INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

ENHANCEMENT OF SKIN PERMEATION OF DILTIAZEM HYDROCHLORIDE GELS THROUGH MOUSE SKIN BY USING OLIVE OIL AS PERMEATION ENHANCERS

S. Ramakrishna Prasad* and V. Sai Kishore

Bapatla College of Pharmacy, Bapatla, Andhra Pradesh, India.

ABSTRACT

In the present study efforts were made to prepare transdermal gels of Diltiazem Hydrochloride using polymers like HPMC, NaCMC, M.C ,Carbopol, PEG6000 and PVP. The gel formulations can be graded in the following order with respect to the rates of release of drug from them: (HPMC) < (MC) < (Carbopol) <(NaCMC) < (NaCMC +PVP)< (NaCMC+ PEG 6000). Olive oil in the concentrations range from 1% -2.5% were incorporated into gels with a view to improve permeability of drug. The correlation coefficient values (r) revealed that the diffusion profiles follows zero order kinetics and the mechanism of drug release was governed by peppas model. The diffusion exponent of release profiles (slope) has a value of ($n \geq 1$), which indicates case II transport diffusion. Formulation - GP_1 (NaCMC +PEG 6000+ Olive oil 2.5%) shown required release rate in comparison with other formulations and was selected as suitable candidate to be delivered through transdermal route at controlled rate.

Key words: Diltiazem Hydrochloride, Olive oil, Eudragit RLPO.

INTRODUCTION

Diltiazem Hydrochloride is a calcium channel blocker. It has been widely used in the treatment of hypertension and many other cardiovascular disorders. Diltiazem Hydrochloride is subjected to an extensive and highly variable hepatic first pass metabolism following oral administration, with reported systemic bioavailability of between 36 and 50%.[1] As its biological half life is about 3.7 h and is eliminated rapidly ,repeated daily administrations are needed to maintain effective plasma levels that makes it suitable candidate to be delivered through transdermal route at controlled rate. Administration of drugs through transdermal route bypasses the first pass metabolism and there by increases the bioavailability. The development of technology for release of drug at controlled rate into systemic circulation using skin as a port of entry has become popular for various reasons.[2] The transdermal entry of drug in to systemic circulation at a desired rate can be achieved by using a suitable rate controlling membrane and a drug reservoir. [3] Earlier studies proved that Eudragit RLPO films could be used as rate controlling membranes for the design of Transdermal Drug Delivery systems. [4] With a view to design a suitable drug reservoir, various types of gel formulations were prepared. The gels are becoming more popular due to ease of application and

better percutaneous absorption, than other semisolids preparations. Gels can resist the physiological stress caused by skin flexion, blinking and mucociliary movement, adopting the shape of the applied area, and controlling drug release. [5] To enhance the permeability of Diltiazem Hydrochloride, olive oil in the concentrations range from 1% -2.5% were incorporated into the gels. The invitro skin permeation experiments are known for their value in studying the rate and mechanism of percutaneous absorption of drugs. To study the effect of permeation enhancers on the release and permeation kinetics of Diltiazem hydrochloride gels, those are evaluated by studying drug diffusion through Eudragit RLPO membrane and mouse skin.

MATERIALS AND METHODS

Diltiazem hydrochloride was obtained as a gift sample from Natco Pharma, Hyderabad. Eudragit RLPO , Ethyl acetate (Qualigens), Dibutyl phthalate (Ranbaxy Laboratories), Sodium CMC(200-300cPs, S. D. fine-chem Ltd.; Mumbai), Carbopol 934(Arihanth traders; Mumbai) Hydroxy Propyl Methyl cellulose(50cPs S. D. fine-chem Ltd.; Mumbai) and Methyl cellulose (28-32%, S. D. fine-chem Ltd.; Mumbai) obtained commercially. All materials were used as received.

Estimation of desired release rate

The mathematical description of drug release that follow zero order kinetics is based on the equation.[6] $K_r^0 = K_e C_d V_d$,Where,K^0_r is zero order rate constant for drug release, K_e is first order rate constant for overall drug elimination, C_d is desired drug level in the body and V_d is volume space in which drug is distributed. For Diltiazem hydrochloride[7] $t_{½}$ = 3.7 h, V_d = 3.1 and C_d = 0.05 µg/ml and therefore the desired drug release rate can be calculated as K^0_r = (0.693/3.7)×0.05 ×3.1 ×70 =2.032 mg/h.

Preparation of Drug Free Films

Solvent evaporation technique was employed in the present work for the preparation of Eudragit RLPO films. The polymer solutions were prepared by dissolving the polymer (8% w/w Eudragit RLPO) in 50 ml of Ethyl acetate. Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer. 20 ml of the polymer solution was poured in a Petri plate (9.4 cm diameter) placed on a horizontal flat surface. The rate of evaporation was controlled by inverting a funnel over the Petri plate. After 24 hours the dried films were taken out and stored in a desiccator.

Formulation of Drug Reservoir gels

Different drug reservoir gels were formulated as per the composition given in Table 1. The required quantities of polymer Sodium carboxy methyl cellulose(Na CMC(or) Methyl cellulose (MC)(or) Hydroxy propyl methyl cellulose (HPMC), was weighed and transferred separately into a mortar. It was triturated with 10 ml of water. Specified amount of Diltiazem Hydrochloride was weighed accurately and dissolved in glycerin.The resulting drug solution was incorporated into the polymer dispersion slowly with continuous trituration to obtain a gel. The gel was transferred in to a measuring cylinder and the volume was made up to 20 ml with distilled water. As shown in the Table1 , specified amount of carbapol 940 was soaked in 15 ml of water over night. Specified amount of Diltiazem hydrochloride was weighed accurately and dissolved in glycerin. The resulting drug solution was incorporated into the polymer dispersion with stirring at 500 rpm ,by a magnetic stirrer for 1 h. Tri ethanolamine (0.5%) was added to brought the PH neutral and the volume was made up to 20 ml with distilled water. Two different hydrophilic polymers viz., Poly vinyl pyrolidine (PVP) & Poly ethylene glycol - 6000(PEG-6000) were incorporated in 1:1 ratio (NaCMC:polymer) into NaCMC gels in formulation G_5 and formulation G_6 respectively. The resulting gels were filled in collapsible tubes.

Preparation of Gels containing permeation Enhancers

To enhance the permeability of Diltiazem Hydrochloride, olive oil in the concentrations range from 1% -2.5% were incorporated into the (NaCMC + PEG 6000) gels. The composition of these gels was given in Table 2.

Evaluation of Drug Reservoir Gels

Drug Diffusion Study

Drug diffusion study was conducted using Franz diffusion cell[7]. The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. Polymeric film was mounted on the donor compartment with the help of an adhesive. The Diltiazem Hydrochloride gel (1 gm containing 50mg of Diltiazem Hydrochloride) was placed into the donor compartment. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 $\pm$ 0.5 ^{0}C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 3 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a U V spectrophotometer at 237 nm.

Permeability Coefficient

From the drug diffusion data the permeability co efficient for various films was calculated using the equation[8] .P_m = ($K_{app.}$ H)/A, Where, K_{app} is Diffusion rate constant (mg/h) calculated from the slope of the linear drug (d/p) diffusion profiles , H is thickness of the film (cm), A is surface area of the film (cm^2).

The rate and the mechanism of release of Diltiazem hydrochloride through the prepared gels were analyzed by fitting the diffusion data into[9], zero-order equation, $Q=Q_0 - k_0t$, where Q is the amount of drug released at time t, and k_0 is the release rate. First order equation, Ln Q=Ln Q_0 – k_1t, where k_1 is the release rate constant and Higuchi's equation, $Q= k_2t^{1/2}$, where Q is the amount of the drug released at time t and k_2 is the diffusion rate constant. The diffusion data was further analyzed to define the mechanism of release by applying the diffusion data following the empirical equation , $M_1/M_\alpha=Kt^n$, where Mt/M_α is the fraction of drug released at time t, K is a constant and n characterizes the mechanism of drug release from the formulations during diffusion process.

In vitro skin permeation studies

Male wistar rats weighing between 130-160g and free from any visible sign of disease were selected for the in vitro studies. The hair on abdominal region was removed using a depilatory preparation one day prior to experiment. On the day of experiment, animals were sacrificed by cervical dislocation and abdominal skin was excised. The fatty material adhere to the dermis was carefully peeled off. Freshly excised rat skin of thickness (2mm) was mounted on the donor comportment .[10] Formulation G_6 and Formulations GP_1, GP_2, GP_3 and GP_4 were evaluated by studying drug diffusion through Eudragit RLPO membrane and mouse skin.

RESULTS AND DISCUSSION

In the present study efforts were made to prepare transdermal gels of Diltiazem Hydrochloride using polymers like HPMC, NaCMC, M.C and Carbopol. To enhance the permeability of Diltiazem Hcl, various hydrophilic polymers namely PEG6000, PVP were incorporated in 1:1 ratio (NaCMC: polymer) in to the NaCMC gels. The results of the in-vitro diffusion study from different gels across the Eudragit RLPO films prepared with Ethylacetate (8) are showed in Figure 1.

The gel formulations can be graded in the following order with respect to the rates of release of Diltiazem Hydrochloride from them: (HPMC) < (MC) < (Carbopol) <(NaCMC) < (NaCMC +PVP)< (NaCMC+ PEG 6000). Formulation G_6 (NaCMC and PEG 6000) has showed good release pattern when compared to other gel formulations which perhaps may be explained by the fact that PEG 6000 enhances solubility of the drug in aqueous vehicle.

The correlation coefficient values (r) revealed that the diffusion profile follows zero order kinetics and the mechanism of drug release was governed by peppas model. The diffusion exponent of release profiles (slope) has a value of 1.0531-1.0819($n \geq 1$), which indicates super case II

transport diffusion.[11] Permeability coefficient values (P_m) of the films towards the Diltiazem hydrochloride gel was calculated from the drug diffusion data and the results were given in Table 3.

Based on permeability coefficient values Formulation G_6 (NaCMC and PEG 6000) was selected for In-vitro skin permeation study .The skin permeation showed a similar pattern as that of the diffusion profile through rate controlling membrane, but the amount of drug permeated through the skin was not satisfactory. Hence olive oil in the concentrations range from 1% -2.5% were incorporated into the gels with a view to improve permeability of Diltiazem hydrochloride.

The results of the in-vitro diffusion study from different gels containing olive oil in the concentrations range from 1% -2.5% across the Eudragit RLPO films and mouse skin are shown in Figure 2. The correlation coefficient values (r) revealed that the diffusion profiles follows zero order kinetics and the mechanism of drug release was governed by peppas model. The diffusion exponent of release profiles (slope) has a value of 1.011-1.077 ($n \geq 1$), which indicates super case II transport diffusion. Permeability coefficient values (P_m) of the films towards the Diltiazem Hydrochloride gel was calculated from the drug diffusion data and the results were given in Table 4.

The concentrations of olive oil used for increasing the permeation of drug could be arranged in the following increasing order according to their permeation rates : 2.5%> 2%> 1.5% > 1%. The increased permeation rate in all these enhancers may be due to surfactant action.

CONCLUSION

These results indicated that the non ionic surfactant olive oil 2.5% improves the permeability characteristics of Diltiazem Hydrochloride when compared with the other concentrations. Formulation - GP_1 ((NaCMC +PEG 6000+ olive oil-2.5%) shown required release rate in comparison with other formulations and was selected as suitable candidate to be delivered through transdermal route at controlled rate.

Table 1: Composition of Transdermal Gels Containing Various Polymers

INGREDIENTS	G_1	G_2	G_3	G_4	G_5	G_6
Diltiazem HCL (mg)	650	650	650	650	650	650
Sodium CMC (200-300cPs) (mg)	950					
Carbopol 934 (mg)		1400				
Methyl cellulose (28-32%) (mg)			750			
HPMC (50cPs) (mg)				1750		
Sodium CMC: PVP (2.4cP) (1:1) (mg)					950	
Sodium CMC: PEG6000 (1:1)(mg)						950
Glycerin (ml)	2	2	2	2	2	2
Distilled water (ml) up to	20	20	20	20	20	20

Table 2: Composition of Transdermal Gels Containing Various Permeation Enhancers

INGREDIENTS	GP_1	GP_2	GP_3	GP_4
Diltiazem HCL (mg)	650	650	650	650
Sodium CMC: PEG6000 (mg) (1:1)	950	950	950	950
Olive oil 1%	0.232			
Olive oil 1.5%		0.348		
Olive oil 2%			0.465	
Olive oil 2.5%				0.581
Glycerin (ml)	2	2	2	2
Distilled water (ml) up to	20	20	20	20

Table 3: Diffusion Characteristics of Diltiazem Hydrochloride From Various Transdermal Gels

FORMULATION	CORRELATION COEFFICIENT (R) VALUES		DIFFUSION RATE CONSTANT (K) VALUE (mg/h)	DIFFUSION EXPONENT VALUE (n)	PERMEABILITY COEFFICIENT ($P_m X10^3$ mg/cm.h)	T_{90} (h)
	ZERO ORDER	PEPPAS MODEL				
G_1 (NaCMC)	0.9996	0.996	2.640	1.0582	2.908	17.04
G_2 (Carbopol)	0.998	0.9999	2.041	1.0536	2.108	22.34
G_3 (MC)	0.9982	0.996	1.902	1.0798	2.095	23.65
G_4 (HPMC)	0.9983	0.9995	1.740	1.0760	1.917	25.86
G_5(NaCMC +PVP)	0.997	0.999	2.982	1.0531	3.285	15.09
G_6(NaCMC+PEG 6000)	0.9996	0.999	3.32	1.0544	3.658	13.55
G_{6A}*(NaCMC+ PEG 6000)	0.9988	0.9998	1.486	1.0819	1.637	30.28

*Permeability study through mice abdominal skin.

Table 4: Diffusion Characteristics of Diltiazem Hydrochloride From Transdermal Gels Containing Various Permeation Enhancers

FORMULATION	CORRELATION COEFFICIENT (R) VALUES		ZERO ORDER RATE CONSTANT (K) VALUE (mg/h)	DIFFUSION EXPONENT VALUE (n)	PERMEABILITY COEFFICIENT ($P_m X10^3$ mg/cm.h)	T_{90} (h)
	ZERO ORDER	PEPPAS MODEL				
GP_1 (olive oil 2.5%)	0.9993	0.9997	2.032	1.077	2.12	22.16
GP_2 (olive oil 2%)	0.9991	0.9998	1.935	1.072	2.02	23.25
GP_3 (olive oil 1.5%)	0.9998	0.9995	1.813	1.011	1.89	24.82
GP_4 (olive oil 1%)	0.998	0.999	1.781	1.076	1.86	25.26

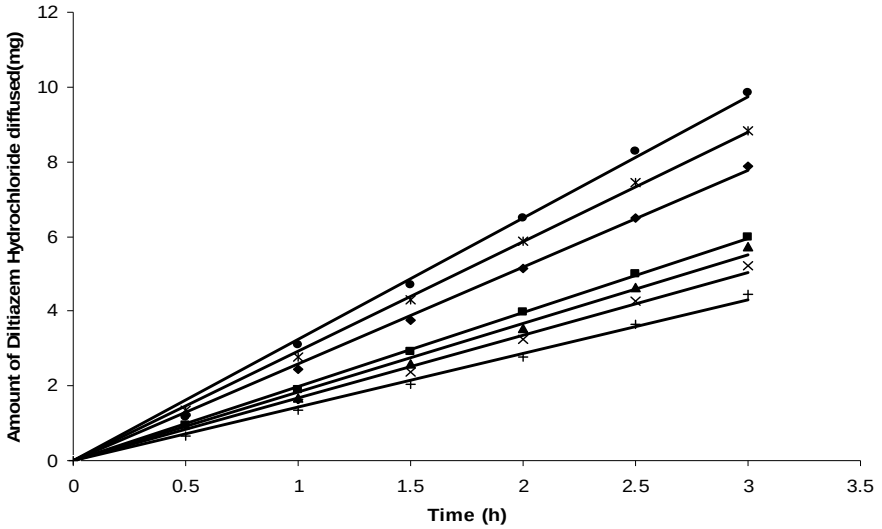

Fig. 1: Diffusion Profiles of Diltiazem Hydrochloride From Transdermal Gels

(-♦-)G_1 (Transdermal gel prepared with NaCMC)
(-■-)G_2 (Transdermal gel prepared with Carbopol
(-+-)G_3 (Transdermal gel prepared with Methyl cellulose)
(-▲-)G_4 (Transdermal gel prepared with HPMC)
(-* -) G_5 (Transdermal gel prepared with NaCMC+PVP)
(-●-)G_6 (Transdermal gel prepared with NaCMC+PEG 6000)
(-×-)G_{6A^*} (Transdermal gel prepared with NaCMC+PEG 6000 through mice abdominal skin

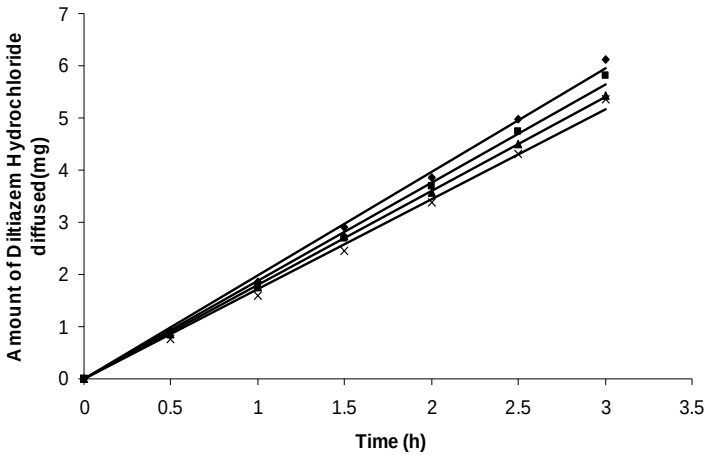

Fig. 2: Diffusion Profiles of Diltiazem Hydrochloride From Transdermal Gels Containing Different Permeation Enhancers

(-♦-) GP_1 (Transdermal gel prepared with olive oil 2.5%)
(-■-)GP_2 (Transdermal gel prepared with olive oil 2%)
(-▲-)GP_3 (Transdermal gel prepared with olive oil 1.5%)
(-×-)GP_4 (Transdermal gel prepared with olive oil 1%)

REFERENCES

1. Murad F In, Gilman AG, Rall WT, Nies SA and Taylor P. Eds.,Good man and Gilman's Pharmacological basis of therapeutics., International, Mc Graw Hill Co., Inc., New York. 1996 ; 9th Edn :762-763.
2. Chein YW. Transdermal controlledsystemic medication. Marcel Dekkar, Inc .,New Work.1976 ;1st Edn: 2-7.
3. Chowdary KPR and Naidu RAS. Preparation and evaluation of cellulose acetate films as rate controlling membranes for transdermal use. Indian Drugs.1992;29:312-315.
4. Sai Kishore V and Saikrishna P. Effect of Casting Solvent and Polymer on Permeability of Glipizide through Rate Controlling Membrane for Transdermal Use. Res J of sci and technol. 2011;3(4):180.
5. Panigrahi L and Goshal S K . Effect of permeation enhancers on the release and permeation kinetics of lincomycin hydrochloride gel formulations through mouse skin. Indian J PharmSci. 2006;68(2):205-211.
6. Robinson JR and Eriksen SP . Theoretical formulation of sustained- release dosage forms.J Pharm Sci.1966;55:1254-1258.
7. Franz TJ. Percutaneous Absorption : On Relvance of Invitro Data,J. Invest.Dermatol. 1975;64:190-194.
8. Fites A L, Banker GS and smolen VF. Controlled Release Through Polymeric Films. J Pharm Sci. 1970;59:610-614.
9. Salomon CJ, Bravo SA and Lamas MA. In-vitro studies of diclofenac sodium controlled-release from biopolymeric hydrophilic matrices. J Pharm Pharmaceut Sci. 2002;5(3):213-219.
10. Rao PR and Diwan PV .Influence of casting solvent on permeability of Ethyl cellulose films for transdermal use. Easteran Pharmacist. 1997;46:135-139.
11. Donald L Wise. Hand book of pharmaceutical controlled release technology, Marcel Dekker, Cambridge. 2005; 1st Edn:187-188.