol. wt., M.P and PSA that effect flux has shown least flux 5.51 µg/cm^2/hr may be attributed to its higher solubility than others basic drugs in the same group where as in acidic drugs glipizide having least 7.4 pH solubility among its group has shown least flux of 13.19 µg/cm^2/hr (figure 6.C). The reason for the least flux shown by glipizide may be due to its higher mol.wt. M.P and PSA that affect the flux to a greater extent rather than solubility.

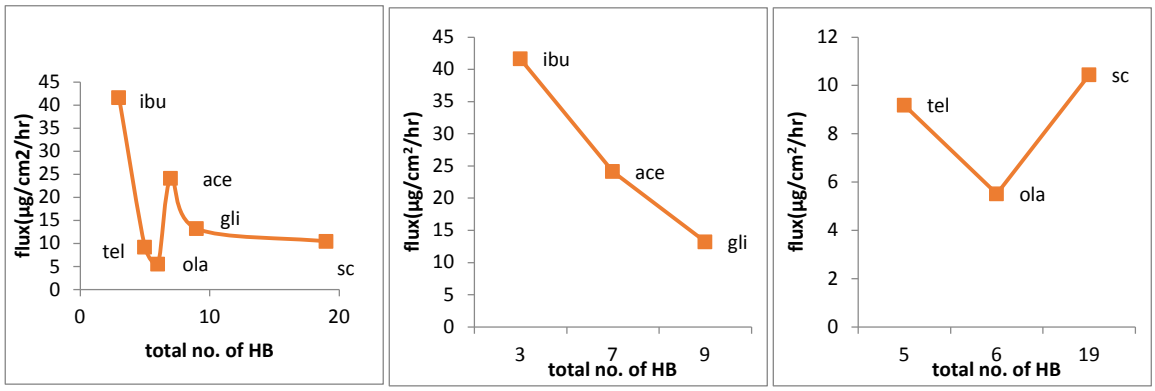

Figure 7. Relation of flux to total no. of H.B. A) All the selected drugs B) Weakly acidic drugs C) Weakly basic drugs.

3.1.6. Effect of hydrogen bonds count on transdermal flux

Though overall the drugs did not show a pattern of increase or decrease in hydrogen bond count with other physicochemical properties, the acidic drugs have shown a decrease in both hydrogen bond acceptors, donors and total no. of bonds with an increase in PSA, mol.wt., M.P and decrease in aqueous solubility.

Hydrogen bond acceptors are known to influence the permeability parameters to a greater extent and also it is one of the 5 factors in Lipinski rule of 5, that states the compounds with number of hydrogen bond donors (OH and NH groups) > 5, and number of hydrogen-bond acceptors (N and O atoms) > 10 show poor absorption and permeability.[1] No, certain pattern has been followed by flux with increase in the total no. hydrogen bonds as can be noted from figure 7.A. That may be ascribed due to lower no. of hydrogen bonds than the specified limits. However, Maximum flux has been represented by ibuprofen with 3 hydrogen bonds and minimum has been recorded for olanzapine with 6 hydrogen bonds, as said higher permeation for compounds with lower no. of hydrogen bonds.

The drugs considered for the study have less than the above criteria of hydrogen bonds, so establishing the relation between the effect of hydrogen bonds on skin permeability parameters becomes tough. But in case of acidic drugs an interesting trend of decrease in flux with increase in hydrogen bond acceptors, donors and total no. of hydrogen bonds from figure 7.B, that may be due to simultaneous increase of mol. wt. and M.P. In case of basic drugs (figure 7.C), olanzapine with 6 hydrogen bond has shown less flux compared to other two drugs with higher (sildenafil citrate with 19 bonds) and lower value (telmisartan with 5 bonds) than 6 that may be due to higher influence of other molecular properties.

3.1.7. Effect of PSA on transdermal flux

The PSA considered for the study increased with increase in mol.wt. and M.P. When the drugs are categorised by their nature, the acidic drugs PSA has been found to be directly proportional to mol.wt. M.P, total no. of hydrogen bonds and inversely to aqueous

Table 2. Correlation values of weakly acidic drugs with respect to their physicochemical properties.

PARAMETERS	R^2
flux v/s mol.wt.	1
flux v/s HB	0.9967
flux v/s MP	0.9942
flux v/s PSA	0.9465
flux v/s log P	0.8789
flux v/s log D	0.4044
flux v/s solubility	0.0011

Table 3. Correlation values of weakly basic drugs with respect to their physicochemical properties.

PARAMETERS	R^2
flux v/s mol.wt.	0.963
flux v/s PSA	0.9477
flux v/s solubility	0.8741
flux v/s log P	0.543
flux v/s log D	0.5337
flux v/s HB	0.3966
flux v/s MP	0.13

solubility. Basic drugs PSA was also seen to be proportional to mol.wt., M.P, log D and inverse to solubility at pH 7.4 .

The PSA of drugs is known to effect its intestinal permeability, earlier research findings have shown that drugs with PSA ≤ 60 $Å^2$ will be absorbed completely with fraction absorbed Fa ≥ 90% and drugs with PSA ≥ 140 $Å^2$ will show a poor absorption with Fa ≤ 10%.[4] The PSA of the drugs have also shown reasonable influence on BBB penetration, the earlier research findings have shown that brain penetration decreases with increasing PSA.[16] The role of PSA on membrane permeability was studied by Jeffrey *et al.*, and concluded that no significant relation could be established between PSA and membrane permeability.[17]

Figure 8.A represents the relation between the PSA and the flux of the drugs. Though a clear limits have not been established for transdermal permeation by this study. Highest flux has been noted for acidic drug ibuprofen with PSA of 37.3 $Å^2$ and lowest was noted for basic drug olanzapine with similar PSA of 30.87 $Å^2$.

For the given set of drugs there has been a decrease in flux with increase in PSA from 30 $Å^2$ to 130 $Å^2$ in case of acidic drugs from figure 8.B, conflictingly in case of basic drugs

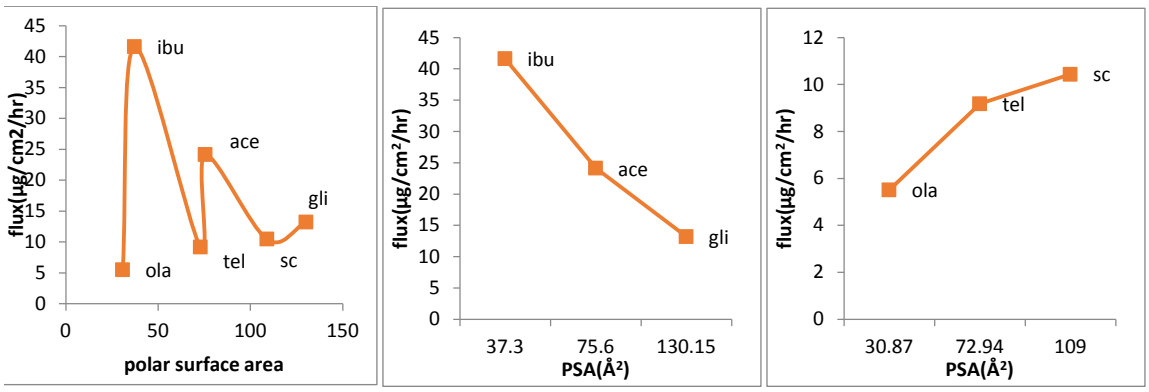

Figure 8. Relation of flux to PSA. A) All the selected drugs B) Weakly acidic drugs C) Weakly basic drugs.

(figure 8.C) there has been an increase in flux with increase of PSA from 30 $Å^2$ to 110 $Å^2$.

By considering the above results, it can be determined that the skin permeability parameters are influenced slightly by PSA and significantly by other physicochemical parameters considered for the study.

3.2 Correlation of skin permeation properties and drug physicochemical properties

From Table 2 and 3, it can be deduced that Flux has shown good correlation with the molecular properties. In acidic drugs, the order of correlation of the physicochemical properties to flux was found to be mol. wt. > total no. of hydrogen bonds > M.P > PSA > Log P > Log $D_{7.4}$ > solubility. In basic drugs, the order of correlation of the physicochemical properties to flux was found to be mol. wt > PSA > solubility > log P > log $D_{7.4}$> total no. of hydrogen bonds> M.P.

In case of acidic and basic drugs, molecular weight has shown the best correlation with R^2 (correlation coefficient) values of 1 and 0.963 respectively, whereas least correlation was found with solubility (R^2 =0.0011) and M.P (R^2 = 0.13). The property considered for the study PSA has acquired 4^{th} rank in acidic drugs with R^2= 0.9465 and 2^{nd} in basic drugs with R^2= 0.9477.

From the above results it can be inferred that along with these important properties, PSA can also effect the transdermal permeation to a considerable extent.

4. Conclusion

Despite the undoubted complexity of the skin permeability process, the correlation of the selected drug properties on permeation properties lead to conclusion that the physicochemical properties considered for the study significantly affected the permeation of drugs across the skin and selected drugs with molecular weight < 500 Da, melting point < 200°C, log P of 2-4, solubility >1mg /ml, < 5 no. of hydrogen bonds have shown better transdermal permeation than others, synonymous with the pre-established ideal properties for the transdermal permeation. PSA, the prime important factor for the study, has showed a tortuous effect on the permeation of the selected drugs. So, further study of PSA in relation to skin permeability parameters by considering larger drug data sets supported with *in-vivo* studies may impart a clearer image of its influence on permeation.

References

[1] Lipinski CA, Lombardo F, Dominy BW and Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced drug delivery reviews* (1997)23: 3-25.

[2] Clark D E, Grootenhuis D J. Predicting passive transport in silico – history, hype, hope. *Current Topics in Medicinal Chemistry* (2003)3(11): 1193 – 1203.

[3] Van de Waterbeemd H, Camenisch G, Folkers G, Raevsky OA. Estimation of Caco - 2 cell permeability using calculated molecular descriptors. *Quantitative Structure-Activity Relationships* (1996)15(6): 480 – 490.

[4] Zakeri-Milani P, Tajerzadeh H, Islambolchilar Z, Barzegar S, Valizadeh H. The relation between molecular properties of drugs and their transport across the intestinal membrane.*DARU* (2006)14(4): 164-171.

[5] Magnusson BM, Anissimov YG, Cross SE & Roberts MS. Molecular size as the main determinant of solute maximum flux across the skin. *J Invest Dermatol* (2004)122(4): 993–999.

[6] Kang L, Yap CW, Lim PFC, Chen YZ, Ho PC, YW Chan YW, Wong GP, Chan SY. Formulation development of transdermal dosage forms: Quantitative structure-activity relationship model for predicting activities of terpenes that enhance drug penetration through human skin. *Journal of Controlled Release* (2007)120: 211–219.

[7] Madhulatha A, Naga Ravikiran T. Formulation and Evaluation of Ibuporfen Transdermal Patches. *International Journal of Research in Pharmaceutical and Biomedical Sciences* (2013)4(1): 351-362.

[8] Prasanthi D, Lakshmi PK. Terpenes: Effect of lipophilicity in enhancing transdermal delivery of alfuzosin hydrochloride. *Journal of Advanced Pharmaceutical Technology & Research* (2012)3(4): 216-223.

[9] S.M. Al-Saidan. Transdermal self-permeation enhancement of ibuprofen. *Journal of Controlled Release* (2004)100: 199–209.

[10] Mutsuo Okumura, Kerij Isugibayashi, Keizaburo Ogawab and Yasunori Morimoto. Skin Permeability of Water-Soluble Drugs. *Chem Pharm Bull* (1989)37(5): 1404-1406.

[11] Yoshikazu Tashiro, Mari Sami, Shozo Shichibe, Yasuki Kato, Eiji Hayakawa, And Kunio Itoh. Effect of lipophilicity on *in-vivo* iontophoretic delivery of B -blockers. *Biol Pharm Bull* (2001)24(6): 671—677.

[12] Samir D Roy and Gordan L Flynn. Transdermal Delivery of Narcotic Analgesics: Comparative Permeabilities Of Narcotic Analgesics Through Human Cadaver Skin. *Pharm Res* (1989)6(10): 825-832.

[13] Vikram Sarveiya, John F. Templeton and Heather A. E. Benson. Ion-pairs of ibuprofen: increased membrane diffusion. *J Pharm Pharmacol* (2004)56: 717–724.

[14] Chandrashekar NS, Shobha Rani RH. Physicochemical and pharmacokinetic parameters in drug selection and loading for transdermal drug delivery. *Indian Journal of Pharmaceutical Sciences* (2008)70(1): 94-96.

[15] Jeffrey E Grice, Sheree E Cross, Craig Brownlie and Michael S Roberts. The application of molecular structural predictors of intestinal absorption to screening of compounds for transdermal penetration. *J Pharm Pharmacol* (2010)62: 750–755.

[16] Kelder J, Grootenhuis PDJ, Bayada DM, Delbressine LPC, Ploeman JP. Polar molecular surface area as a dominating determinant for oral absorption and brain permeation of drugs. *Pharm Res* (1999)16: 1514 – 1519.

[17] Bijaya Ghosh, Harivardhan Reddy L. Effect of physicochemical parameters on skin permeability of anti hypertensives. *Indian J Exp Biol* (2001)391: 710-714.

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