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Research article

A COMPARATIVE RELEASE STUDY OF LISINOPRIL FROM DIFFERENT VEHICLES

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ABSTRACT

The aim of the present study was to investigate the *in-vitro* release properties of Lisinopril from different topical vehicles. By the unique advantages over the traditional drug delivery, transdermal drug delivery is becoming increasingly important and has got a vital interest in pharmaceutical industries. An *in vitro* diffusion cell experiment was designed to reveal the rate of release of Lisinopril from three different topical vehicles: (*i*) an oil-in-water cream; (*ii*) a gel; and (*iii*) an ointment. *In vitro* release of Lisinopril from the three bases to an aqueous receptor phase through pig skin was monitored spectrophotometrically at a wavelength of 258 nm. In vitro release study results showed that the steady state fluxes of the drug from vehicles rank according to the following order: ointment >cream >gel. Ointment base showed considerably higher drug release than other vehicles. By monitoring and attempting to explain the many possible reasons for the different rates of drug release from the three vehicles, it was hope that the experiment would confer essential information concerning factors affecting the release of drugs from topical formulations.

Keywords : Lisinopril, Topical formulation, *In vitro,* Pig skin.

INTRODUCTION

In the past two decades, transdermal drug delivery has moved from a clinical reality to the point where it represents a viable diagnostic tool for noninvasive diagnosis. As research is pursued, along many more applications are on the rise. The advantages of this mode of drug administration are numerous, the patient conveniences and therapeutic optimization of using patch transdermal systems being major positive features. However, impermeability of human skin is still a fundamental problem limiting its widespread therapeutic use. The first challenge of creating effective transdermal system ultimately involves ensuring adequate drug permeability through the stratum corneum. Moreover it is also important to ensure that the drug

delivery systems do not irritate the skin, and the drug is not unduly metabolized and delivered according to the desired pharmacokinetics and pharmacodynamics.[1]

The main problem associated with the oral drug delivery include an uneven bio-distribution, lack of drug targeting specificity, the necessity of large doses to achieve local concentration and adverse side effects due to such high dose. Hence novel drug delivery methods are of vital interest to pharmaceutical industries and development of transdermal drug delivery systems (TDDS) is one of them[2].

As we are aware that the delivery vehicle markedly affects the permeability of drug across the membrane. In this study we have designed three donor drug system (1) oil in water cream; (2) a glycero-gelatin gel and (3) a paraffin ointment. By monitoring the rate of drug release using Franz-diffusion cell from the three vehicle can explain, how the rate of drug release depend on physicochemical parameters[3].

Lisinopril is an ACE inhibitor that is routinely used in the management of hypertension. TDDS is particularly desirable for drugs that need prolonged administration at controlled plasma level. Hence theoretically this is a good candidate for transdermal delivery.

MATERIALS AND METHODS

Materials

UV Visible Spectrophotometer SHIMADZU UV-1700 PC, Shimadzu Corporation, Japan, was used. Lisinopril was a gift sample from Lupin laboratories, Bhopal, India; Franz-diffusion cell was designed by Peekay scientific glass wares, Bhopal, India. Pig skin was obtained from local slaughter house. All the reagents/chemicals used were analytical grade and obtained from SD Fine-Chem, Mumbai India.

Procedure for analytical method development

50 mg of Lisinopril was accurately transferred in to 50 ml volumetric flask and dissolved in small quantity of phosphate buffer pH 7.4. The volume was made up with the buffer to 50 ml to produce stock solution having a concentration of 1 mg/ml. A standard solution having a concentration of 20 mcg/ml was prepared by appropriately diluting the stock solution. The standard solution was scanned between the wavelength ranges of 200 to 350 nm in Shimadzu UV spectrophotometer to determine the wavelength of maximum absorbance.

Working standard solutions ranging in concentration from 10 to 50 mcg/ml

were prepared by appropriately diluting the standard solution with phosphate buffer pH 7.4. The absorbance of each working standard solution was measured at 258 nm using a Shimadzu UV spectrophotometer using phosphate buffer of pH 7.4 as a blank. Data for each and every experiment was obtained in triplicates and statistically analyzed.

Preparation of different vehicle for Lisinopril

Lisinopril was incorporated into three bases (1) oil in water cream; (2) a glycerol-gelatin gel and (3) a paraffin ointment at concentration 1.5 percent (45 mg in 3 g of base).

Preparation of skin membrane

From a local abattoir, ear was obtained from freshly slaughtered pigs. The skin was removed carefully from the outer regions of the ear and separated from the underlying cartilage with a scalpel. After separating the full thickness skin, the fat adhering to the dermis side was removed using a scalpel and isopropyl alcohol. Finally the skin was washed with tap water and stored at refrigerator in aluminum foil packing and was used within two days[4,5].

Procedure of *in vitro* permeation studies

The *in vitro* permeation studies were conducted using vertical type Franz diffusion cell having a receptor compartment capacity of 50 ml. The excised skin was mounted between the half-cells with the dermis in contact with receptor fluid (phosphate buffer pH 7.4) and was equilibrated for 1 h. The area available for diffusion was about 1.21 cm^2. The donor cell was covered with an aluminum foil to prevent the evaporation of vehicle. The fluid in the receptor compartment was maintained at 37 ± 0.5°C. Under these conditions, the temperature at the skin surface was approximately 32°C. 1 g vehicle having concentration 1.5% of Lisinopril was placed in the donor compartment. The entire assembly was kept on a magnetic stirrer and the solution in the receiver compartment was stirred continuously using a magnetic bead. The sample solution was withdrawn from the receptor compartment at regular intervals and assayed for drug release[6].

Data analysis

The cumulative amount permeated was plotted against time, and the slope of the linear portion of the plot was estimated as the steady state flux.

Permeability coefficient were calculated using following formula[7].

$$K_P = J_{SS} / C_d$$

The diffusion coefficients of Lisinopril from each vehicle was calculated using Higuchi equation[8].

$$Q = 2\, C_d\, (Dt/\pi)1/2$$

where K_P is the permeability coefficient, J_{SS} is the steady state flux, Q is the cumulative amount of drug released per unit area, C_d is the donor drug concentration in the vehicle, D is the diffusion coefficient and t is the time.

RESULTS AND DISCUSSION

Lisinopril was scanned in the UV wavelength region of 200-350nm for maximum absorption (λ_{max}). The λ_{max} was found to be at 258nm. A linear relationship was observed between the concentration and absorbance values in the range of 10 to 50 mcg/ml (R^2 = 0.9939) and slope was found 0.0199 (Figure-1).

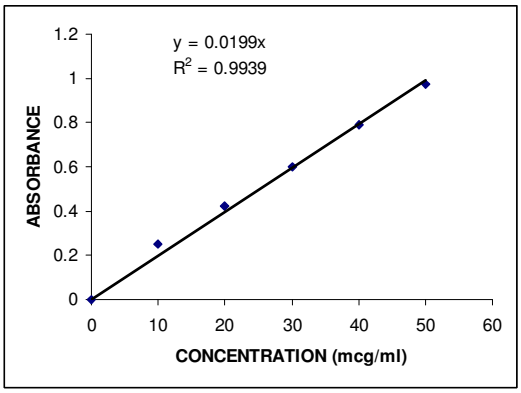

Fig. 1 : Calibration curve for Lisinopril in phosphate Buffer pH 7.4

The influence of the vehicle on release profiles of formulations, each possessing different physicochemical properties was investigated by using pig skin membrane. The different rates of Lisinopril delivery from the three vehicle types can clearly be seen from the graphs of permeation versus time.(Fig. 2) Lisinopril delivery was much greater from the ointment formulation (Fig. 2) than from either the gel or cream vehicles. This suggests that physical parameters in the donor vehicle are more influential in controlling Lisinopril release from the ointment than are chemical factors.

Lisinopril is highly water soluble and therefore has a high affinity for the aqueous gel formulation. It will therefore only partition to a small extent into the lipophillic environment of the pigskin membrane. Hence the slow flux rates observed as these processes are concentration gradient dependent. Conversely it is proposed that Lisinopril has a relatively greater affinity for the membrane than for the ointment vehicle and will therefore demonstrate higher partition and flux parameters from this vehicle and higher flux rate that have been observed. The cream is a lipophilic/hydrophillic mixture from which flux rate of Lisinopril was found between the flux range of ointment and gel. (Fig. 2).

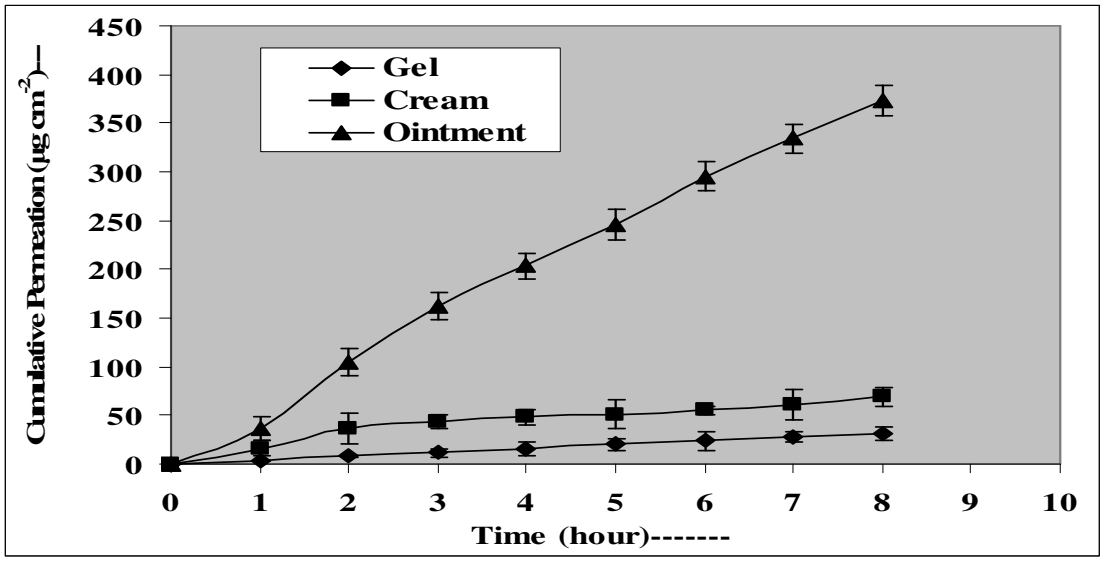

Fig. 2 : Cumulative permeation profile of Lisinopril at different donor vehicle. (Each y-bar indicating standard error)

The steady state flux rate of Lisinopril released from the different formulation calculated from the linear portion of the graph yields a delivery rate of 42.785µg/cm^2.h for the ointment which was very higher than other two. The diffusion coefficients of Lisinopril from each vehicle were calculated using Higuchi equation was found considerable higher in case of ointment than other two. Result obtains in our study for diffusion coefficients and permeability coefficients are given in Table1.

Table 1 : Steady state flux, permeability coefficient and diffusion coefficient of Lisinopril in different vehicles.

Donor system	Steady state flux (µg cm^{-2}h^{-1})	Permeability coefficient (cm h^{-1})	Diffusion coefficient (cm^2 s^{-1})
Gel	3.9675	0.002645	0.6713× 10^{-7}
Cream	4.9795	0.003319	3.321× 10–7
Ointment	42.785	0.028523	98.53× 10–7

For mass transfer to take place the drug must have some, and preferably greater, affinity for the membrane than for the vehicle, thereby maximizing the thermodynamic leaving potential. Differential drug delivery rates have been explained in terms of the partitioning of the drug between the formulation and the membrane, and in terms of the ease of diffusion of the drug in the delivery vehicle to replenish the depletion zone at the vehicle/membrane interface.[9]

In vitro release study results showed that the steady state fluxes of the drug from

vehicles rank according to the following order: ointment >cream >gel. Ointment base showed considerably higher drug release than other vehicles. By monitoring and attempting to explain the many possible reasons for the different rates of drug release from the three vehicles, it was hope that the experiment would confer essential information concerning factors affecting the release of drugs from topical formulations.

CONCLUSION

The in vitro release studies are considered to be useful in pre-formulation step to predict the best vehicle in further experiments. Due to the release of the drug from pig skin membrane, the choice of an appropriate vehicle is particularly crucial in the development of topical formulations. According to our results, ointment base is a good candidate for the topical delivery of Lisinopril, giving considerably higher drug release than the other vehicles.

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