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Article

Effect of pH on weakly acidic and basic model drugs and determination of their *ex vivo* transdermal permeation routes

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The aim of the present study was to investigate the effect of donor pH on the transdermal permeability of the model drugs across rat skin and also to determine the major route of transport of the drugs. Weakly acidic drugs (partition coefficient) ibuprofen (3.6), aceclofenac (3.9), glipizide (1.9) and weakly basic drugs olanzapine (3.6), telmisartan (6.0), and sildenafil citrate (1.9) were selected for the study. The ex vivo permeation studies of these drugs at different donor pH (pH – 1.2, 4, 5, 6.8, 7.4, and 8) using Franz diffusion cell (area, 7.54 cm^2) has shown a pH-dependent permeability. Among these drugs the weakly acidic drugs has shown higher permeation rates compared to the weakly basic drugs. The permeability coefficient and the distribution coefficient of the weakly basic drugs increased on increasing the pH whereas the weakly acidic drugs showed an inverse relation. The weakly basic drugs also showed an increase in permeation with increase in the fraction of unionized species indicating dominance of transcellular route of permeation. With an exception of sildenafil citrate, a weakly basic salt form of the drug which showed a high permeation value at pH 7.4 where 57% of the drug was unionized, indicating the involvement of both paracellular and transcellular route in its permeation.

Keywords: Donor pH/effects. Weakly acidic drugs. Weakly basic drugs. pH solubility. Distribution coefficient. Ionization.

INTRODUCTION

Skin, the largest organ of the body offers a large surface area along with pervasive circulatory and lymphatic network making it the preferred noninvasive route of drug delivery. Delivery of a drug through the skin for local or systemic pharmacological effect has been an assuring concept since a long time.

It is noted that pH has an effect on the permeation of drugs through biological membranes such as oral mucosa, intestinal membrane etc., affecting the route of permeation. Thus implicating the importance of examining the effect of pH on transdermal drug delivery that also determines the penetration route, which is an intrinsic factor for the selection of penetration enhancer to improve the drug permeability. General absorption of ionizable drugs across gastrointestinal tract has been explained by the pH partition theory whereas not much has been documented for the dermal and transdermal delivery of drugs (Hadgraft, Valenta, 2000).

Weakly acidic and weakly basic drugs show a pH-dependent. It is assumed that penetration of the drug through dermis is influenced by its ionic condition and ionized species are known to permeate poorly compared to nonionized species (Hadgraft, Valenta, 2000). Increase in the amount of nonionised drug may lead to enhanced permeability, which can be attained by a change in pH of the drug delivery system.

Dermal penetration of the drugs is also strongly influenced by its partition coefficient (log p) and distribution coefficient (log D). Drug permeation studies of narcotic analgesics revealed that drug distribution coefficient across dermis at constant concentration was proportional to its partition coefficient (Roy, Flynn, 1989). Partition coefficient effect on dermal permeation was also studied for antihypertensives (Ghosh, Reddy, 2001), β-blockers (Chantasart, Hao, Li, 2013) etc. Thus both the pH and partition coefficient has a remarkable effect on the dermal permeation of the drugs.

Noticeably, the pH of the drug delivery system

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influences the route of penetration of the drug (Mashru et al., 2005), making it important to know the major pathways of drug penetration through the skin. The two major pathways for passive drug penetration include paracellular and transcellular route.

The drug flux through the membrane for paracellular route under sink condition is written as equation 1

$$J_p = \frac{D_p \varepsilon}{h_p} C_d \quad (1)$$

where D_p = the diffusion coefficient of the permeate in the intercellular spaces, h_p = path length of the paracellular route, ε = area fraction of the paracellular route, and C_d = donor drug concentration.

The drug flux through the membrane for transcellular route under sink condition can be written as equation 2

$$J_c = \frac{(1-\varepsilon) D_c K_c}{h_c} C_d \quad (2)$$

where, K_c= partition coefficient between lipophilic cell membrane and the aqueous phase, D_c = diffusion coefficient of the drug in the transcellular spaces, and h_c = path length of the transcellular route.

The aim of the present study was to investigate the effect of pH and ionization on permeation and to understand in vitro transport across rat skin based on varying pH using weakly acidic drugs ibuprofen, aceclofenac, and glipizide and weakly basic drugs olanzapine, telmisartan, and sildenafil citrate as model drugs.

MATERIALS AND METHODS

Ibuprofen, aceclofenac, glipizide, olanzapine and telmisartan, sildenafil citrate were gifted by Sri Krishna pharmaceuticals Ltd , Hyd and SD Fine –Chem Pvt, Mumbai respectively. Sodium hydroxide, sodium acetate (tri-hydrate), and potassium di hydrogen ortho phosphate were procured from SD Fine-Chem Pvt., Mumbai.

The representative weakly acidic drugs were ibuprofen, aceclofenac, and glipizide and the weakly basic drugs were olanzapine, telmisartan, and sildenafil citrate used in the study as model drugs. The pH solubility profile and the partition and distribution coefficient at different pH of 1.2, 4, 5, 6.8, 7.4, and 8 were studied.

Solubility study

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 h 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 (Kang et al., 2007). The filtrates were diluted appropriately and assayed spectrophotometrically (at 222.4 nm, 273.6 nm, 276.2 nm, 254.4 nm, 295.5 nm, and 291.8 nm respectively). Similar procedure was followed for all the drugs to determine their saturated solubilities at different pH of 1.2, 4, 5, 6.8, 7.4, and 8.

Partition coefficient

N-octanol was used to represent the biomembrane. The partition coefficients between n-octanol and water at 37ºC were determined by shake-flask method which was known in the literature to have been slightly modified to determine the partition coefficient of the drug. *n*-Octanol and water solution was co-saturated with each other for 24 h at 37 °C before use (Madhulatha, Ravikiran, 2013). To the pre-equilibrated water (10 mL), specified amount of drug (ibuprofen [400 mg], aceclofenac [500 mg], glipizide [200 mg], olanzapine [50 mg], telmisartan [100 mg,] and sildenafil citrate [5 mg]), was dissolved in aqueous solution. Ten milliliters of octanol was added to an equal volume of aqueous solution of the drug and kept for intermittent shaking for 3 h. The concentration of the drug in each phase was determined spectrophotometrically by measuring absorbance at their respective wavelengths in the aqueous phase.

Ex Vivo skin permeation studies

Preparation of rat abdominal skin

The experimental protocol was approved by the institutional animal ethical committee (IAEC) (ID number: PCE/ACE-6). Male Wistar rats (150-180 g) were used for the permeation study. The animal was sacrificed by excessive ether anesthesia and the hair was removed on abdomen using an animal hair clipper. Abdominal skin section was excised and observed for existence of cuts and wounds. The fat adhering on dermis was removed using scalpel and finally it was washed under tap water. The skin was stored at −20 °C and used within 48 h.

For the permeation studies, locally fabricated Franz diffusion cells with an area of 7.54 cm^2 and receptor volume of 25 mL were used. The receptor compartment was filled with 25mL of phosphate buffer solution with a pH of 7.4. The thawed rat skin was mounted onto the diffusion cell such that the dermis side was in constant contact with the receptor solution. Five milliliter's of saturated drug solution was poured onto the stratum corneum facing

the donor compartment and the hydrodynamics in the receptor compartment were maintained by stirring using a magnetic stirrer at 600 rpm. Two milliliters of sample was withdrawn at predetermined time intervals for 6 h and the drug content was analyzed using the UV-VIS double beam spectrophotometer at respective absorptive maxima of drugs (Prasanthi, Lakshmi, 2012).

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

The percentage of drug that was ionized or unionized at a particular pH was calculated using the Henderson–Hasselbach equation.

RESULTS AND DISCUSSION

The solubility, distribution coefficient, ionization, and skin permeability parameters at different pH of selected weakly acidic and weakly basic drugs are listed in Table I, II, III and IV, V, VI, respectively. As expected, the increase in pH showed an increase in the solubility of the drug and an in increase in the percentage of ionized drug. The distribution coefficient decreased with increase in the donor pH, inverse to the solubility. An inverse relation of solubility, distribution coefficient, and unionized form of the drug to variation in donor pH was seen in both weakly basic drugs and weakly acidic ones. Increase in pH led to decrease in solubility and percentage of unionized form of weakly basic drug and an increase in its distribution coefficient.

The effect of solubility and partition coefficient on skin permeability is a well-documented phenomenon. The selected weakly acidic drugs have shown compliant results, their respective skin permeability has shown an increase with increase in distribution coefficient (Figure 1) and a decrease with increase in solubility in selected pH range (Figure 2). The percentage of unionized drug in the donor compartment has also shown a remarkable effect on the skin permeability of the selected drugs. The increase in unionized form of the drug increased the permeability of the drug through the skin.

Permeation of the drug through skin and the pathway of permeation of acidic drugs is guided intensely by the pH of the systems. This effect of the pH system on permeation is individualized for each of the acidic drugs. (Katayama et al., 2001)

In the case of weakly basic drugs, a similar pattern of increase in distribution coefficient (Figure 3) and decrease in solubility had led to increase in skin permeability with increase in the donor pH (Figure 4). The increase in

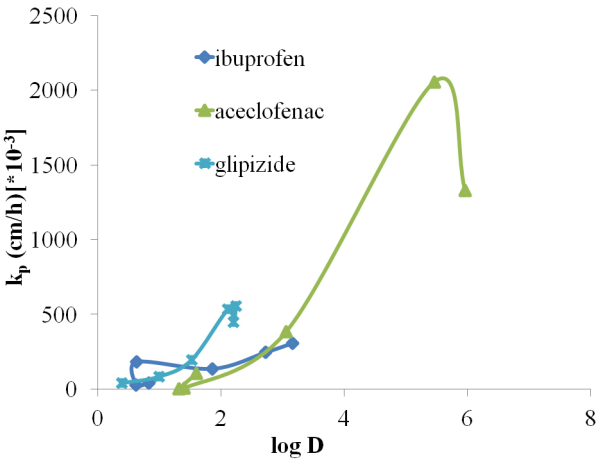

FIGURE 1 - log D vs. Kp of weakly acidic drugs.

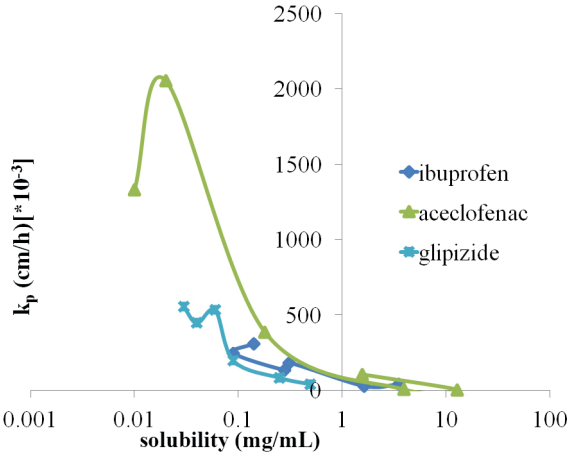

FIGURE 2 - Solubility vs. Kp of weakly acidic drugs.

unionized percentage of drug has markedly increased the skin permeability of the drug with variation in donor pH.

Effect of donor pH on weakly acidic drugs

The highest flux of ibuprofen was determined at pH 8 (Table I). The flux increased as the pH increased from pH 1.2 to pH 8. However, flux at pH 1.2 showed a higher value than at other acidic pH. A linear relationship ($y = 51.561x - 71.979$; $R^2 = 0.8948$) between the permeability coefficient and fraction of unionized ibuprofen suggests that diffusion was mostly as a result of partition and transfer of unionized ibuprofen present in the donor phase, and the significant intercept indicate that the contribution of ionized species was less. The permeability coefficient of ibuprofen increased with decrease in pH. The highest permeability coefficient was determined at pH 1.2 (Figure 5), when more than 95% of ibuprofen was unionized. It is interesting to note that the steady state

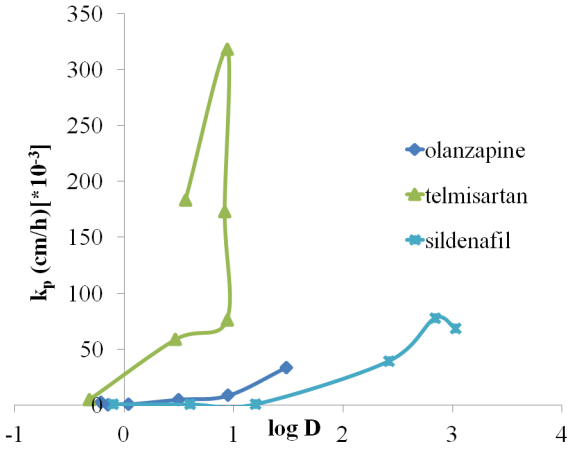

FIGURE 3 - log D vs. Kp of weakly basic drugs.

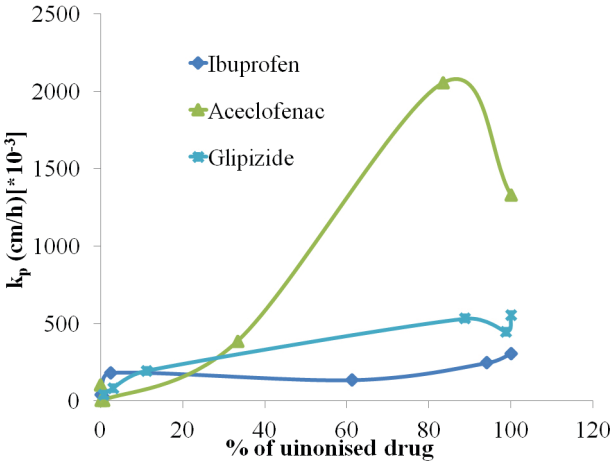

FIGURE 5 - % of unionized drug vs. Kp weakly acidic drugs.

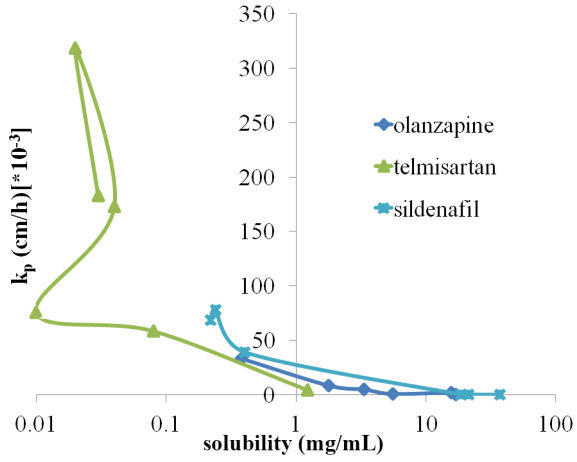

FIGURE 4 - Solubility vs. Kp of weakly basic drugs.

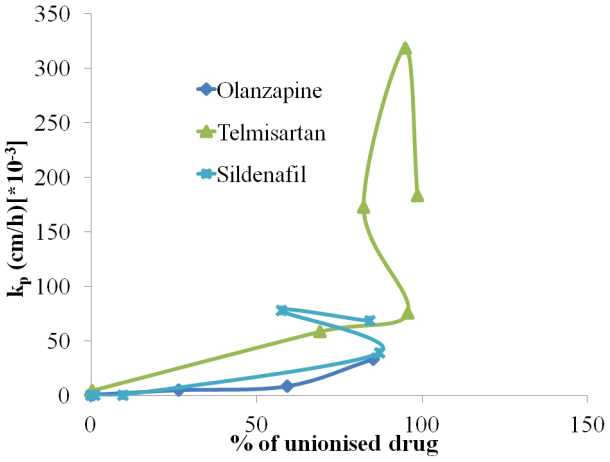

FIGURE 6 - % of unionized drug vs. Kp of weakly basic drugs.

flux of ibuprofen was greater at higher pH, whereas its permeability coefficient was higher at lower pH when the fraction of unionized species was greater. Previous studies have suggested that at higher pH the lower permeability of the ionized species is more than compensated for by the increased solubility (Rachel et al., 2013).

In the case of aceclofenac, flux at lower pH is dominated by ionized species. The highest flux was determined at pH 8 (Table II). The flux increased as the pH increased from pH 1.2 to pH 8. However, a variation in the increasing trend was noted at pH 6.8 and 7.4. A higher value of flux at pH 4(41.12 µg/cm^2/h) and 5 (69.46 µg/cm^2/h) compared to flux at pH 6.8 (20.06 µg/cm^2/h) and 7.4 (33.76 µg/cm^2/h) may be attributed to the pK_a (≈4.7) of

TABLE I - Solubility, distribution coefficient, Percentage of unionized drug and skin permeability parameters of ibuprofen

pH	Solubility (mg/mL)	log D	Percentage unionized	Flux	Kp (cm/h) [*10^{-3}]
1.2	0.14	3.16	99.99	43.11	307.91
4	0.09	2.72	94.06	22.15	246.12
5	0.28	1.86	61.31	37.9	135.37
6.8	0.31	0.63	2.45	56.56	182.46
7.4	1.63	0.62	0.63	46.19	28.34
8	3.51	0.83	0.16	139.18	39.65

aceclofenac. Unlike ibuprofen, flux and solubility of aceclofenac did not show a good correlation, even though solubility decreased from pH 7.4 to 8, the flux at pH 8 was found to be 163.74 μg/cm²/h whereas at pH 7.4 the flux was 33.76 μg/cm²/h.

A linear relationship ($y = 295.34x - 626.71$ $R^2 = 0.6111$) between the permeability coefficient and fraction unionized aceclofenac suggests that the diffusion was mostly a result of partition and transfer of unionized aceclofenac present in the donor phase, but on observation of partition coefficient 2055.85 (cm/h)[$*10^{-3}$] at pH 4 (> 80% unionized) and kp value 104.96 (cm/h)[$*10^{-3}$] at pH 8 it could be suggested that aceclofenac may have shown slight permeation of ionized species through pore pathway higher concentration. The permeability coefficient of aceclofenac increased with decrease in pH. The highest permeability coefficient was determined at pH 4 (Figure 5), when more than 80% of aceclofenac was unionized. Interestingly, the highest permeability coefficient was found to be at pH 4 coinciding with aceclofenac pKa value of ≈4.7. It is noted that the steady state flux of aceclofenac is greater at higher pH, whereas its permeability coefficient is higher at lower pH when the fraction of unionized species is greater. This suggests that at higher pH there is lower permeability of the ionized species. Dave et al. has reported a similar result, that raising pH of formulation from 6 to 8 decreased the apparent permeability coefficient (Dave, Paliwal, 2014).

The highest flux of glipizide was determined at pH 5 (Table III). The flux increased as the pH increased from pH 1.2 to pH 8 as a normal trend, with an exception of a sharp variation in the flux noted at pH 5 with a maximum flux of 31.94 μg/cm²/h which may be attributed to the pK_a (≈5.9) of glipizide. Unlike ibuprofen and aceclofenac, the flux and solubility of glipizide did not show a good correlation, even though solubility increased from pH 1.2 to 8, the flux did not correlate with the solubility. A linear relationship ($y = 104.53x - 153.1$; $R^2 = 0.8817$) between the permeability coefficient and fraction unionized glipizide suggests that the diffusion was mostly a result of partition and transfer of unionized glipizide present in the donor phase and the significant intercept indicates the less contribution of ionized species. The permeability coefficient of the ibuprofen increases with decrease in pH, with an exception of kp value 532.35 (cm/h)[$*10^{-3}$] that showed a slight increase in the trend may be due to pKa value glipizide being ≈5.9 The highest permeability coefficient was determined at pH 1.2 (Figure 5), when more than 99% of glipizide was unionized.

Effect of donor pH on weakly basic drugs

Olanzapine is a weakly basic drug, with an ideal log P of 2. In the case of olanzapine, flux at lower pH is dominated by the unionized species. The highest flux

TABLE II - Solubility, distribution coefficient, % of unionized drug and skin permeability parameters of Aceclofenac

pH	Solubility (mg/mL)	log D	Percentage unionized	Flux	Kp (cm/h) [$*10^{-3}$]
1.2	0.01	5.96	99.97	13.28	1328.2
4	0.02	5.46	83.37	41.12	2055.85
5	0.18	3.06	33.39	69.46	385.89
6.8	3.91	1.4	0.79	20.06	5.13
7.4	12.85	1.32	0.2	33.76	2.63
8	1.56	1.6	0.05	163.74	104.96

TABLE III - Solubility, distribution coefficient, percentage unionized, and skin permeability parameters of Glipizide

pH	Solubility (mg/mL)	log D	Percentage unionized	Flux	Kp (cm/h) [$*10^{-3}$]
1.2	0.03	2.24	100	16.67	555.5
4	0.04	2.2	98.76	17.88	446.9
5	0.06	2.11	88.82	31.94	532.35
6.8	0.09	1.52	11.18	17.62	195.77
7.4	0.25	0.99	3.07	20.89	83.57
8	0.49	0.39	0.79	20.14	41.09

was determined at pH 4 (Table IV). Though a clear trend of flux was not observed with pH, flux decreased as the pH increased from pH 6.8 to pH 8, with an exception at pH 4 where a sharp variation in the flux was noted with maximum flux reaching up to 35.78 µg/cm^2/h. Comparatively olanzapine has shown more flux at basic pH than at acidic one, though there was a decrease in solubility with increase in pH. A linear relationship ($y = 0.3121x - 0.4711$;$R^2 = 0.7985$) between the permeability coefficient and fraction unionized olanzapine suggests that the diffusion was mostly as a result of partition and transfer of unionized olanzapine present in the donor phase, and the insignificant intercept indicates the contribution of ionized species. The permeability coefficient of the olanzapine increases with increase in pH. The highest permeability coefficient was determined at pH 8 (Figure 6) when more than 85% of olanzapine is unionized. It is interesting to note that the steady state flux of olanzapine is greater at acidic pH of 4, whereas its permeability coefficient is higher at higher pH when the fraction of unionized species is greater. This suggests that at higher pH the permeability is also high despite a decrease in solubility. Chantasart et al., have reported similar results for the basic β blocker drugs (Chantasart, Hao, Li, 2013).

Telmisartan is a weakly basic drug, with a log P of 3.2. The highest flux was determined at pH 6.8 (Table V). Though a clear trend of flux was not observed with pH, flux decreased as the pH increased in acidic and basic pH regions, from pH 1.2 to pH 5 and pH 6.8 to pH 8, in addition a noted variation of increased flux at pH 6.8 was seen which showed a maximum flux of 6.91 **µg/cm**^{2}/h which may be attributed to the Pka value 6 of the drug. Similar to olanzapine, telmisartan has shown more flux at basic pH's than at acidic ones, interpreting an inverse relation with solubility. A linear relationship ($y = 1.993x - 10.997$; $R^2 = 0.4393$) between the permeability coefficient and fraction unionized telmisartan suggests that the diffusion was mostly a result of partition and transfer of unionized telmisartan present in the donor phase. The permeability coefficient of the telmisartan increases with increase in pH, with a decrease at pH 8, which may be due to decrease of distribution coefficient from pH 7.4 to 8. The highest permeability coefficient was determined at pH 7.4 (Figure 6), when more than 90% of telmisartan is unionized. It is interesting to note that the steady state flux of telmisartan is greater at pH 6.8, unlike its permeability coefficient.

Sildenafil citrate is a weakly basic drug, with a log P of 2.7. The highest flux was determined at pH 1.2 (Table VI). Though a clear trend of flux was not observed with pH, flux increased as the pH increased from pH 4 to pH 7.4 whereas a noted variation of decrease in flux at pH 8 from pH 7.4 may be attributed to the Pka value 7.2 of the drug. Similar to olanzapine, telmisartan has shown more flux at basic pH's than acidic ones, with an exception of highest

TABLE IV - Solubility, distribution coefficient, percentage unionized, and skin permeability parameters of olanzapine

pH	Solubility (mg/mL)	log D	Percentage unionized	Flux	Kp (cm/h) [*10^{-3}]
1.2	16.91	−0.15	0	6.77	0.4
4	15.7	−0.21	0.06	35.78	2.28
5	5.55	0.04	0.57	5.09	0.92
6.8	3.35	0.5	26.47	16.75	5
7.4	1.79	0.95	59.18	15.35	8.57
8	0.38	1.48	85.19	12.74	33.52

TABLE V - Solubility, distribution coefficient, percentage unionized, and skin permeability parameters of telmisartan

pH	Solubility (mg/mL)	log D	Percentage unionized	Flux	Kp (cm/h) [*10^{-3}]
1.2	1.23	−0.32	0.35	5.76	4.69
4	0.08	0.47	69.14	4.69	58.62
5	0.01	0.94	95.72	4.56	75.94
6.8	0.04	0.92	82.39	6.91	172.72
7.4	0.02	0.94	94.9	6.36	318.19
8	0.03	0.56	98.67	5.49	183.09

flux (19.04 (μg/cm^2/h) at a pH 1.2 that could be possibly due to its higher solubility (37.25 mg/mL) at that pH. A linear relationship ($y = 0.7275x + 2.1975$; $R^2 = 0.6993$) between permeability coefficient and fraction unionized sildenafil suggests that diffusion was mostly a result of partition and transfer of unionized sildenafil citrate present in the donor phase and also passive transport of ionized species by paracellular route. The permeability coefficient of the sildenafil citrate increases with increase in pH, with the highest permeability coefficient determined at pH 7.4 (Figure 6), where sildenafil citrate is nearly 57% unionized, suggesting the contribution of both ionized and unionized species for the total permeation of the drug. Unlike olanzapine and telmisartan, both maximum flux and permeability coefficient for sildenafil citrate was found at the same pH 7.4. Jiahorng Liaw *et al.* (2001) reported that the permeability coefficients of sildenafil changed with pH, and the higher permeation rates fell in the pH range of 8–11. This is because major nonionized form of sildenafil has higher permeation due to increasing partition coefficient of sildenafil in mouse skin above pH 7.0 (Liaw, Chang, 2001).

Prediction of the dermal route of penetration of the drug

The drugs are mostly weakly acidic and basic in nature, hence they show a pH−dependent solubility and dermal permeation. It is established that if the drug species is transported via paracellular route, the permeability of the drug should be independent of partition coefficient. Conversely, if the drug is transported via the transcellular route, the permeability of the drug should vary with the partition coefficient. Thus, the pH dependence of the permeation of ionizable drugs actually reflects the drug penetration route, because the partition coefficient of ionizable drugs is pH dependent. If a drug is transported via the transcellular route, the drug absorption rate is also pH dependent (Panigrahi, Pattnaik, Ghosal, 2005).

The acidic drugs ibuprofen, aceclofenac, and glipizide have shown a proportional permeation with diffusion coefficient (ie, pH-dependent permeation) and also the permeation increased with increase in the fraction of unionized species indicating that unionized species have shown more permeation and the transcellular route of permeation was dominant for the above weakly acidic drugs.

In case of weakly basic drugs, olanzapine and telmisartan have shown a pH-dependent permeation that vary with partition coefficient. These drugs have also shown increase in permeation with increase in fraction of unionized species indicating the dominance of transport of these species (Table VII). Hence, it can be concluded that the permeation of these drugs is dominated by the transcellular route.

TABLE VII - Preferred route of drug permeation

Drug	Percentage unionized	Kp (cm/h) [*10^{-3}]	Predominated route of transport
Ibuprofen	99.99	307.91	Transcellular
Aceclofenac	83.37	1328.20	Transcellular
Glipizide	99.99	555.5	Transcellular
Olanzapine	85.19	33.52	Transcellular
Telmisartan	98.67	75.13	Transcellular
Sildenafil Citrate	57.44	77.91	Both transcellular and paracellular

TABLE VI - Solubility, distribution coefficient, % unionized and Skin permeability parameters of sildenadil citrate

pH	Solubility (mg/mL)	log D	Percentage unionized	Flux	Kp (cm/h) [*10^{-3}]
1.2	37.25	−0.1	0	19.04	0.51
4	21.19	0.6	1.06	10.78	0.508
5	18.53	1.2	9.67	12.69	0.685
6.8	0.4	2.42	87.11	15.78	39.45
7.4	0.24	2.84	57.45	18.7	77.92
8	0.22	3.03	84.3	15.05	68.41

Sildenafil citrate, a weakly basic salt form, though has shown permeation dependent on pH and partition coefficient, interestingly has a high permeation value which was obtained at pH 7.4 where 57% of the drug was unionized reflecting that both ionized and unionized species have participated in dermal permeation. Hence it can be concluded that the transport of sildenafil citrate is by both paracellular and transcellular route.

CONCLUSION

The ex vivo permeation studies at different pH conditions for the selected drugs have shown a pH-dependent permeability. The selected weakly acidic and basic drugs have shown good correlation of solubility, distribution coefficient to the skin permeability. They also showed an increase in permeation with increase in the fraction of unionized species indicating dominance of transcellular route of permeation. With an exception, sildenafil citrate, a weakly basic salt form has shown high permeation value at pH 7.4 where 57% of the drug is unionized, indicating the significance of both paracellular and transcellular route in it's permeation.

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