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Original research paper

Development and evaluation of carvedilol transdermal patches

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Transdermal patches of carvedilol with a HPMC-drug reservoir were prepared by the solvent evaporation technique. In this investigation, the membranes of Eudragit RL100 and Eudragit RS100 were cast to achieve controlled release of the drug. The prepared patches possessed satisfactory physicochemical characteristics. Thickness, mass and drug content were uniform in prepared batches. Moisture vapour transmission through the patches followed zero-order kinetics. *In vitro* permeation studies were performed using a K-C diffusion cell across hairless guinea pig skin and followed the super case II transport mechanism. The effects of non-ionic surfactants Tween 80 and Span 80 on drug permeation were studied. The non--ionic surfactants in the patches increased the permeation rate, Span 80 exhibiting better enhancement relative to Tween 80. The patches were seemingly free of potentially hazardous skin irritation.

Keywords: carvedilol, transdermal patches, *in vitro* permeation, permeation rate

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Carvedilol is a novel, multiple-action cardiovascular drug that is currently approved in many countries for the treatment of hypertension. The reduction in blood pressure produced by carvedilol results primarily from beta-adrenoceptor blockade and vasodilation, the latter resulting from alpha 1-adrenoceptor blockade. These actions as well as several other carvedilol activities are associated with cardioprotection in animal models that occurs to a degree that is greater than that observed with other drugs. The multiple actions of carvedilol may also provide the underlying rationale for the use of the drug in the treatment of coronary artery disease and congestive heart failure (1).

Carvedilol is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver; its absolute bioavailability is about 25%. It has a half-life of 2.2 ± 0.3 h; longer half-lives of about 6 h have been measured at lower concentrations (2, 3).

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Carvedilol was chosen as the model candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a transdermal drug delivery system: low molecular mass, high lipid solubility, effective in low plasma concentration as well as a high degree of first-pass metabolism. It also means multiple daily administration with subsequent lack of patient compliance. The aim of this study was to develop and evaluate transdermal patches of carvedilol so as to prevent its first-pass metabolism and achieve controlled release.

EXPERIMENTAL

Material and methods

Carvedilol was a gift from Sun Pharmaceutical Industries Ltd. (India). Eudragit RL100 was kindly supplied by Intas Lab. Pvt. Ltd. (India). Torrent Research Centre (India) donated Eudragit RS100. Polyvinyl pyrrolidone K30, propylene glycol, Span 80 and Tween 80 were purchased from Otto Kemi Ltd. (India). All the other chemicals were of analytical grade.

Drug partition coefficient

The partition coefficient study was performed using *n*-octanol as the oil phase and phosphate buffer pH 7.4 as the aqueous phase. The two phases were mixed in equal quantities and were saturated with each other on a mechanical water bath shaker at 37 °C for 24 h. The saturated phases were separated by centrifugation at 2000 rpm. Standard plots of the drug were prepared from both phosphate buffer pH 7.4 and *n*-octanol. Equal volumes (10 mL) of the two phases were placed in hexaplicate in conical flasks and, to each, 100 mg of drug was added. The flasks were shaken at 37 °C for 6 h to achieve complete partitioning at 100 rpm. The two phases were separated by centrifugation at 1000 rpm for 5 min and were then analyzed for respective drug contents (4).

Preparation of patches

Transdermal patches containing carvedilol were prepared by the solvent evaporation technique in cylindrical glass molds with both sides open (5). The bottom of the mold was wrapped with aluminum foil, on which the backing membrane was cast by pouring a 4% (*m*/*V*) polyvinyl alcohol (PVA) solution followed by drying at 60 °C for 6 h. The drug reservoir was prepared by dissolving hydroxyl propyl methyl cellulose (HPMC) in distilled water. Propylene glycol 30% (*m*/*m*) of polymer composition was used as a plasticizer. The drug 0.292% (*m*/*V*) (in 5 mL methanol) was added into the homogeneous dispersion under slow stirring with a magnetic stirrer. The uniform dispersion was cast on a PVA backing membrane and dried at 45 °C for 6 h. The rate-controlling membrane was cast on the drug reservoir using 2% (*m*/*V*) of Eudragit RL100 (ERL) or Eudragit RS100 (ERS) with 0.10% (*m*/*V*) of polyvinyl pyrrolidone K30 (PVP) in dichloromethane and 30% (*m*/*m*) propylene glycol. 1% (*m*/*V*) of permeation enhancer (Tween 80, Span 80) was incorporated in the drug reservoir of formulations T-4, T-5, T-6 and T-7

Table I. Composition of transdermal patches

Formulation	Backing layer (4%, *m/V*)	Drug reservoir[a] (3%, *m/V*)	Rate-controlling membrane[b] (2%, *m/V*)	Permeation enhancer (1%, *m/V*)
T-1	PVA	HPMC	–	–
T-2	PVA	HPMC	ERS	–
T-3	PVA	HPMC	ERL	–
T-4	PVA	HPMC	ERS	Tween 80
T-5	PVA	HPMC	ERS	Span 80
T-6	PVA	HPMC	ERL	Tween 80
T-7	PVA	HPMC	ERL	Span 80

PVA – polyvinyl alcohol, HPMC – hydroxypropyl methylcellulose, ERL – Eudragit RL100, ERS – Eudragit RS100
[a] With carvedilol (0.292%, *m/V*).
[b] With PVP (0.1%, *m/V*).

(Table I). The films were cut into small patches (3.14 cm^2) containing 3.25 mg of carvedilol and stored between sheets of wax paper in a desiccator.

Evaluation of patches

Thickness. – The thickness of patches was measured at three different places using a micrometer (Mitutoyo Co., Japan) and mean values were calculated (6).

Mass variation. – The patches were subjected to mass variation by individually weighing 10 randomly selected patches. Such determinations were carried out for each formulation (7).

Folding endurance. – This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance (8).

Moisture vapour transmission (MVT). – MVT is defined as the quantity of moisture transmitted through unit area of film in unit time (9). Glass cells were filled with 2 g of anhydrous calcium chloride and a film of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH) at 27 ± 2 °C for 24 h.

Drug content uniformity. – Patches of specified area (3.14 cm^2) were dissolved in 5 mL of dichloromethane and the volume was made up to 10 mL with phosphate buffer pH 7.4; dichloromethane was evaporated using a rotary vacuum evaporator at 45 °C. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45-μm membrane, diluted suitably and absorbances were read at 242 nm in a double beam UV-Vis spectrophotometer (Thermospectronic-1, UK).

In vitro *permeation studies*. – Films measuring 3.14 cm^2 were subjected to an *in vitro* permeation study using a modified Keshary-Chien diffusion cell (cell capacity 75 mL). Male guinea pigs (Hartley strain, $n = 5$ for each formulation), each weighing 250 to 300 g and 6 months of age were used in the present study. They were housed in cages in the

animal house under controlled temperature (27 ± 2 °C) and light conditions. They were fed a standard laboratory diet; water was provided *ad libitum.* Guinea pigs were killed by cervical dislocation and dorsal skin was removed. After removing the epidermal hairs and subcutaneous fat, the skin was thoroughly washed and placed overnight in contact with the receptor phase, phosphate buffer pH 7.4 (10, 11).

Guinea pig dorsal skin was clamped between the donor and recipient compartments. The film was placed in the donor compartment over the skin and covered with parafilm. The temperature of receptor phase was maintained at 37 ± 1 °C throughout the experiment. The compartment was in contact with the ambient environment. The amount of drug permeated through guinea pig skin was determined by withdrawing samples of 1 mL at predetermined time intervals and replacing them with an equal volume of prewarmed buffer (37 ± 1 °C). The samples were analyzed for drug content at 242 nm.

Primary skin irritancy studies. – Albino rabbits of either sex, each weighing 1.5 to 2.0 kg and 24 months of age were used in this study (n = 5 in each group). They were housed in cages in the animal house under controlled temperature (27 ± 2 °C) and light conditions. They were fed a standard laboratory diet; water was provided *ad libitum.* The dorsal surface of the rabbits was cleared and the hairs were removed by shaving. The skin was cleared with rectified spirit. The patches were applied to the shaved skin of rabbits and secured using adhesive tape USP (Leucoplast^{TM}). On one side of the back, a control patch (without any drug, group I) and on the other side an experimental patch (group II) were secured. A 0.8% (V/V) aqueous solution of formaldehyde was applied as a standard irritant (group III) and its effect was compared with test. The animals were observed for any sign of erythema or oedema for a period of 7 days and scored as reported by Draize *et al.* (12).

Ethical clearance for the handling of experimental animals was obtained from the institutional animal ethical committee (IAEC) formed for this purpose.

RESULTS AND DISCUSSION

n-Octanol and *in vitro* study fluid (here phosphate buffer, pH 7.4) are considered to be the standard system for determining the drug partition coefficient between skin and *in vitro* fluid (4). The logarithmic value of the partition coefficient (log P) was found to be 0.79 ± 0.03. The results obtained indicate that the drug possesses sufficient lipophilicity, which meets the requirements of formulating it into a transdermal patch.

In the present study, transdermal patches of carvedilol were formulated using the hydrophilic polymer matrix of hydroxyl propyl methyl cellulose and the effect of Eudragit RL100 and Eudragit RS100 as rate-controlling membrane was studied. The prepared patches were characterized for physicochemical properties, *in vitro* permeation profile across excised hairless guinea pig skin and skin irritation studies in albino rabbits.

The physicochemical properties of carvedilol transdermal patches are presented in Table II. The thickness of patches varied from 81.5 ± 0.01 to 96.8 ± 0.0 μm (n = 5); casting of the rate-controlling membrane increased the thickness. The mass was found to be uniform in the prepared batches and varied from 38.1 ± 0.0 to 79.1 ± 0.01 mg per patch. The

Table II. Evaluation of transdermal patches[a]

Parameter	T-1	T-2	T-3	T-4	T-5	T-6	T-7
Thickness (μm)	81.5±0.0$_1$	90.1±0.0$_1$	90.8±0.0	96.2±0.0	96.8±0.0	93.3±0.0	93.9±0.0
Mass of 2.0 cm diameter discs (mg)	38.1±0.0	64.9±0.0$_3$	72.3±0.1	69.5±0.0$_3$	68.5±0.0	79.1±0.0$_1$	77.4±0.0$_3$
Folding endurance	302.7±7.4	324.3±5.0	339.4±2.3	320.1±4.0	319.0±5.2	334.1±7.4	331.0±5.4
MVT in 24 h (mg cm^{-2} h^{-1})	0.168±0.004	0.132±0.001	0.115±0.002	0.141±0.007	0.149±0.005	0.123±0.003	0.130±0.005
Drug content (mg per patch)	3.25±0.02	3.25±0.01	3.24±0.02	3.24±0.01	3.24±0.01	3.24±0.01	3.25±0.02
Permeation rate (mg cm^{-2} h^{-1})	3.18±0.01	0.87±0.02	0.98±0.01	0.93±0.01	1.19±0.01	1.03±0.02	1.32±0.01

[a] Results are expressed as mean ± SD (n = 5).

folding endurance measures the ability of patch to withstand rupture; folding endurance was in the range of 302.7 ± 7.4 to 339.4 ± 2.3 (n = 5); patch T-1 representing the least value. The patch formulated with HPMC alone showed maximum MVT of 0.168 ± 0.004 mg cm^{-2} h^{-1}, which can be attributed to the hydrophilic nature of the polymer. The casting of the HPMC-drug reservoir with the rate-controlling membrane of Eudragit RS100 decreased the values of the moisture vapour transmission rate. Incorporation of non-ionic surfactant in the patches increased the MVT. The MVT through the patches followed a pattern close to zero-order kinetics. For various formulations, the drug content was between 3.24 ± 0.01 to 3.25 ± 0.02 mg per patch. The drug content analysis of the prepared formulations has shown that the process employed to prepare patches in this study was capable of giving films with a uniform drug content and minimum batch variability.

Release of the drug from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. *In vitro* permeation studies are predictive of *in vivo* performance of a drug. In this study, different formulations released variable amounts of carvedilol through guinea pig skin in the *in vitro* fluid. To examine the drug permeation kinetics and mechanism, the data were fitted to models representing zero-order, first-order and Korsmeyer-Peppas (13, 14). Drug permeation profiles from different formulations are shown in Fig. 1. It was found that 95.1% of drug was released within 9 h from T-1 (without the rate-controlling membrane) and followed first-order kinetics. This means the patch is to be applied several times a day. Therefore rate-controlling membranes of Eudragit RL100 and Eudragit RS100 with PVP were cast with the aim to achieve controlled release of carvedilol from drug reservoirs of HPMC. The cumulative amount of drug permeated after 24 h from T-2 (ERS as the rate-controlling membrane) and T-3 (ERL as the rate-controlling membrane) was found to be 64.5 and 66.4%, respectively. Two surfactants differing in their hydrophile-lipophile balance (HLB) number were therefore,

considered. The non-ionic surfactants Tween 80 (HLB = 15.0) and Span 80 (HLB = 4.3) were incorporated in the patches to enhance the drug permeation across guinea pig skin. *In vitro* permeation studies of patches with enhancers indicate that 66.9, 80.3, 72.9 and 89.8% of the drug permeated at the end of 24 h from T-4, T-5 (ERS as the rate-controlling membrane), T-6 T-7 (ERL as the rate-controlling membrane), respectively. There was improvement in the drug permeability across guinea pig skin in the formulations containing a permeation enhancer. Permeation rates of the patches with non-ionic surfactants were about 1–1.5 fold higher than in those without enhancers. The permeation rate for formulations T-4 to T-7 was in the range 0.929–1.322 mg cm^{-2} h^{-1}. The highest permeation rate was observed in the patches containing Span 80, followed by the patches containing Tween 80. The effectiveness of permeation enhancers was determined by comparing drug flux in the presence and absence of each enhancer and their ratio was defined as the enhancement factor (13). The non-ionic surfactant Span 80 showed the best enhancement with an enhancement ratio of 1.35 and 1.38 for patches T-5 (ERS as the rate-controlling membrane) and T-7 (ERL as the rate-controlling membrane), respectively. The presence of Tween 80 in the patches also enhanced the permeation rate but to a lesser extent, with enhancement ratio of 1.05 and 1.22 for T-4 and T-6, respectively. Span 80, which was of the lower HLB number, was more effective than Tween 80 in increasing the solubility, and thereby increasing the permeation rate of carvedilol. These results indicate that the nature of the enhancer head group greatly influences cutaneous barrier impairment. The more hydrophobic surfactant Span 80 enhanced the carvedilol skin penetration probably due to changes in the barrier properties of the skin and in the vehicle-stratum corneum partition coefficient.

The kinetic parameters of drug permeation for different formulations are presented in Table III. The zero-order plots of T-2, T-3, T-4, T-5, T-6 and T-7 were found to be fairly linear, as indicated by their high regression values. Therefore it was ascertained that the drug permeation from these formulations could follow either near zero or zero-order kinetics. Hence, to confirm the exact mechanism of drug permeation from these patches, the data were fitted according to the Korsmeyer-Peppas model (14). Korsmeyer *et al.* used a simple empirical equation to describe the general solute release behaviour from controlled release polymer matrices:

$$m_t/m_\infty = k\ t^n$$

where m_t/m_∞ is the fraction of drug released, k is the kinetic constant, t is release time and n is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism (14, 15). The value of n gives an indication of the release mechanism: when $n = 1$, the release rate is independent of time (zero-order) (case II transport), $n = 0.5$ stands for Fickian diffusion and when $0.5 < n < 1.0$, diffusion and non-Fickian transport are implicated. Lastly, when $n > 1.0$, super case II transport is apparent. n is the slope value of log m_t/m_∞ *vs.* the log time curve (16).

In the present study, the coefficient of determination (R^2) was found to be much closer to 1 for the Korsmeyer-Peppas equation. Slope values ($n > 1.0$) suggest that the drug permeation from transdermal patches (T-2 to T-7) followed the super case II transport mechanism, possibly owing to chain disentanglement and swelling of hydrophilic

Table III. Kinetics of in vitro *carvedilol permeation across guinea pig skin from transdermal patches*

Code	Zero-order		First-order		Korsmeyer-Peppas	
	k_0 (mg h^{-1})	R^2	k_1 (h^{-1})	R^2	n	R^2
T-1	0.327	0.963	–0.130	0.990	0.660	0.957
T-2	0.088	0.990	–0.018	0.962	1.098	0.999
T-3	0.094	0.982	–0.022	0.974	1.118	0.993
T-4	0.099	0.991	–0.020	0.969	1.082	0.996
T-5	0.121	0.991	–0.031	0.961	1.206	0.998
T-6	0.104	0.990	–0.024	0.986	1.080	0.997
T-7	0.134	0.989	–0.041	0.929	1.208	0.995

polymer, HPMC. Formulation T-7 with ERL as the rate-controlling membrane and Span 80 was found to be better, since constant and about 90% of the drug permeation was observed up to 24 h. The higher proportion of quaternary ammonium groups in ERL resulted in rapid hydration and drug release, whereas the lower proportion of ammonium groups in ERS is responsible for prolonged release of carvedilol (17).

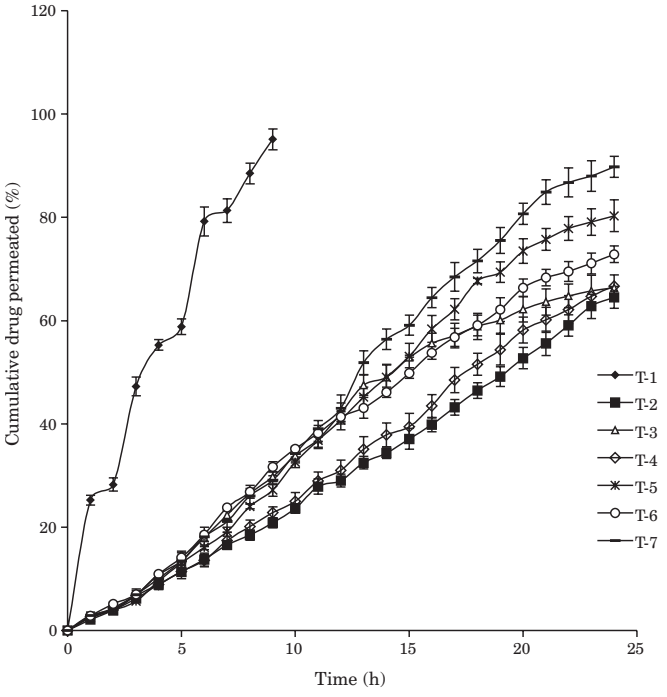

Fig. 1. *In vitro* permeation profiles of carvedilol through excised hairless guinea pig skin (mean ± SD, n = 5).

Patches T-4, T-5, T-6 and T-7 were subjected to skin irritation studies. No signs of erythema, oedema or ulceration were observed on the skin of albino rabbits after 7 days.

CONCLUSIONS

Transdermal patches consisting of the HPMC-drug reservoir with Span 80 as permeation enhancer and rate-controlling membranes of Eudragit RS100 and Eudragit RL100 demonstrated sustained and controlled release of the drug across guinea pig skin during *in vitro* permeation studies. Further, their potential to improve carvedilol bioavailability in humans needs to be investigated in further studies.

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S A Ž E T A K

Priprava i vrednovanje transdermalnih flastera karvedilola

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Metodom evaporacije otapala pripravljeni su transdermalni flasteri karvedilola s HPMC-lijek rezervoarom, s membranama od Eudragita RL100 i Eudragita RS100 koje kontroliraju oslobađanje. Flasteri su bili zadovoljavajućih fizičko-kemijskih svojstava, ujednačene debljine, mase i sadržaja ljekovite tvari. Prijelaz vlage i pare kroz flastere slijedio je kinetiku nultog reda. *In vitro* permeacija praćena je na koži zamorca pomoću K-C difuzijske ćelije, a slijedila je super II transportni mehanizam. Također je ispitivan učinak neionizacijskih površinski aktivnih tvari Tween 80 i Span 80 na permeaciju karvedilola. Rezultati su pokazali da su obje površinski aktivne tvari povećale permeaciju, ali Span 80 više. Flasteri nisu nimalo uzrokovali iritaciju kože.

Ključne riječi: karvedilol, transdermalni flasteri, *in vitro* permeacija, brzina permeacije

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