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RESEARCH ARTICLE

PREPARATION AND EVALUATION OF CAPTOPRIL TRANSDERMAL PATCHES

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Transdermal matrix patches of captopril were prepared by casting method employing different ratios of polyvinyl alcohol, ethyl cellulose, polyvinyl pyrrolidone and hydroxypropyl methylcellulose. The prepared matrix patches were evaluated for physicochemical characteristics such as thickness, weight variation, folding endurance, drug content, percent moisture content, water vapour transmission and *in vitro* drug permeation studies. The results of all physical parameters were satisfactory for the prepared formulations. Drug permeation studies revealed that P21 (EC:PVP K30::3:1) exhibited the highest drug release in 24 h (99.82%) followed by diffusion mechanism as evidenced by Higuchi model (r^2=0.9-0.99). The hydrophilic and hydrophobic polymers in combination showed sufficient potential for the development of transdermal drug delivery system of captopril.

Key words: Captopril, Transdermal drug delivery system, Matrix film, Hypertension, Goat skin.

INTRODUCTION

Literature is enriched with several findings in which techniques for sustained and controlled delivery of drugs have been reported (Dahiya and Gupta, 2011; Kumar and Dureja, 2011; Tripathi *et al* 2011). Transdermal drug delivery system (TDDS) is one of the controlled release system consisting of formulations which are topically applied to deliver drug for systemic effects at a predetermined and controlled rate. The potential advantage of transdermal drug delivery include enhanced efficiency, increased safety, greater convenience, improved patient compliance and avoidance of first-pass gut. (Chien, 1992; Banker and Rhodes, 1990). A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication (Ansel *et al* 1999).

Captopril is an orally active inhibitor of an angiotensin converting enzyme and widely used in the treatment of hypertension and some of the congestive heart failure. The drug is considered for the treatment of antihypertensive therapy due to its low toxicity (Nur and Zhang, 2000). Captopril shows 70% oral bioavailability but presence of food reduces the oral absorption by 25-40%. Captopril is freely water soluble, has a relatively short elimination half life in plasma (1.6-1.9 h) (Jarrott *et al* 1982). Therefore, the objective of the present study was to develop the controlled release polymeric transdermal films and improve the therapeutic effect of drug.

MATERIALS AND METHODS

Captopril was a gift sample from Wockhardt Limited, Mumbai. PVP K30, HPMC K15M, ethyl cellulose (EC), polyvinyl alcohol (PVA) and dibutyl phthalate were purchased from CDH, Mumbai. Solvents used were of AR grade.

Drug polymer compatibility studies

The drug-polymer compatibility study was carried out using differential scanning calorimetry (DSC-Jade) to confirm the absence of

any possible physical or chemical interaction between the captopril and polymers HPMC, PVP, PVA and EC.

Preparation of transdermal patches

The films were prepared by casting method (about 3.1 mg/square centimeter patch) using solvent evaporation technique (Arora and Mukherjee, 2002). Dibutyl phthalate was incorporated as a plasticizer at a concentration of (1%, 2%, 3%, 4% 5%, 6% *v/v*). Backing membranes were casted by pouring and then evaporating 4% aqueous solution of polyvinyl alcohol in petridish, at 60°C in hot air oven for 6 h. The matrices were prepared by pouring the homogeneous dispersion of captopril with different blends of either type of lipophilic polymer (EC or HPMC) with PVP in chloroform on the backing membrane in prefabricated glass moulds. The above dispersion was evaporated slowly at 40°C for 2 h to achieve a drug-polymer matrix patch. The dry patches were kept in desiccators until use. Before final formulations, the patches were made with different ratios of polymers and the optimized polymer combination was further selected to develop drug loaded patches (**Table 1**).

Table 1. Optimization study of transdermal patches without drug

Formulation code	Polymer EC:PVP (*w/v*)	Polymer HPMC:PVP (*w/v*)	Plasticizer	Solvent (ml)	Result
P1	-	3:1, 3:2, 1:1	Glycerol (1 %)	Ethanol: Methanol (1:1)	Polymers were found to be insoluble with solvent system. Separations of different layers was observed
P2	-	1:3, 2:3, 4:1	Glycerol (1 %)	Ethanol: Methanol (1:1)	Polymers were found to be insoluble with solvent system. Separations of different layers was observed.
P3	-	3:1, 3:2, 1:1	*n*-Dibutyl phthalate	Ethanol: Water (1:3)	Polymers were found to be insoluble with solvent system. Separations of different layers was observed
P4		1:3, 2:3, 4:1	*n*-Dibutyl phthalate	Ethanol: Water (1:3)	Polymers were found to be insoluble with solvent system. Separations of different layers was observed
P5	-	2:3	n-Dibutyl phthalate	Water: Ethanol (1:3)	Polymers were found to be insoluble with solvent system.
P6	-	2:3	n-Dibutyl phthalate	Chloroform	Very thin, slightly wet, broken layer of polymeric film was observed
P7	3:1, 3:2, 1:1	-	Glycerol	Ethanol	Polymers were found to be insoluble with solvent system. Formulated polymeric film is found to be hazy or milky-like in appearance
P8	1:3, 2:3, 4:1	-	Glycerol	Ethanol + water	Polymers were found to be insoluble with solvent system. Film is found to be hazy or milky-like
P9	3:1, 3:2, 3:3	-	Glycerol	Ethanol + water	Polymers were found to be insoluble with solvent system. Separations of different layers have been observed
P10	3:1, 3:2, 3:3	-	Glycerol	Ethanol: Methanol	Polymers were found to be insoluble with solvent system. Formulated polymeric film is found to be hazy or milky-like in appearance
P11	3:1, 3:2, 3:3	-	Glycerol	Methanol	This composition was observed unsuitable for the formulation of the desired polymeric film
P12	3:1, 3:2, 3:3	-	*n*-Dibutyl phthalate	Ethanol: Methanol	This composition was observed unsuitable for the formulation of desired film

Table 1. *Contd.*

P13	3:1, 3:2, 3:3	-	Glycerol	Chloroform	Very thin, slightly wet, braked layer of polymeric film was observed.
P14	1:3, 2:3, 4:1	-	Glycerol	Chloroform	Very thin, slightly wet, braked layer of polymeric film was observed
P15	3:1, 3:2, 3:3	-	*n*-Dibutyl phthalate	Chloroform	Very thin, slightly wet, broken layer of polymeric film was observed
P16	1:3, 2:3, 4:1	-	*n*-Dibutyl phthalate	Chloroform	Very thin, slightly wet, braked layer of polymeric film was observed
P17	3:1	-	*n*-Dibutyl phthalate (1-6%)	Chloroform	Hard, breakable, tough
P18	3:1	-	*n*-Dibutyl phthalate (4%)	Chloroform	Flexible, smooth, tough
P19	3:1	-	*n*-Dibutyl phthalate (5%)		Less sticky, glossy, wet film was observed
P20	3:1	-	*n*-Dibutyl phthalate (4%)	Chloroform	Flexible smooth less sticky film observed. This concentration was further used for formulation
P21	3:1	-	*n*-Dibutyl phthalate (5%)	Chloroform	Flexible smooth less sticky film observed. This concentration was further used for formulation
P22	3:1	-	*n*-Dibutyl phthalate (6%)	Chloroform	Sticky, glossy, wet film was observed

*Backing membrane PVA: P13-P22 - 4%, **Penetration enhancer Span 80:P20-P22 -1%

Evaluation of transdermal patch uniformity of thickness and uniformity of weight

The thickness of the patches was measured at five different sites on three patches from each batch using vernier caliper and the average was calculated. Weight variation test of captopril was done by weighing three patches individually from each batch. The average weight of the patch was taken as original weight (Kanig and Goodman, 1962; Rajagopal *et al* 2005).

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it either breaks or develops visible cracks on folding number of times manually, which was considered satisfactory to reveal good patch properties (Khurana *et al* 2000). This is important to check the ability of sample to withstand folding. This also gives an indication of brittleness. The number of times the films could be folded at the same place without breaking gives the value of folding endurance (Raghuraman *et al* 2002).

Drug content

Dissolve the patch (3 cm^2 in diameter) from each batch in 10 ml of phosphate buffer pH 7.4 for 12 h under occasional shaking. The 5 ml solutions were taken and diluted with phosphate buffer pH 7.4 up to 10 ml, and the resulting solution was filtered through whatmann filter paper no. 2. The drug content was determined after proper dilution at 214 nm using a UV spectrophotometer (Shimadzu 1700). Drug content was determined using slope of standard curve (Deshmane *et al* 2009).

Water vapour transmission

Glass vials (transmission cell) filled with 1 g anhydrous calcium chloride and adhesive spreaded across its rim. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37±2°C (Singh *et al* 2008). The difference in weight after 24 h, 3rd day and 1 week of storage was calculated. The experiments were carried out in triplicate and vapor transmission rate (VTR) was obtained as follow:

$$VTR = \frac{\text{Amount of moisture transmitted}}{\text{Area x Time}}$$

Moisture content

The film was weighed and kept in a desiccator containing anhydrous calcium chloride at 40°C for 24 h. The film was weighed until it showed a constant weight (Koteshwar, 1992).

$$\text{Moisture content} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Tensile strength

The tensile strength (T.S.) of prepared matrix patch was determined by fixing both the ends of the film between the adhesive tapes to give support while fixing between two iron plates, the weights required to break the patch was noted, simultaneous elongation was measured with the help of a pointer mounted on the assembly (Allen *et al* 1972; Khanna *et al* 1970) and calculated the tensile strength using the following formula:

$$\text{Tensile strength} = \frac{\text{Break force}}{\text{a x b}} \times 1 + dl/l$$

where, l, a and b are length, width and thickness of the test strip respectively and dl is the elongation at break.

In vitro permeation study

Modified Franz diffusion cell with a receiver compartment volume of 200 ml, effective permeation area of 2.5 cm^2 was used for this study. *In vitro* drug permeation study was performed using goat skin in phosphate buffer pH 7.4 (Murthy and Hiremath, 2001). Fresh abdominal skin of goat were collected from slaughter house and used in the permeation experiments. Abdominal skin hairs were removed and skin was hydrated in normal saline solution. The adipose tissue layer of the skin was removed by rubbing with a cotton swab. Skin was kept in phosphate buffer solution pH 7.4 and stored at 0-4°C (Chang *et al* 2006).

To perform skin permeation study, treated skin was mounted horizontally on the receptor compartment with the stratum corneum side facing upward towards the donor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment and capacity of receptor compartment was 200 ml. The receptor compartment was filled with phosphate buffer solution pH 7.4 maintained at 37±0.5°C and stirred by a magnetic bar at 100 rpm. Patch (2 cm^2) placed on the top of the diffusion cell was covered. At appropriate time interval, 5 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffer. The sample was analyzed spectrophotometrically at 214 nm (Tanwar, 2005; Nayak, 2010).

RESULTS AND DISCUSSION

The results of DSC studies showed absence of interactions between polymers and drug (**Figure 1, 2**). Precipitation or turbidity occurs in some of batches (P1, P2, P3, P4, P5, P6, P7, P8, P9, P10, P11, P12, P13, P14, P16, P17 and P22) of patches containing captopril which could be due to presence of glycerol and solvent system at accelerated temperature. Hence, these batches were discarded and remaining batches (P18, P19, P20 and P21) were considered for further study (**Table 1**). The thickness and weight of matrix films were found to be uniform, as indicated by low standard deviation values among different batches. This suggested an even distribution of the drug and the polymers in the matrix film casted over the PVA as a backing membrane. Good drug content uniformity among the batches was observed for all the formulations indicating that the drug was homogenously dispersed in the matrix films. The moisture content was found to increase slightly with increasing concentration of the hydrophilic polymer PVP in the films (**Table 2**). The moisture present in the matrix aided in preventing drying and brittleness of the films. Water vapour transmission studies indicated that the films were permeable to water vapour and followed Higuchi kinetics.

The patch formulation containing EC:PVP (3:1), plasticizer concentration (4% and 5%) and permeation enhancer 1% were physically stable. Hence these four formulations were considered for *in vitro* diffusion study. Captopril release data was fitted to zero order first order, the Higuchi and Peppas empiric mathematical model. The *in vitro* drug release were found to follow Higuchi release, as correlation coefficient (r^2=0.9-0.99), indicating that the drug governed by Fickian diffusion mechanism. Water soluble drugs are released from the polymer matrix primarily by diffusion, while poorly water soluble drugs are released predominantly by erosion mechanism. The results suggested that, PVP being a hydrophilic polymer, permeation and physical

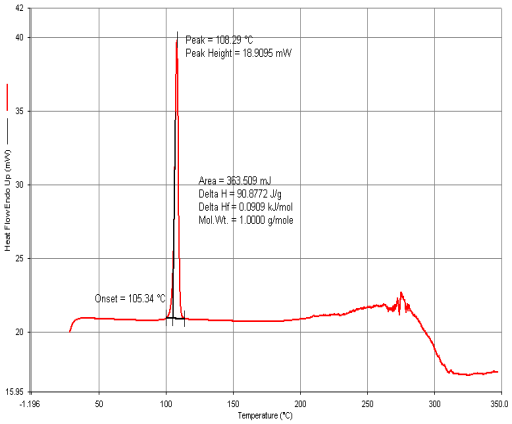

Fig. 1. DSC spectrum of Captopril (ACE inhibitor)

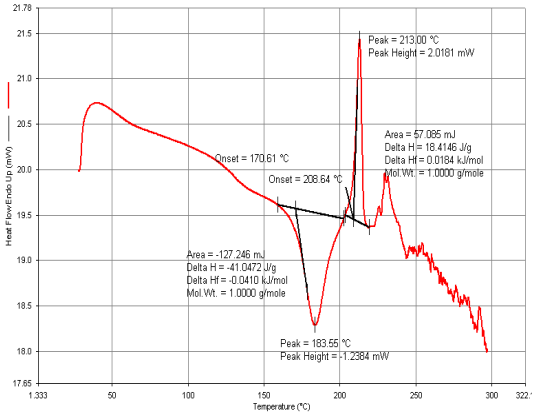

Fig. 2. DSC spectrum of drug with HPMC, EC, PVP and PVA

Table 2. Evaluation and characteristics of transdermal patches

S. No.	Evaluation Parameters	Batch code			
		P18	P19	P20	P21
1	Uniformity of thickness (mm)	0.231±0.004	0.212±0.002	0.125±0.003	0.179±0.010
2	Weight variation (mg)	No change	0.5	No change	No change
4	Folding Endurance	>350	>350	>350	>350
5	Drug content (%)	94.40±1.23	95.60±1.63	98.80±2.05	96.00±1.09
6	Water vapour transmission ($gcm^{-2}h^{-1}$)	6.88×10^{-3}	8.47×10^{-3}	5.87×10^{-3}	4.85×10^{-3}
7	Moisture content (mg)	0.5309±0.003	0.4213±0.005	0.4379±0.007	0.3745±0.002
8	Tensile strength	0.275±0.001	0.243±0.004	0.193±0.003	0.198±0.003

characteristics of the films, increased with increase in proportion of *n*-dibutyl phthalate in formulations P18-P21. Thus, based on physical attributes of matrix films and satisfactory release and permeation profile, formulation P21 was selected as the best among formulated systems. The results indicated that dibutyl phthalate acted as permeation enhancer, though it is being used as plasticizer in various pharmaceutical dosage forms. The 5% DBP not only exhibited good film forming properties, but along with span 80 and EC, also enhanced drug diffusion and permeation rate.

CONCLUSION

The formulation containing 3:1 (EC:PVP), 5% *n*-dibutyl phthalate with 1% span 80 showed optimum release followed by diffusion mechanism. Based on the study results, it can be concluded that span 80 were better suited with *n*-dibutyl phthalate as plasticizer as well as permeation enhancer for the development of captopril transdermal patch. However, advanced pharmacokinetic and pharmacodynamic studies are required to be carried out before establishing the therapeutic usefulness of the developed patches.

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