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Der Pharmacia Lettre, 2013, 5 (6):171-175
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The effect of penetration enhancers on the permeation of sulfonyl urea derivative

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ABSTRACT

Now a day transdermal drug deliveries are increasing rapidly for the treatment of various diseases so the present study was conducted on different penetration enhancers for permeation of antidiabetic drug, glipizide (sulfonyl urea derivative) through skin. Different types of penetration enhancers such as terpenes and terpenoids, pyrrolidones, oxazolidinones, fatty acids etc are used for permeation enhancement of different drug molecule according to their chemical and physical nature. The experimental data demonstrated that in all penetration enhancers used in the study the N-methyl-2-pyrrolidone significantly enhanced the flux of glipizide across the skin. Propylene glycol showed less permeability than control. This may be due to less partitioning of drug to stratum corneum from propylene glycol than control. Propylene glycol appears to have a protective effect on skin with respect to reducing barrier damage. After N-methyl-2-pyrrolidone, oleic acid significantly increases the flux.

Key words: Penetration enhancer, sulfonyl urea derivative, N-methyl-2-pyrrolidone, Propylene glycol.

INTRODUCTION

Transdermal drug delivery offers many advantages over other routes of conventional drug delivery[1]. However, only a few drug candidates have been successfully developed into suitable transdermal formulations because of the formidable skin barrier [2]. The topmost layer of the skin, stratum corneum, is only approx 10–20 µm thick across most parts of the human body, but provides a formidable barrier to the passive permeation of drugs. Multiple layers of dead corneocytes embedded in lipid bilayers present a strongly hydrophobic barrier which prevents large hydrophobic molecules and most hydrophilic molecules including proteins and peptides from passing through[3,4]. This limitation calls for methods which can reversibly permeabilize the skin without causing irritation in the viable epidermal region. Efforts to facilitate drug molecule transport across skin include the use of chemical [5, 6] and physical[7,8,9] methods for flux enhancement.

Use of chemical permeation enhancers (CPEs) is one such method for making the skin permeable to small molecules as well as larger macromolecular drugs [6, 10]. Chemical permeation enhancers collectively refer to the group of compounds spread across different structural classes which are known to permeabilize the skin [11].

Ethanol is the most commonly used alcohol as a transdermal penetration enhancer. It also acts as a vehicle for menthol in increasing the penetration of methyl paraben[12]. Terpenes and terpenoids are suitable skin penetration enhancers with low toxicity and irritancy [13]. Oxazolidinones such as 4-decyloxazolidin-2-one has been reported

to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers [14]. Cyclic urea permeation enhancers are biodegradable and non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism [15]. Pyrrolidones like N-methyl-2-pyrrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch [16]. Dimethyl sulfoxide (DMSO), the most important compound belonging to the category of sulfoxides and similar compounds, enhances the transdermal permeation of a variety of drugs, like β -blockers, ephedrine hydrochloride, and papaverine hydrochloride [17,18]. A large number of fatty acids and their esters have been used as permeation enhancers. Oleic acid was found to be the most efficient enhancer for piroxicam, followed by linoleic acid [19]. Sodium oleate was found to be a better permeation enhancer than oleyl oleate when tested on indomethacin and urea [20].

Glipizide, an oral hypoglycemic agent, is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus [21]. It is practically water-insoluble, but the absolute bioavailability is close to 1. Thus, it belongs to class 2 of Biopharmaceutic Classification System (BCS). Glipizide has a relatively short elimination half-life (2–4 h), thereby requiring twice daily dosing in large number of patients [22, 23] which often leads to non-compliance.

MATERIALS AND METHODS

Materials

Dionex high-performance chromatograph with a reversed phase UVD170U Column: PC-MicraNPS RP18, Pump: P 680 HPLC, system software: Chromeleon was used.

Ethanol, methanol, sodium hydroxide, potassium dihydrogen orthophosphate and hydrochloric acid were obtained from S.D. Fine-Chem., Mumbai, India. All solvents and sample solutions were filtered through 0.22 μ m nylon filter (Millipore) using filtration assembly with vacuum pump and ultrasonicated using ultrasonic water bath.

Preparation of skin membrane

Abdominal skin of guinea pig (weighing 800 to 900 gm) was used for permeation studies. The animals required for the study were procured and housed in the animal house with free access to standard laboratory food. They were kept at $25^{\circ}\text{C} \pm 1^{\circ}\text{C}$ and 45-55 % RH with 12 h light/dark cycle. The hairs of the dorsal surface were removed with the help of hair removing spray 24h before the surgical removal of skin patch. Next day the animal was humanely sacrificed by using diethyl ether anesthesia. The full thickness skin was removed surgically and washed with normal saline solution. The adhered fats and other subcutaneous tissues were removed carefully with scissors and scalpel to get fat free epidermal layer.

10 mg of Glipizide was dissolved in 5 ml of PB (pH 7.4): ethanol (85:15) and placed in donor compartment. Ethanol was used as co-solvent to dissolve Glipizide because only PB (7.4 pH) could not solubilize the required quantity. To achieve the required flux various penetration enhancers were investigated for their enhancing effect on permeation of Glipizide. Dimethyl sulfoxide, N-methyl-2-pyrrolidone, Oleic acid, and propylene glycol were added to the donor compartment in 5% v/v concentration. The donor compartment was covered with aluminum foil to minimize the evaporation of solution.

Selection of receptor medium

Phosphate buffer (PB) pH 7.4 is commonly used as receptor medium. The receptor compartment was filled with the medium and skin was allowed to equilibrate with receptor medium for 15 min. The receptor medium was stirred by star-head magnetic bar (size 10 $\times$ 10 mm) (Hi-media) rotating at a constant speed of 600 rpm by motorless magnetic stirrer (Whirlmatic –mega, spectralab). The temperature in the bulk of the solution was maintained at $32^{\circ}\text{C} \pm 1^{\circ}\text{C}$ using constant temperature circulating water bath.

Data analysis

Steady State flux (J_{ss}) [24]: The cumulative amount of drug permeated per unit skin surface area plotted against time and slope of the linear portion of the plot is estimated as Steady State flux ($\mu\text{g}/\text{cm}^2/\text{h}$).

Permeability Coefficient (Kp): can be calculated by following equation.

$$K_p = J_{ss} / C_v$$

Where C_v is initial concentration in donor compartment.

Q_{24} = cumulative amount of drug permeated ($\mu\text{g}/\text{cm}^2$) at 24 h.

Required flux (permeation rate): It can be estimated from the pharmacokinetic parameters by using following equation.

$$\text{Required flux (D)} = C_p \times V_d \times K_e$$

Where C_p is minimum effective plasma concentration, V_d is apparent volume of distribution, K_e is elimination rate constant.

It can also be calculated by equation,

$$\text{Required flux [25] (D)} = C_p \times Cl_T, \text{ where } Cl_T \text{ is clearance of drug.}$$

Enhancement ratio (E_R): This is calculated to measure the effect of enhancer or solvent system on penetration enhancement of the drug.

$$E_R = K_p (\text{Permeability Coefficient}) \text{ with enhancer or solvent system} / K_p \text{ with water.}$$

Lag Time [26]: This is the estimation of time lag required to reach the plasma concentration up to steady state. It can be obtained from the X-intercept of extrapolated linear portion of curve towards X-axis.

Statistical analysis

The steady state flux values obtained with different penetration enhancers were compared by means of the one way ANOVA followed by Dunnett test to compare the effect of the penetration enhancers with the control (with out enhancer)

RESULTS AND DISCUSSION

Skin permeability of a drug is strongly influenced by its physicochemical parameters. According to Doh and coworkers[27] drug candidates for transdermal delivery should have molecular weight around 200–500 Da. Glipizide having molecular weight of 445 fits into the category but two of its properties, solubility and pKa, are not favorable for transdermal permeation. Glipizide is slightly soluble in water and hence to deliver it at adequate concentration, the binary vehicle of PB–ethanol was used.

Table 1.: Effect of various penetration enhancers on permeation parameters

Penetration enhancer (5% w/w)	Steady state flux ($\mu\text{g}/\text{cm}^2/\text{h}$)	Permeability coefficient ($\text{cm}/\text{h} \times 10^3$)	(Er)	Drug retained in skin ($\mu\text{g}/\text{mg}$)	Lag time (h)	Q_{24} ($\mu\text{g}/\text{cm}^2$)
Control	11.524 ± 0.8	4.93 ± 0.7	1.10	1.75 ± 0.21	5.7 ± 0.2	99.01 ± 5.9
Dimethyl sulfoxide	17.35 ± 1.9	8.01 ± 1.7	1.86	2.1 ± 0.79	5.1 ± 0.3	297.9 ± 11.36
N-methyl-2-pyrrolidone	28.24 ± 2.4	15.11 ± 2.4	2.72	3.8 ± 0.42	3.4 ± 0.3	427.6 ± 16.23
Propylene glycol	3.01 ± 0.25	1.96 ± 0.3	0.47	0.43 ± 0.04	7.1 ± 0.5	63.51 ± 4.32
Oleic acid	19.21 ± 1.5	9.46 ± 2.9	1.52	2.4 ± 0.57	5.8 ± 0.3	236.83 ± 7.92

$n=3$, all readings mean ± S.D.

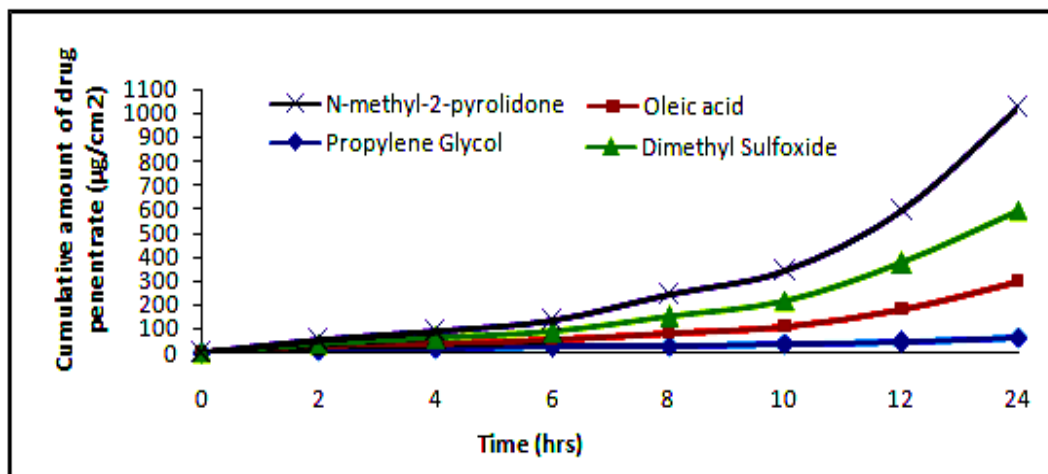


Figure 1. Effect of various penetration enhancers of permeation of Glipizide.

As the intrinsic permeation rate of Glipizide was not adequate, various penetration enhancers were tried to increase the permeability. All the penetration enhancers except propylene glycol significantly ($P < 0.01$) increase the flux values of Glipizide. Amongst all the penetration enhancers, N-methyl-2-pyrrolidone showed maximum flux value. Propylene glycol showed less permeability than control. This may be due to less partitioning of drug to stratum corneum from propylene glycol than control. Propylene glycol appears to have a protective effect on skin with respect to reducing barrier damage. After N-methyl-2-pyrrolidone, oleic acid significantly increases the flux.

CONCLUSION

Penetration study of different permeation enhancers was carried out through guinea pig skin using K-C diffusion cell. The permeation studies were carried out for 24 h and samples were analyzed by HPLC method.

To achieve the required flux various penetration enhancers were investigated for their enhancing effect on permeation of Glipizide. The steady state flux values obtained with different penetration enhancers were compared by mean of the one way ANOVA.

All the penetration enhancers except propylene glycol significantly ($P < 0.01$) increase the flux values of Glipizide. Amongst all the penetration enhancers, N-methyl-2-pyrrolidone showed maximum flux value. Conclusively the receptor medium composition (PB:Et 85:15) and N-methyl-2-pyrrolidone was found to be most effective penetration and used for further development of TDDS.

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