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Studies in Formulation and Pharmacotechnical Evaluation of Controlled Release Transdermal Delivery System of Bupropion

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ABSTRACT

The objective of the present study was to design and evaluate unilaminate transdermal adhesive matrix systems capable of diffusing bupropion base at a constant rate over an extended period of time as an alternative route of administration. Unilaminate transdermal adhesive matrices have been fabricated with different concentrations of Eudragit E as the adhesive and rate-controlling polymer. The in vitro release and epidermal flux through human cadaver skin were studied. The release of drug from the matrices obeyed zero order release kinetics (r^2= 0.9810 to 0.9960). The delivery rate of bupropion ranged from 10.5 mg to 31.4 mg per day from a 3.14 cm^2 area of matrix. The relation between concentration of bupropion base in matrix and epidermal flux, concentration of drug in matrix, and epidermal adsorption of bupropion during diffusion follow hyperbolic fashion. Triethylcitrate (TEC) and dibutylphthalate (DBP) have no influence on the diffusion of bupropion through human cadaver skin when used as plasticizers. Incorporation of succinic acid in the adhesive matrix retarded diffusion due to the formation of rigid cross linking of the polymer, while propylene glycol and myristic acid, alone or in combination, significantly enhanced the flux of bupropion through human cadaver skin.

KEYWORDS: unilaminate transdermal adhesive matrix, bupropion free base, in vitro release study, epidermal flux, plasticizers, release modifiers

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INTRODUCTION

Bupropion hydrochloride is an antidepressant drug belonging to the aminoketone class and is widely used for the treatment of minimal brain dysfunction, tardive dyskinesia, impaired mental alertness (on ingestion of ethanol), and psychosexual dysfunction. An advantage of bupropion hydrochloride is that it does not cause the functional impairment and drowsiness associated with the administration of benzodiazepine.[1]

Typically the drug is administered orally in the form of immediate release and sustained release tablets. Bupropion hydrochloride has some shortcomings, especially when administered orally. It undergoes extensive first-pass metabolism resulting in poor bioavailability and also in accumulation of fatal metabolites (erythroamino alcohol and hydroxy metabolites) in the liver. To address the dose-related risk of seizures associated with high peak concentration of the drug following oral administration, bupropion hydrochloride is administered in divided doses. In chronic cases, tablets are given thrice daily.[2,3]

Rate-controlling transdermal delivery systems have been successfully developed to deliver various drugs via skin into the systemic circulation with considerable biomedical benefits.[4-6] Some of the systems have used release modifiers to achieve desired therapeutic plasma levels of the drug.[7-9]

Controlled delivery of bupropion free base (BP) through the skin would prevent first-pass metabolism of the drug and thus reduce the accumulation of fatal metabolites in the liver. Additionally, it would be possible to reduce the dosing frequency and eliminate peak plasma levels of the drug if the system is able to deliver the drug at a constant rate for an extended period of time.

A unilaminate transdermal adhesive matrix system of bupropion base consisting of Eudragit E 100 and dif-

Table 1. Composition of Bupropion Transdermal Adhesive Matrix

Ingredients	Matrix I	Matrix II	Matrix III	Matrix IV	Matrix V	Matrix VI
Bupropion (mg/cm^2)	30	30	30	30	30	30
Eudragit E 100 (mg/cm^2)	130	110	90	75	60	50
Triethylcitrate (mg/cm^2)	13	11	9	7.5	6	5
Acetone:IPA:Alcohol	50:30:20	50:30:20	50:30:20	50:30:20	50:30:20	50:30:20
% wt/wt BP/cm^2(C_0)	17.3	19.9	23.3	26.7	31.3	35.3
% wt/wt Eudragit E 100	75.2	72.9	69.8	66.7	62.5	58.8
Thickness of unilaminate (mm)	0.17	0.17	0.16	0.15	0.14	0.14

ferent plasticizers/release modifiers was designed to provide a constant amount of BP for an extended period of time. The system was evaluated to understand the effect of different plasticizers and release modifiers on the diffusion kinetics of the drug release using human cadaver skin.

MATERIALS AND METHODS

Materials

Bupropion hydrochloride was obtained from Sun Pharmaceuticals, Baroda, India. Eudragit E 100 was received from Rhom, Kirchenalle, Darmstadt, Germany. Propylene glycol (PG), myristic acid (MA), and succinic acid were received from S. D. Fine Chemicals, Mumbai, India. Alcohol was received from Baroda Chemicals, Baroda India. Acetone, isopropyl alcohol, and other chemicals used were of analytical grade. CoTran™ polyethylene backing membrane and Scotchpack™ release liner were received from 3M Delivery Systems, Tokyo, Japan.

Preparation of Free Bupropion Base

BP can be prepared by chemical treatment and solvent extraction. A 5.0-g sample of bupropion HCl was dissolved in 20 mL 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°C under vacuum to get oily free base. The base so prepared was stored under nitrogen gas at 2 to 8°C.

Preparation of Bupropion Transdermal Adhesive Matrix

The unilaminate transdermal adhesive matrix was prepared by casting method. Eudragit E 100 was dissolved in a mixture of acetone, isopropyl alcohol, and ethanol (50:30:20) with continuous stirring at 25°C in a closed system. Triethylcitrate (TEC) or dibutylphthalate (DBP) was added followed by the addition of propylene glycol/myristic acid/propylene glycol and myristic acid/succinic acid with continuous stirring. BP was added to the solution of the adhesive matrix. The solution was poured onto the backing membrane. The solvent was allowed to evaporate at room temperature overnight to form dry adhesive matrix. Six formulations were prepared with different polymer concentrations for formulation I to VI (**Table 1**). A 30-mg amount of BP per cm^2 adhesive matrix was incorporated.

In Vitro Diffusion Study

A Franz diffusion cell was used for drug release study from the adhesive matrix. Phosphate buffered saline (PBS; 20 mL, pH 7.4) was used as the receptor fluid. The receptor fluid was agitated at 100 rpm by a teflon-coated magnetic stirrer. A 3.14 cm^2 section of whole human skin (thickness, 0.2 ± 0.03 cm) was mounted on the cell with the stratum corneum facing the donor phase. The adhesive matrix was placed on the skin and the cell maintained at 37 ± 0.5°C during the drug release study. Samples were collected from the sampling port at every hour and analyzed at 298 nm using a UV/VIS spectrophotometer (Shimadzu, Kyoto, Japan). An in vitro release study was also car-

Table 2. Diffusion Kinetic Parameters of Bupropion Adhesive Matrices

Parameter	Matrix I	Matrix II	Matrix III	Matrix IV	Matrix V	Matrix VI
In-vitro release rate ($Q/T^{1/2}$ ($mg/cm^2/h^{1/2}$))	1.402 (± 0.12)	1.785 (± 0.17)	2.025 (±0.21)	2.194 (±0.22)	2.448 (±0.22)	2.866 (±0.31)
Epidermal flux (Jss, $\mu g/cm^{-2}/h^{-1}$)	139.5 (±11.5)	192.0 (±19.1)	275.7 (±31.7)	309.7 (±34.4)	362.3 (±27.8)	417.1 (±42.3)
Cs mg/cm^3	4.30±0.5	6.61±1.2	8.40±0.9	9.78±1.6	10.6±1.7	10.8±1.2
Delivery rate ($mg/3.14\ cm^2$/ day)	9.5	13.9	22.5	24.1	28.3	35.4
($mg/12.5\ cm^2$/ day)	41.2	60.3	80.7	95.1	104.6	130.1
r^2 (Zero order kinetic)	0.9960	0.9876	0.9810	0.9930	0.9914	0.9912
Release rate constant (k)	0.14	0.20	0.27	0.31	0.37	0.42
Thickness of skin (cm)	0.21	0.20	0.17	0.17	0.22	0.22

ried out similarly by omitting skin. For 12.56 cm^2 area patches, a Franz diffusion cell with 50-mL capacity was used.

RESULTS AND DISCUSSION

Conversion of hydrochloride salt to free base increases the lipophilicity of the permeant molecules. The reported value of the logP of bupropion free base is 3.21 and its pKa is 7.9, which indicates the relative affinity of the free bupropion base toward the nonpolar phase. Polar nature and low skin permeability of the hydrochloride salt make it unsuitable for transdermal application. Because of high permeability, favorable logP value, and greater pKa, free base was selected for the development of transdermal adhesive matrix of bupropion. PBS (pH 7.4, 20 mL) was used as the receptor fluid as it simulates the physiologic condition of the mammalian skin. The solubility of the BP free base is 10 mg/mL at 25°C in PBS, which is just sufficient to provide sink effect during in vitro diffusion study.

Effect of Polymer Concentration on Epidermal Flux

Different unilaminate transdermal adhesive matrices of bupropion were prepared by varying the concentration of Eudragit E 100 from 75.2% to 58.5% wt/wt. Triethylcitrate at 10% wt/wt of polymer was added in each matrix. In vitro drug release study was carried out with and without skin with all 6 matrices. The release rates of the bupropion from the diffusional formulations containing Eudragit E 100 as the adhesive and rate-controlling polymer and TEC as the plasticizer (formulation I to VI) were observed to follow zero order release kinetics over an extended period of time. These release data were obtained by plotting the amount of bupropion released per cm^2 against time. The data revealed that an increase in Eudragit E 100 concentration from 58.8% to 75.2% wt/wt in the formulation, decreased the release of bupropion from the adhesive matrix (**Table 2**). The percutaneous release profiles of bupropion from matrix I to VI are shown in **Figure 1**. Eudragit E 100 is cationic and insoluble in the entire physiological pH range. This polymer possesses a defined swelling capacity and permeability with respect to water and dissolved drug.[10] The predominant release mechanism through this polymer is believed to be diffusion.[11]

A hyperbolic relationship was observed between flux (Jss, across the human cadaver skin) and concentration (C_0 % wt/wt) of the drug in the adhesive matrix (**Figure 2**). The epidermal flux increased linearly with increase in concentration of bupropion from 17.3% to 23.3% wt/wt. Further increase in the drug concentration (26.7% to 35.3% wt/wt) did not show a proportional increase in the epidermal flux. A steady state concentration is established in human skin at low

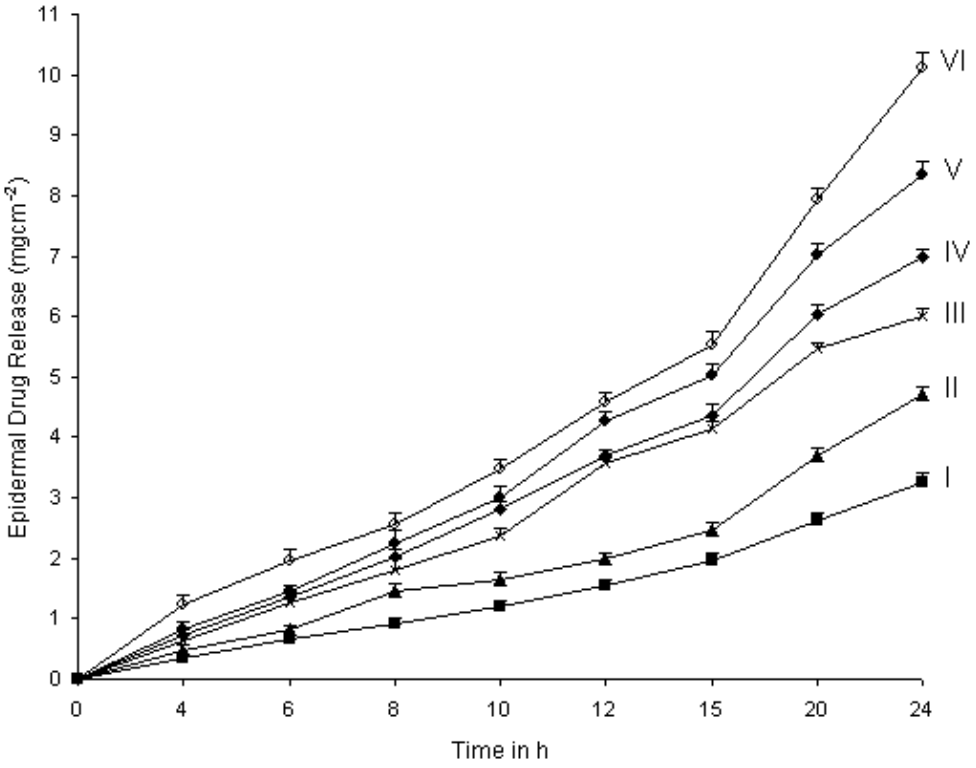

Figure 1. Epidermal flux of bupropion through human cadaver skin from unilaminate adhesive patches of the different formulations.

concentration of the permeant molecules because of the heterogeneous barrier structure of the skin. But at the terminal phase of the curve (high concentration of the permeant molecules), skin partially becomes saturated with adsorption of drug molecules and a proportional rise in epidermal flux was not observed.

Similarly, hyperbolic relation was observed between the epidermal flux of bupropion and the amount of the bupropion adsorbed during the diffusion (**Figure 3**). Amount of the drug adsorbed in the skin (Cs) was calculated from the values of Jss, Initial concentration of the drug (C_0), thickness of the skin and initial lag time by following equation:

$$Jss = \frac{Ks \times Ds}{h} = Cs \qquad (1)$$

where Jss is the epidermal flux, Ds is the diffusion coefficient, Ks is the partition coefficient, T_L is the lag time and h is the thickness of the skin used.

Results revealed that as the concentration of bupropion increased from 17.3% wt/wt to 35.3% wt/wt in the matrix, drug diffusion increased proportionally. Concentration gradient across the skin is increased with increased in the C_0. Simultaneously, the amount of drug adsorbed in the skin increased from 4.3 mg/cm^3 to 10.8 mg/cm^3. The profile shows that at a higher concentration of bupropion in the matrix, a plateau region was observed at which there was no further increase in epidermal adsorption of bupropion. Beyond a 26.7% wt/wt concentration of BP in the matrix, the epidermis partially gets saturated. With a further increase in the concentration of bupropion (31.3% and 35.3% wt/wt), the skin became saturated with permeant molecules. At this saturated phase, known as the plateau region, mass balance was observed between epidermal flux and amount diffused. Thus, by increasing the concentration of permeant molecules in the system, the epidermal flux increased in hyperbolic fashion and finally reached plateau level.

In the case of the in vitro drug release study (performed by omitting skin), $Q/T^{1/2}$ increased proportionally with an increase in the % wt/wt concentration of bupropion in the matrix. In vitro release study profiles of unilaminate explain by Higuchi equation of release kinetics as at the terminal phase of the release

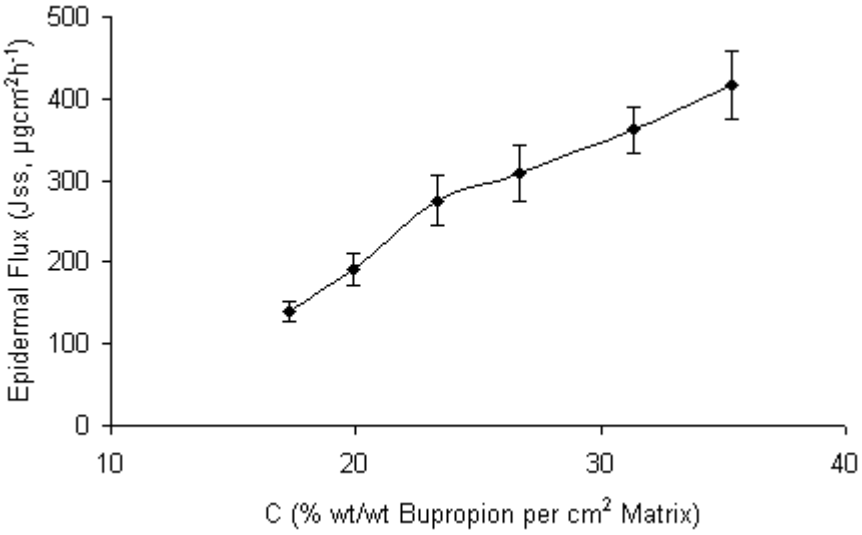

Figure 2. Effect of bupropion concentration (C_0, % wt/wt) in adhesive matrix on the epidermal flux of bupropion (Jss) through human cadaver skin.

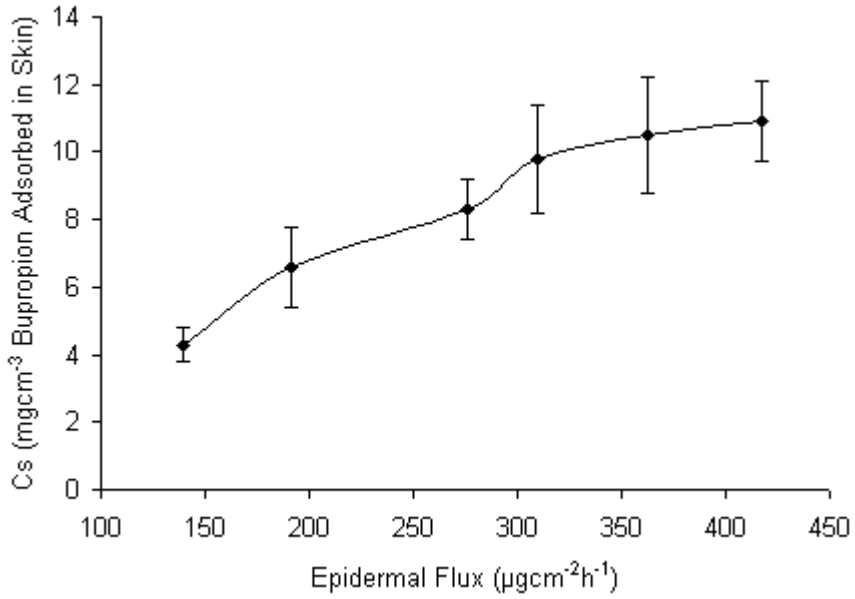

Figure 3. Hyperbolic relationship of amount of drug adsorbed (Cs, mg/cm^3) in human skin with epidermal flux (Jss).

study concentration gradient across the matrix decreased. In vitro drug release rate ($Q/T^{1/2}$) is higher than in vitro permeation rate (Jss) for each matrix. Higher amount of drug is available at permeation interface than skin uptake. This result shows that human skin acts as a barrier in epidermal drug release. A hyperbolic plot is obtained with an in vitro release study and epidermal flux across the human cadaver skin (**Figure 4**). At the initial phase of the hyperbolic curve, the system is rate controlling and at the plateau phase the stratum corneum became the rate-controlling factor.

The release behavior of bupropion from unilaminate adhesive matrices shows that all 6 formulations follow zero order drug release kinetics with r^2 values of

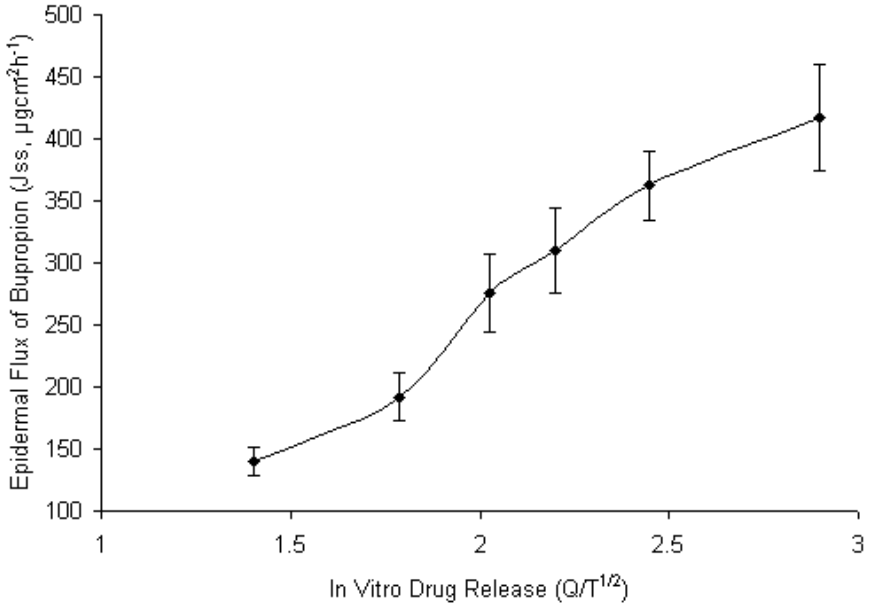

Figure 4. Hyperbolic relationship of in vitro drug release ($Q/T^{1/2}$) and epidermal flux of bupropion (Jss) across the human cadaver skin.

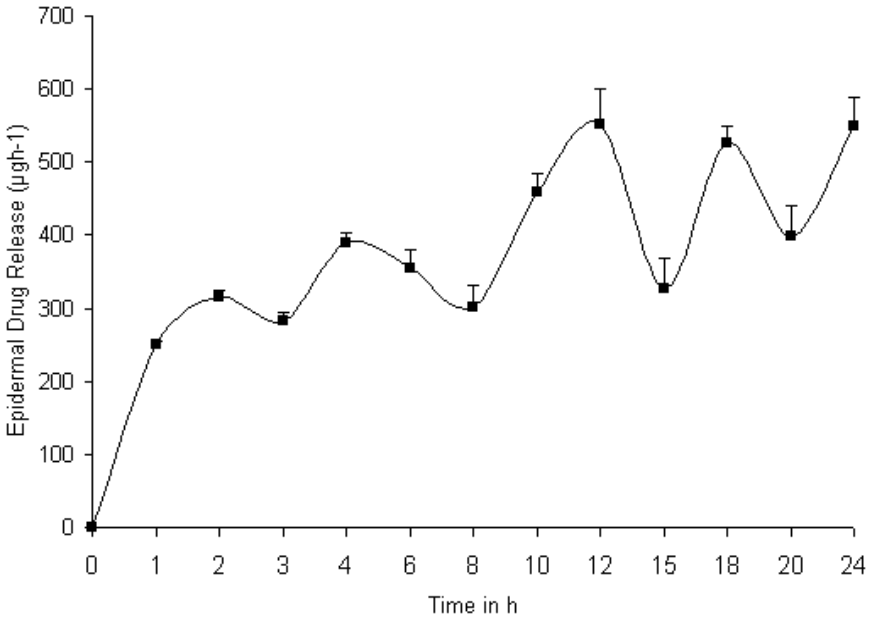

Figure 5. Epidermal drug release of bupropion per hour from the adhesive matrix (I) through human skin under simulated condition (PBS as the receptor fluid).

0.9810 to 0.9960 (**Table 2**). Drug release efficiency of the matrix depends largely on the concentration of drug and polymer. Selection of optimized concentration of drug or polymer led to a constant drug release system of required concentration. In the present study, all 6 formulations (matrix I to VI) were shown to release bupropion at a constant rate from a constant area per day. The epidermal release rate of bupropion (mg/h) from matrix VI is shown in **Figure 5**: the in

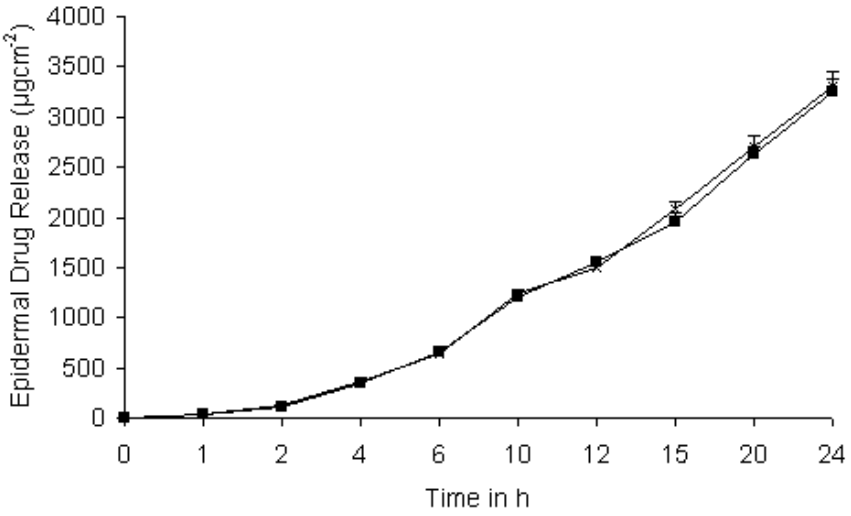

Figure 6. Comparative epidermal release profile of bupropion through human cadaver skin from adhesive matrix (I) consisting of Eudragit E 100 as the controlling polymer and Triethylcitrate (■) and Dibutylphthalate (x) as plasticizers ($P < .05$).

vitro release of bupropion from epidermis was constant with minimum peak and trough.

Prepared formulations exhibited a delivery rate of bupropion from 9.5 mg to 35.4 mg from 3.14 cm^2 area per day. It was found that by increasing the size of matrix from 3.14 cm^2 to 12.56 cm^2, the delivery rate per day increased nearly 4 times. The delivery rate of bupropion was found to be 41.2 to 130.1 mg per day from a 12.56 cm^2 area of the matrix. These results suggest that the required drug delivery rate of bupropion could be achieved by proper selection of drug/polymer concentration and the size of the system.

Effect of Plasticizer

Effects of the plasticizers (DBP and TEC) on the epidermal flux of bupropion from transdermal adhesive matrix were compared. In both the cases, the in vitro diffusion pattern was found to be zero order. The diffusion kinetics of bupropion formulation (I) containing TEC was not significantly different from the diffusion pattern of formulation containing DBP (**Figure 6**). The epidermal flux with TEC was 139.5 compared to 142.0 $\mu gcm^{-2}h^{-1}$ with DBP. No significant change was observed in epidermal flux through skin ($P < .05$). Rafiee-Tehrani et al noted a similar pattern from a unilaminated device of acrylic resin patch containing estradiol.[12,13]

Effect of Release Modifiers on the Diffusion of Bupropion from Adhesive Matrix

The effect of PG, MA, and succinic acid as release modifiers at 10% wt/wt polymer concentration on the diffusion behavior of bupropion from transdermal adhesive matrix containing TEC as a plasticizer is depicted in **Figure 7**. A significant ($P < .05$) increase in the release of bupropion from the transdermal matrix system was observed when propylene glycol was used as the release modifier. Epidermal flux increased from 139.5 to 156.3 $\mu gcm^{-2}h^{-1}$ with use of propylene glycol. The in vitro release of steroids from 2 topical gel formulations with carbopol 934P was found to be enhanced by increasing the propylene glycol content.[14] It is assumed that the major effect of PG arises from a solvent drag effect of bupropion. The observed change in the epidermal flux in the presence of PG may be because of a difference in thermodynamic activity and the solubility of free base in the matrix. The epidermal flux is proportional to a gradient of thermodynamic activity rather than the concentration, because drug activity will change in different solvents at definite concentrations. Furthermore, a similar observation was noticed when a bupropion percutaneous study was carried out in a phosphate buffer solution of drug with PG. The diffusion of bupropion from adhesive matrix containing myristic acid as a release modifier has increased markedly from 139.5 to 174.7

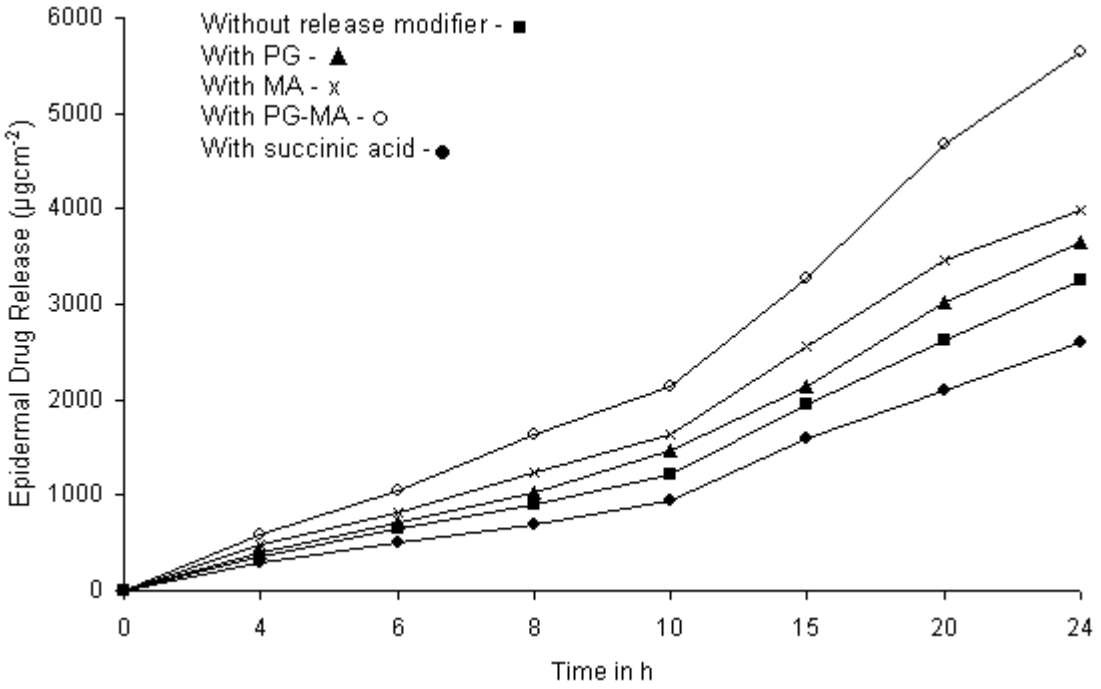

Figure 7. Comparative epidermal drug release of bupropion from matrix (I) consisting of PG, MA, and succinic acid as release modifiers (n = 3).

$\mu gcm^{-2}h^{-1}$. Epidermal flux was further increased to 243.6 $\mu gcm^{-2}h^{-1}$ in an adhesive matrix containing myristic acid (5% wt/wt of polymer) in the presence of PG. Fatty acids were reported to be the most effective penetration enhancers for lipophilic drugs when PG was used as cosolvent.[15,16] An opposite phenomenon was observed when succinic acid was added to the adhesive matrix as the release modifier. It is believed that succinic acid acts as a cross-linking agent with the acrylic polymer thus forming a rigid matrix. Cross-linking of the matrix leads to retardation of drug diffusion from the adhesive matrix. An ionic reaction takes place between succinic acid and cationic Eudragit E 100. Epidermal flux decreased to 111.7 $\mu gcm^{-2}h^{-1}$ from the initial epidermal flux without release modifier. Complex formation between methacrylate (Eudragit E 100) and succinic acid was confirmed by differential scanning calorimetry carried out at a heat flow rate of 10°C/min. Results of DSC revealed that the onset value of succinic acid at 188°C disappeared in the complex, thus providing strong evidence of formation of a cross-linked product.

CONCLUSION

The studies showed that Eudragit E 100 is a suitable polymer for the preparation of bupropion transdermal adhesive matrix. Plasticizers did not influence drug release from the systems (epidermal flux with TEC and DBP was 139.5 and 142.0 $\mu gcm^{-2}h^{-1}$, respectively). The use of PG and MA increased the release of bupropion from the transdermal adhesive matrix. Succinic acid, a cross-linking agent for methacrylate, retarded the drug diffusion from the adhesive matrix. Epidermal flux of bupropion was found to be 156.3, 174.7, and 243.6 $\mu gcm^{-2}h^{-1}$ with PG, MA, and PG-MA as release modifiers, while succinic acid showed epidermal flux of 111.7 $\mu gcm^{-2}h^{-1}$. Comparative epidermal release profiles show that epidermal flux through skin from adhesive matrices largely depends on the ratio of drug to polymer and the release modifiers. A hyperbolic relation of epidermal flux was observed with the concentration of permeant and drug adsorption in the skin during the diffusion study. This study offers the possibility of preparing adhesive matrices with the desired drug release by use of Eudragit E 100 and different release modifiers.

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