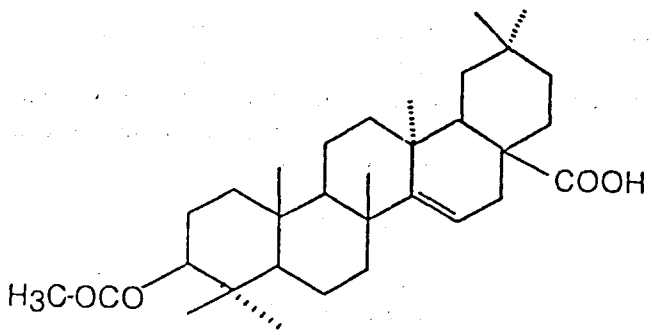

(I)

the effect on prothrombin time[3] and on six bacteria and four fungi. The antibacterial activity was carried out by disc diffusion method[4] and antifungal activity by cup-plate method[5]. In the former study, the compound showed a concentration-dependent increase in prothrombin time compared to aspirin (Table 1). In the antimicrobial study, it exhibited mild antibacterial activity against *Klebsiella pneumoniae* and mild antifungal activity against *Candida albicans* and *Aspergillus niger* while no inhibition against other microbes was observed in the concentrations studied (Table 2). Minimum inhibitory concentration was studied by double dilution method.[5]

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Enhanced Transdermal Permeation of Bupropion Hydrochloride by Chemical Modification

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Bupropion, a monocyclic aminoketone is used primarily for the treatment of major depression. On oral administration, the drug undergoes extensive first pass metabolism. Delivery of bupropion via transdermal route would minimize some of the deficiencies associated with the oral delivery. In the present study, effect of various vehicles and penetration enhancers on diffusion kinetics of the salt and free drug through the human cadaver skin was studied using a modified diffusion

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cell. The diffused drug was quantified by UV spectrophotometry at 298 nm in phosphate buffer saline. A 100-fold increase in permeability rate was observed with free base compared to salt form. As a vehicle, alcohol was found to be superior compared to phosphate buffer saline and propylene glycol in permeation of free base. Permeation was enhanced by up to 30 % with linseed oil and myristic acid when propylene glycol was used as a vehicle. The study provides suitable clues for delivery of bupropion by the transdermal route.

Bupropion hydrochloride is an aminoketone class of antidepressant used to treat bipolar depression, chronic fatigue syndrome and cocaine craving. It also helps to quit smoking and to reduce lower back pain[1]. The drug undergoes extensive first pass metabolism resulting in poor bioavailability. Several of the known metabolites of bupropion are pharmacologically active and are reported to be fatal on accumulation[2-3]. The drug is administered orally, maximum up to 300 mg per day in divided doses, generally with gradual escalation of dose in a manner most likely to minimize the risk of seizure. If it is possible to deliver the drug through the transdermal route, some of the side effects associated with the oral delivery could be minimized. Transdermal drug delivery system of bupropion avoids increased formation of unwanted or adverse metabolites produced by gastrointestinal tract and liver.

Transdermal drug delivery system has its own challenges, attributed mainly to the properties of the stratum corneum. The fatty nature of the stratum corneum imparts considerable hydrophobicity to the skin, which in turn influences the diffusivity of drug molecules. Poor diffusivity has been reported for salts of various drug molecules[4-6]. The physicochemical properties of the drug in combination with the drug delivery system needs to be exploited to ensure that the medicament is delivered at the desired rate.

Present work establishes the epidermal permeation of bupropion, both as a mineral acid salt and its free base. Further effect of water miscible and hydrophobic vehicles on permeability of bupropion through human cadaver skin with and without penetration enhancers was evaluated in modified diffusion cell.

Bupropion Hydrochloride was received from Sun Pharmaceuticals, Vadodara. Propylene glycol (PG) and myristic acid (MA) were received from Merck India, Mumbai. Alcohol was received from Baroda Chemicals, Vadodara. Dimethylsulphoxide (S. D. Fine Chemicals, Mumbai), polysorbate 80 (ICI India, Mumbai) and linseed oil (Krishna Chemicals, Ahmedabad) were used as received. All other chemicals used were of analytical grade.

Free bupropion base (BP) can be prepared by chemical treatment and solvent extraction. Five grams bupropion HCl was dissolved in 20 ml of distilled water and basified to pH 10 with slow addition of dilute ammonia. The liberated free base was extracted into chloroform, which was dried over anhydrous potassium carbonate and evaporated at 40° under vacuum to get the oily free base. The base so prepared was stored under nitrogen gas at 2 to 8°.

Diffusion cell described by Zuber *et al*[7] was used in the present study with minor modifications (Side screen of the basket dissolution test apparatus was covered with aluminum foil. Skin was mounted inside the basket on the bottom screen and samples to be tested were applied on the skin. The entire assembly was half dipped in the agitated receptor fluid). A 3.14 sq. cm area human cadaver skin (thickness 0.2±0.03 cm) was mounted in the assembly and the drug solution (in phosphate buffer saline or propylene glycol or alcohol) equivalent to 100 mg bupropion was placed on the skin. Receiver compartment was filled with 100 ml phosphate buffered saline (PBS), pH 7.4. The temperature of the receptor fluid was maintained at 37±0.5°. The content of the receiver compartment was stirred with a Teflon coated magnetic bar at 100 rpm. Samples from the receiver compartment were withdrawn at regular time intervals and analyzed for bupropion by UV spectrophotometer at 298 nm.

Partition coefficient of bupropion from the control and modified solutions in stratum corneum was determined by modifying the method described by Singh *et al*[8]. Entire human skin was used instead of the pulverized stratum corneum so as to mimic the actual condition exerted during the percutaneous penetration study. Sample solutions in various solvents with known concentration of drug were placed on the 3.14 sq. cm area of the skin and allowed to equilibrate for 6 h at 37°. After 6 h of contact time, the extra solution was scraped and analyzed for the drug content. Amount of the bupropion partitioning in the skin was determined by subtracting the amount of drug in sample from the total amount of the drug in the solution at initial time.

The cumulative amount of bupropion permeated per unit

surface area of skin was plotted against time, and the slope of the linear portion of the plot was estimated as the steady state flux (Jss). The permeability coefficient (P) and permeability rate (P') were calculated as[9] P=Jss/C.. (i) and p=Jss.h.. (ii), where C is the donor phase concentration of the bupropion sample, h is the thickness of the membrane. The permeability enhancement ratio (ER_p) due to the presence of the penetration enhancer was calculated as[8] ER_p= permeability of bupropion with enhancer/permeability of bupropion with out enhancer..(iii).

Permeability coefficient can also be expressed as P=KD/h...(iv), where K is the partition coefficient, D is the diffusion coefficient and h is the thickness of the skin. The enhancement ratio of the diffusion coefficients (ER_{dc}) can be expressed as[8] $ER_{dc} = D_{treatment}/D_{control}$....(v). The lag time ($T_L$) to reach steady state can be calculated as $T_L=h^2/6D$...(vi). The partition coefficient (K) was calculated as partition coefficient (K)= amount of bupropion in the skin/amount in the sample...(vii).

The penetration of bupropion hydrochloride (BP HCl) was found to be poor through human cadaver skin. The epidermal flux of BP HCl was 0.03 mg/cm^2 h compared to 3.05 mg/cm^2 h of free bupropion base. Conversion of the salt to free base increases the lipophilicity of the molecule, which leads to enhanced permeability rate. In the present study, permeability rates of bupropion salt and free base through skin were observed to be $0.6x10^{-2}$ and $58.x10^{-2}$ mg/cm.h. The permeability rate of the free base was 96.6 times more than that of the salt (ERp, 96.6). Partition coefficient of salt form and free base further support the above results. Partition coefficients of BP salt form and free base were found to be 32 and 98.7, respectively in skin. Results in Table 1 indicate that free base has greater partitioning towards lipophilic skin compared to salt form.

Effect of various vehicles on diffusion kinetics of the salt and free base was studied. The epidermal flux values of bupropion free base in PBS, PG and alcohol were 3.05, 4.06 and 5.79 mg/cm^2 h respectively, while permeability rates were $58x10^{-2}$, $85.3x10^{-2}$ and $98.4x10^{-2}$ mg/cm.h respectively. Partition coefficient values with PBS, PG and alcohol were 98.7, 127.9 and 173.7, respectively. Alcohol shows maximum permeability rate compared to other vehicles tested (fig. 1). These results suggest that vehicle has definite effect on the

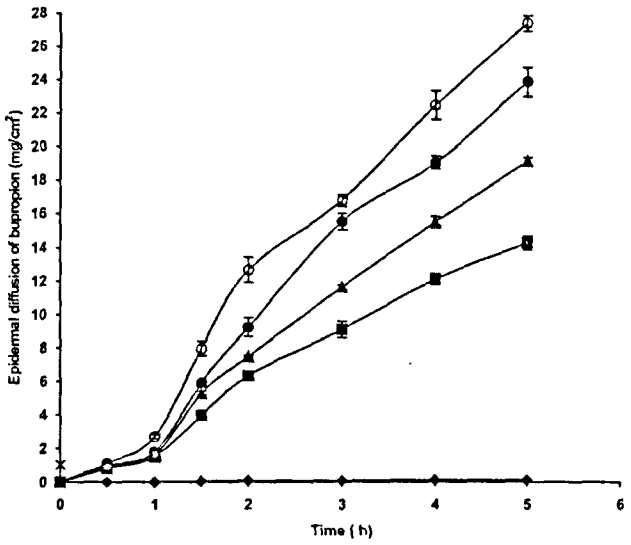

Fig. 1: Comparative epidermal diffusion profile of bupropion through human cadaver skin.

Bupropion HCl in PBS (–♦–), Bupropion free base in PBS (–▫–), Bupropion free base in PG (–▲–), Bupropion free base in Alcohol (–○–), Bupropion free base in PG-MA (–●–), (n=6).

TABLE 1: DIFFUSION KINETIC PARAMETERS OF BUPROPION SALT AND FREE BASE THROUGH HUMAN SKIN.

Treatment	Jss	P x 10^{-3}	P' x 10^{-2}	K	ERp	ERdc
BP HCl in PBS	0.03	0.3	0.6	32	-	-
BP in PBS	3.05	30.5	57.95	98.7	96.6	31.3
BP in PG	4.06	40.6	85.26	127.6	142.1	35.6
BP in alcohol	5.79	57.9	98.43	173.7	164.1	30.2

Thickness of the human cadaver skin used in study (h) is 0.2±0.03 cm, amount of drug in donor compartment is100 mg. BP HCl, Bupropion Hydrochloride; PG, propylene glycol; Jss, Steady state flux (mg/cm^{2}h); P, Permeability coefficient (cm/h); P', Permeability rate (mg/cm.h); K, Partition coefficient; ERp, Permeability ratio enhancement; ERdc, Diffusion ratio enhancement.

TABLE 2: EFFECT OF PENETRATION ENHANCERS ON EPIDERMAL FLUX OF BUPROPION FREE BASE IN THE PRESENCE OF PROPYLENE GLYCOL.

Penetration enhancer	Concentration	Jss	P x 10^{-3}	P' x 10^{-2}
Dimethyl Sulfoxide	10 % w/w	4.1	41.0	73.8
Polysorbate 80	10 % w/w	3.89	38.9	77.8
Linseed oil	10 % w/w	5.21	52.1	114.6
Myristic acid	10 % w/w	5.14	51.4	118.2

Thickness of the human cadaver skin used in study (h) is 0.2±0.03 mm, amount of drug in donor compartment is 100 mg, Jss, Steady state flux (mg/cm^{2}h); P, Permeability coefficient (cm/h); P', Permeability rate (mg/cmh).

epidermal diffusion kinetics of bupropion free base. The observed change in the epidermal flux in different solvents/ vehicles may be because of differences in thermodynamic activity and solubility of the bupropion. Solubility of bupropion free base was found to be 10, 200 and 348 mg/ml in phosphate buffer saline, propylene glycol and alcohol respectively. Increased solubility of the drug molecules increases the thermodynamic activity of the drug in that vehicle and hence, facilitates the mobility of the lipophilic drug towards non-polar phase[10-13].

The partition coefficient value is an index of the relative affinity of the drug to the vehicle and the skin. It plays significant role in establishing the flux particularly when the membrane provides the sole or the major source of diffusional barrier. The predicted log partition coefficient for bupropion free base for stratum corneum/phosphate buffer saline pH 7.4 is 2.6 while observed value for the same was 2.4, which shows relative affinity of bupropion for stratum corneum. These values changed with change in the pH of the aqueous medium.

Four different penetration enhancers dimethylsulfoxide (DMSO), polysorbate 80, linseed oil and myristic acid (MA) were tried. It was observed that fatty acids and fatty oil along with propylene glycol exhibited good penetration enhancing effect. No significant improvement was noticed in diffusion kinetic parameters with DMSO and polysorbate 80 as penetration enhancers ($P<0.05$). Linseed oil and myristic acid, when incorporated along with PG showed significant enhancement in epidermal flux, permeability rate and partitioning in skin (Table 2). Because of their lipophilic nature, these penetration enhancers may partition into skin and interact with its constituents. These enhancers are known to reducing the resistance of the skin to drug diffusion.[14,15]

From the above study it can be concluded that permeability of the poorly permeable drug molecule bupropion hydrochloride can be increased by chemically modifying it in to non polar free base. Various vehicles have shown significant effect on epidermal flux of bupropion. The results suggest that fatty acid as penetration enhancer is more effective in the presence of propylene glycol in comparison to other enhancers studied. Present work can be exploited for the fabrication of a controlled release transdermal drug delivery system of bupropion base.

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