Biosciences, Biotechnology Research Asia Vol. **4**(2), 761-764 (2007)

Effect of enhancers on permeation kinetics of ramipril for transdermal system

B.M. DINESH, Y. ANAND KUMAR*, B. SRINIVASALU and B.G. DESAI

K. L. E. Society's College of Pharmacy, II block, Rajajinagr, Bangalore - 560 010 (India)
*V.L. College of Pharmacy, Raichur (India)

(Received: September 19, 2007; Accepted: October 08, 2007)

ABSTRACT

Transdermal drug delivery system has seen a veritable explosion in the past decades. In the present scenario, very few transdermal patches are commercially available. Ramipril being an anti-hypertensive drug requires chronic administration. Since the drug has an extensive first pass metabolism. An attempt was made to develop transdermal drug delivery system for patient compliance. In this study, flux and permeation enhancement trials of ramipril was carried out using modified Franz diffusion cells through siloxane membrane for eight hours. hylouronidase as a permeation enhancer showed the best permeability as compared to sodium tauroglycholate, sodium lauryl sulphate etc. One long-standing approach for improving transdermal drug delivery uses penetration enhancers (also called sorption promoters or accelerants), which penetrate into skin to reversibly decrease the barrier resistance.

Key words: Ramipril, transdermal permeation studies.

INTRODUCTION

Ramipril[1,2], is used for the treatment of anti hypertensive, Ramipril inhibits angiotensin converting enzyme(ACE) in human subjects and animals**.** The pharmacokinetic profile of ramipril pKa 3.18, Oral absorption is good, biotransformation 55-65%, half-life is 13-17 h LogP is 1.6c.

The principle of transdermal drug delivery systems is to deliver drug across epidermis to achieve systemic effect over a prolonged period of time. For these attributes, transdermal drug delivery systems offers many advantages such as reduced side effects, improved patient compliance, elimination of first-pass metabolism and sustained drug delivery.

There has been a giant leap by the pharmaceutical industry with respect to innovations in the new drug delivery arena in the past 2 decades. These innovations and changes in strategy present newer challenges and brighter opportunities for the application of new methodologies in the drug delivery process. Drug delivery through intact skin is of utmost importance for controlled release of drug for their extended and safe use, which is yet to be successfully used for a large number of drugs. Formulations on skin can be classified into two categories according to the target site of action of the containing drugs. One has systemic action after drug uptake from the cutaneous microvascular network and the other exhibits local effects in the skin. The current study focuses on the drug release kinetics from the rate limiting membrane by varying the type of solvent used, polymeric films and drug loading in transdermal delivery systems.

MATERIAL AND METHODS

The ramipril was a gift sample from Torrent pharmaceuticals, Gujrat, dimethyl sulphoxide, sodium lauryl sulphate, dimethyl fluride, citric acid sodium taurocholate, eugenol obtained from S.d. fine

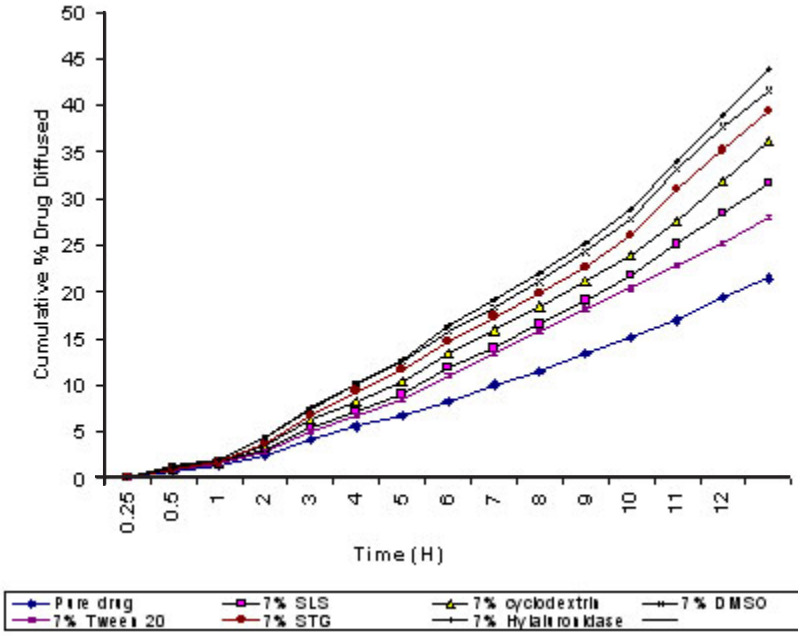

Fig. 1: Study of pre-formulation screening of ramipril with different enhancers (n=3).

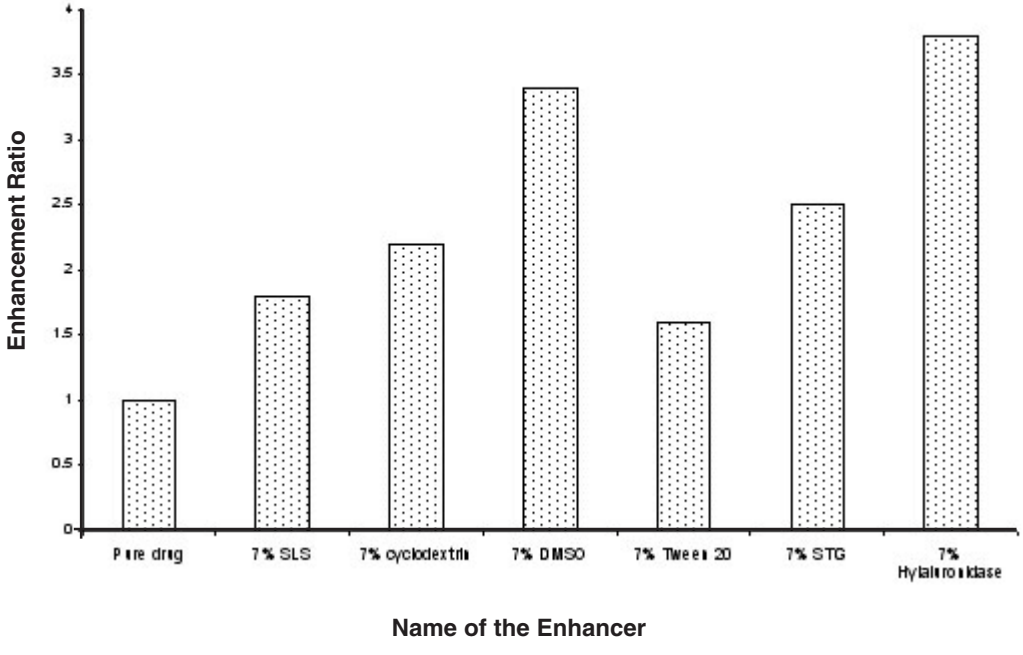

Fig. 2: Bar graph showing enhancement ratio of ramipril with different enhancers(n=3)

chemicals, Bombay and hyaluronidase was obtained from Charles Pharma ltd. All the solvents and other reagents were of analytical or pharmacopoeial grade.

Partition coefficient of drug in octanol / buffer system[3 - 6]

The partition coefficient of the drug was determined by taking equal volume of 1-octanol and aqueous solution in a separating funnel.10mg of drug was dissolved in 10 ml buffer solutions of pH 6.2, 7, 7.4 & 8 to which 10ml of octanol was added and kept in a separating funnel for 24h. The aqueous layer was collected and the concentration of Ramipril was measured spectrophotometrically at 208 nm using buffer of the respective pH as blank .

Permeability study[7-15]

The siloxane membrane was washed under running water for 3-4 h in order to remove glycerol which is induced as a humectants. Removal of sulphur compounds can be accomplished by treating the tubing with a 0.3% w/v solution of sodium sulphide at 80° for 1 min. wash with hot water (60°) for 2mins, followed by acidification with a 0.2%v/v solution of sulphuric acid, then rinse with hot water to remove the acid. This tubing will retain most proteins of molecular weight 12,000 or greater.

The drug solution was prepared as per the dose 10mg of drug per 2 ml of buffer (7.4 pH) was taken in the donor compartment. The siloxane membrane was mounted on the space between the donor and the receptor compartments. The receptor cell contained Phosphate buffer of pH 7.4 as the medium. The samples were withdrawn after every hour. The medium was magnetically stirred for uniform drug distribution and was maintained temperature of 37±1°. The amount of drug diffused was estimated spectrophotometrically at 262 nm. The release details are given in the results.

The enhancers considered for the study were Sodium laurylsulphate (SLS), Dimethylsulfoxide (DMSO), Dimethyl formamide (DMF), Hyaluronidase and Sodium tauro Glycholate(STG), Hyaluronidasetween 20 and beta cyclodextrin. The donor compartment contained a suspension of the drug and 1% w/w concentration of different enhancers. Siloxane membrane was used as the barrier. All the other experimental conditions and analytical techniques were followed similar to that reported in permeability study section.

RESULTS AND DISSCUSION

Partition coefficient

The partition coefficient of ramipril was studied in the octanol / buffer system. The partition coefficient increased with increase in the pH of the buffer solution. The partition coefficient results were found to be 3.16.

Permeation studies

The permeation studies were carried out using a passive diffusion cell and the membrane used was dialysis membrane. The permeability coefficient and flux of ramipril was found to be 21.62cm/hr and 129 mg/cm^2/hr respectively.

The enhancement ration of the drug with different enhancers has been studied using passive diffusion cell through dialysis membrane. The permeability coefficient, flux and enhancement ratio of ramipril with hylauronidase (1%) was found to be 80.27 cm/hr, 481.62 mg/cm^2/h and 3.7 % respectively. The permeability coefficient, flux and enhancement ratio of ramipril with dimethyl sulphoxide (1% DMSO) was found to be 74.56cm/hr, 447 mg/cm^2/h and 3.448% respectively. The permeability coefficient, flux and enhancement ratio of ramipril with Sodium lauryl sulphate (1%SLS) was found to be 30.23cm/hr, 181.38mg/cm^2/h and 1.391% respectively. The permeability coefficient, flux and enhancement ratio of ramipril with cyclodextrin (1%) was found to be 46.79cm/hr, 280mg/cm^2/h and 2.16% respectively.

The permeability coefficient, flux and enhancement ratio of ramipril with sodium tauro glycholate (1%STG) was found to be 58cm/hr, 349mg/cm^2/h and 2.690% respectively. The permeability coefficient, flux and enhancement ratio of ramipril with SLS (1%) was found to be 30.94cm/hr, 181.4mg/cm^2/h and 1.309% respectively. The permeability coefficient, flux and enhancement ratio of ramipril with tween 20 (1%) was found to be 33.42cm/h, 200 mg/cm^2/h and 1.542% respectively.

REFERNCES

1. David B. Jack., handbook of clinical pharmacokinetic data, Macmilan publishers Ltd, 32-34 (1992).
2. Martindale: the complete drug reference, Pharmaceutical press, London, The enhancement effect of surfactants on the penetration of lorazepam through rat skin. 33rd, 853-854 (2007).
3. Jonathan Hadgraft and Majella E. Lane. Skin permeation: The years of enlightenment. *Int. J. Pharm,* **305:** 2-12 (2005)
4. Vijay Sutariya, Rajasree Mashru, Sunkalia MS. Transbuccal delivery of lomotrigine across procine buccal mucosa invitro determination of roots of buccal transport., *J. Pharm. Sci.,* **8**: 54-62 (2005).
5. Rajashree Mashru, Vijay Sutariya[1], Mayur Sankalia, Jolly Sankalia Transbuccal delivery of lamotrigine across porcine buccal mucosa: in vitro determination of routes of buccal transport. *J. Pharm. Pharmaceut. Sci.,* **8** (1): 54-62 (2005).
6. Shah J.C.,Ross J S. Reduction in skin permeation of n,n-diethyl-m-toluamide by altering the skin/vehicle partition co-efficient. *J.control release,* **67**: 211-221 (2000).
7. Pugh,W.J., Hadgraft,J., prediction of human skin permeability coefficients, *Int. J. Pharm.,* **103**: 163-178 (1994).
8. Jonathan Hadgraft and Majella E. Lane. Skin permeation: The years of enlightenment. *Int. J. Pharm.,* **305**: 2-12 (2005).
9. Gihan R. Nanayakkara, Ann Bartlett, Ben Forbes, Chris Marriott, Phil J. Whitfield and Marc B. Brown. The effect of unsaturated fatty acids in benzyl alcohol on the percutaneous permeation of three model penetrants., Int. *J. Pharm.,* **301**: 129-139 (2005).
10. Taravat Ghafourian, Parinaz Zandasrar, Hamed Hamishekar and Ali Nokhodchi The effect of penetration enhancers on drug delivery through skin: a QSAR study. *J. Contr. Rel.,* **99**(14), 113-125 (2004).
11. Jonathan Hadgraft. Skin deep, E. J. *Pharm. and Bio.,* **58,** 291-299 (2004).
12. N. Kanikkannan and Mandip Singh. Skin permeation enhancement effect and skin irritation of saturated fatty alcohols. *Int. J. Pharm.,* **248**: 1-2(6) 219-228 (2002).
13. Tomoko Akimoto, Kazunari Kawahara, Yu Nagase and Takao Aoyagi, Polymeric transdermal drug penetration enhancer: The enhancing effect of oligo dimethyl siloxane containing a glucopyranosyl end group. *J. Contr. Rel.,* **77**, 1-2(9): 49-57 (2001).
14. Copoví O., Díez-Sales, J.V., Herráez-Domínguez and M. Herráez-Domínguez., Enhancing effect of alpha-hydroxyacids on “in vitro” permeation across the human skin of compounds with different lipophilicity, *Int. J. Pharm.,* **314**(1): 31-36 (2006).
15. A. Nokhodchi, J. Shokri, A. Dashbolaghi, D. Hassan-Zadeh, T. Ghafourian and M. Barzegar-Jalali. The enhancement effect of surfactants on the penetration of lorazepam through rat skin, *Int. J. Pharm.,* **250**, 2(16): 359-369 (2003).
16. Jonathan Hadgraft. Passive enhancement strategies in topical and transdermal drug delivery, *Int. J. Pharm.,* **184**(1): 1-6 (1999).