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Effect of penetration enhancers on the release and skin permeation of bupranolol from reservoir-type transdermal delivery systems

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Abstract

A reservoir-type transdermal delivery system (TDS) of bupranolol (BPL) was designed and evaluated for different formulation variables like gel reservoirs (made with anionic and nonionic polymers), rate controlling membranes and penetration enhancers on the drug release and in vitro skin permeation kinetics of the devices. Keshary–Chien type diffusion cells and pH 7.4 phosphate buffered saline (PBS) were used for drug release studies and excised rat skin was used as a barrier for permeation experiments. The release rate of BPL from nonionic polymer gel reservoirs [hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC)] was much higher than anionic polymer gel reservoirs [carboxymethyl cellulose (CMC), sodium carboxymethyl cellulose (Na CMC) and sodium alginate)]. Among different rate controlling membranes, Cotran™ -polyethylene microporous membrane demonstrated highest release rate for BPL than all other membranes. An optimized TDS formulation with HPC gel and Cotran™ -polyethylene microporous membrane was used to study the effect of penetration enhancers on the release and skin permeation rate of BPL from the TDS. Permeation rates of the devices containing 5% (w/v) pyrrolidone (PY) or 1-methyl-2-pyrrolidone (MPY) were about 3- and 1.5-fold higher than control (no enhancer, $P < 0.01$) indicating PY to be better penetration enhancer for BPL than MPY. The permeation rates of devices containing partially methylated β-cyclodextrin (PMβCD) and PMβCD–BPL complex were about 2.5- and 1.4-fold higher than control ($P < 0.01$). Inclusion of 10 and 30% w/v propylene glycol (PG) in the devices increased the permeation rate by 1.4- and 1.8-fold higher than control ($P < 0.05$). In conclusion, reservoir-type TDS of BPL was developed and penetration enhancers increased the skin permeation of BPL at 4–5 times higher levels than the desired target delivery rate.

Keywords: Bupranolol; Transdermal; Patches; Penetration enhancer

1. Introduction

Transdermal delivery is a successful controlled release technology in terms of the number of approved

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products, which are on the market (Guy, 1996). The feasibility of transdermal route for systemic drug delivery has lead to successful development and marketing of transdermal delivery systems (TDS) of several drugs. It is expected that many more drugs will be included in the list of successful TDS formulations. Presently several classes of drugs are under investigation to determine their potential for TDS development. The penetration through stratum corneum is the rate-limiting step for delivery of most of the drugs and this has lead to considerable activity towards different percutaneous penetration enhancement technologies (Prausnitz et al., 2004). Chemical penetration enhancement has been studied most extensively and is expected to play a leading role in the introduction of more TDS products

Bupranolol (BPL) is a potent nonselective beta-blocking agent, without intrinsic sympathomimetic activity (Weisser et al., 1989). Upon oral administration it undergoes an extra-ordinary first-pass metabolism (>90% in humans) and is rapidly eliminated with a biological half-life of ∼2.0 h (Waller et al., 1982, Wellstein et al., 1986). This demands multiple ingestion of high oral dose of BPL for its clinical effects (100–400 mg per day in divided doses, Raynolds, 1996). The physicochemical, pharmacokinetic and pharmacological properties of this drug make it well suited for TDS development. The skin permeation of BPL base was enhanced by using penetration enhancers (Green et al., 1989), and microemulsion bases saturated with BPL (Kemken et al., 1992). Cordes et al. (1988) developed an adhesive matrix TDS of BPL containing a hydrophilic modulator and demonstrated excellent bioavailability and beta-blocking activity of BPL. Recently Ogiso et al. (2001) demonstrated higher skin permeation rates of BPL in vitro and in vivo using penetration enhancers in a Carbopol gel base in rabbits.

Reservoir-type TDS consists of a drug reservoir (as a solution or gel) in between the impermeable backing laminate and a rate controlling membrane. The rate controlling membrane can be either a microporous (e.g., polypropylene) or a nonporous polymeric membrane (e.g., ethylene vinyl acetate copolymer with a specific drug permeability). On the external surface of the polymer membrane is a thin layer of drug/enhancer compatible, pressure sensitive adhesive polymer, to provide intimate contact of TDS with skin surface (Ocak and Agabeyoglu, 1999; Kim et al., 2001). Several TDS have been successfully developed from this technology and approved by FDA for marketing, e.g., Transderm-Nitro™ Estraderm™, Duragesic™ (Chien, 1992; Southam, 1995).

The objective of the present investigation was to develop a reservoir-type TDS of BPL using various gel formulations and skin penetration enhancers. The effect of gelling agent, rate controlling membrane and skin penetration enhancer was investigated in order to optimize the delivery of BPL from a reservoir-type of TDS through rat skin as a permeation barrier.

2. Materials and methods

2.1. Materials

Bupranolol hydrochloride was provided by Schwarz Pharma AG (Manheim, Germany) as a generous gift sample. Bupranolol base was prepared from its HCl salt as reported earlier (Babu and Pandit, 2004) and BPL base was used in this study. Both BPL base and BPL–PMβCD (1:1) inclusion complex were prepared and characterized as described earlier (Babu and Pandit, 2004). Partially methylated β-cyclodextrin (PMβCD) was a gift from Rue Ballu (Paris, France). 1009 Scotchpak™ Film, 1022 Scotchpak™ Liner, 9871 CoTran™-pharmaceutical grade transfer adhesive (PGTA), 9702 CoTran™-ethylene vinyl acetate membrane (EVA) and 9711 CoTran™-polyethylene membrane (PE) were obtained as gifts from 3M Pharmaceuticals (St. Paul, MN, USA). Cellulose acetate nitrate membrane (CAN) and Nylon membranes were procured from Millipore Corporation (Bangalore, India) and Filtech Pharmalab (Bombay, India), respectively. Hydroxypropyl methyl cellulose E4M (HPMC) and Hydroxypropyl cellulose (HPC) H and M grades were kindly provided by Dow Chemical Company (Midland, MI, USA) and Hercules Chemicals (Singapore), respectively. Carboxymethyl cellulose (CMC), Sodium carboxymethyl cellulose (Na CMC), both high viscosity grades and Sodium alginate were procured from Central Drug House (Bombay). 2-pyrrolidone (PY) and 1-methyl-2-pyrrolidone (MPY) were obtained from Merck-Schuchardt, (bei Munchen, Germany) and Fluka Chemie AG (Buchs, Germany), respectively. All other chemicals were obtained from Qualigens Ltd. (Bombay, India).

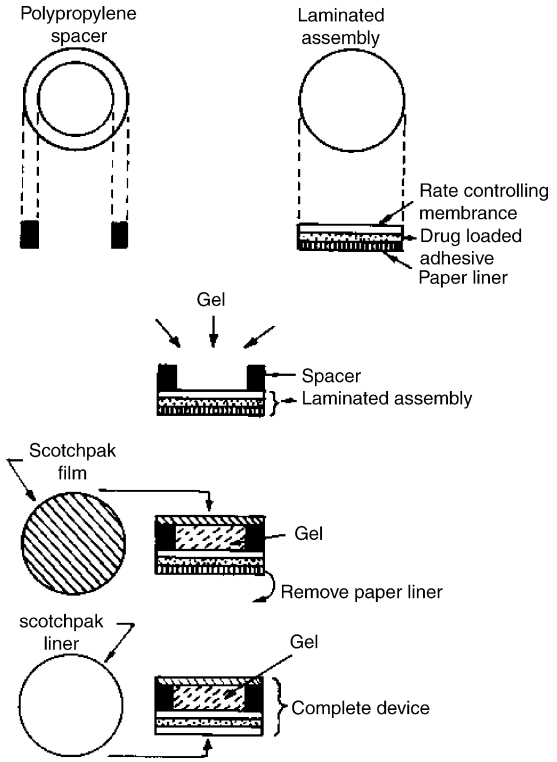

Fig. 1. Schematic of various components in the preparation of reservoir-type TDS of BPL.

2.2. Preparation of reservoir TDS

Reservoir-type TDS were prepared with an active membrane release area of 3.14 cm^2. Fig. 1 shows the schematic of TDS preparation in the present study.

2.2.1. Preparation of BPL gels

The composition of various batches of gel formulations is given in Table 1. In all cases the drug was dissolved in isopropyl alcohol (IPA) in screw-capped vials and diluted with water whilst stirring. The drug thus precipitated was then gelled by addition of an appropriate gelling agent by stirring for about 2 h at 3000 rpm. Various enhancers were incorporated in the gel formulations before addition of the gelling polymer. In the case of PMβCD–BPL complex, the complex was directly suspended in IPA-water mixture whilst stirring and gelling polymer was added and stirred well to form a gel. The drug content uniformity was tested for all the batches of gels. The gels (0.1 g) were weighed into screw-capped vials and mixed well with 10 ml of phosphate buffered saline. The drug content of samples was determined spectrophotometrically at the λ_{max} of 275 nm.

2.2.2. Preparation of 'drug-loaded adhesive-membrane laminates'

CoTran™-pharmaceutical grade transfer adhesive on a release liner was used in the preparation of reservoir TDS. The thickness and content per area of the adhesive layer were 50 μm and 5 mg/cm^2, respectively. The drug (5%, w/w of polymer or 0.25 mg/cm^2) was dissolved in 25 ml of IPA and cast on a leveled surface of the adhesive layer (edges slightly raised to hold the drug solution) and allowed to dry at room temperature for 24 h. A clear layer of drug-in-adhesive was obtained and the drug content uniformity of the adhesive layer was ensured to be within ±5% of coefficient of variation. Different membranes under study were cut into circular discs of 4.91 cm^2 area and laminated with drug loaded adhesive on release liner thus an 'adhesive-membrane laminate' was obtained.

2.2.3. Preparation of a complete device

Polypropylene spacers (internal diameter, 20 mm and thickness, 3.2 mm) were used to hold the gel in the device. The capacity of the spacer was 1 cm^3. The spacer was attached to the 'drug-loaded adhesive-membrane laminate' using an epoxy resin to obtain an empty device. The spacer was filled with 1 g of BPL gel (as prepared above) and heat sealed with a Scotchpak™ backing film. The paper liner covering the adhesive layer was peeled off and covered with a transparent Scotchpak™ Polyester Liner, thus complete devices were obtained.

2.3. In vitro release and skin permeation studies of TDS

Wistar rats of either sex (200–300 g) were sacrificed by cervical dislocation. Hair on the abdominal area was removed by trimming with a clipper followed by shaving with an electrical shaver. Care was taken not to damage the stratum corneum. The hair-free abdominal skin was excised with a surgical blade and the adhering subcutaneous fat, tissue and capillaries were removed with a pair of scissors.

Table 1
Composition of gel formulations in the preparation of reservoir-type TDS

(%, w/v)	Batch code											
	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12
CMC	3.0	–	–	–	–	–	–	–	–	–	–	–
Na CMC		3.0										
HPMC	–	–	3.0	–	–	–	–	–	–	–	–	–
Na alginate	–	–	–	5.0	–	–	–	–	–	–	–	–
HPC-M	–	–	–	–	5.0	–	–	–	–	–	–	–
HPC-H	–	–	–	–	–	5.0	5.0	5.0	5.0	5.0	5.0	5.0
PY	–	–	–	–	–	–	5.0	–	–	–	–	–
MPY	–	–	–	–	–	–	–	5.0	–	–	–	–
PMβCD	–	–	–	–	–	–	–	–	10.0	–	–	–
BPL-complex	–	–	–	–	–	–	–	–	–	5.92[a]	–	–
PG	–	–	–	–	–	–	–	–	–	–	10	30
BPL	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	–	1.0	1.0
IPA	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Water q.s.	100	100	100	100	100	100	100	100	100	100	100	100

Amount of gel prepared = 15 g per batch. CMC: carboxymethyl cellulose; Na CMC: sodium carboxymethyl cellulose; HPMC: hydroxypropyl methyl cellulose; HPC-M: hydroxypropyl cellulose-medium viscosity; HPC-H: hydroxypropyl cellulose -high viscosity; PY: 2-pyrrolidone; MPY: 1-methyl 2-pyrrolidone; PMβCD: partially methylated β cyclodextrin; BPL-complex: burpanolol-PMβCD complex; PG: propylene glycol; BPL: bupranolol; IPA: isopropyl alcohol.

[a] Equivalent to 1.0 g of BPL.

Vertical glass diffusion cells (Keshary–Chien type) were used for release and skin permeation studies. The skin was mounted between donor and receptor compartments, such that the epidermal surface facing the donor compartment. The TDS was fixed on the epidermal surface, donor and receptor compartments were clamped together and placed in a water bath maintained at $37 \pm 0.5\,^{\circ}C$. The volume of receptor cell was 17 ml and the effective surface area available for permeation was 3.14 cm^2. The receptor cell was filled with pH 7.4 phosphate buffered saline (PBS) containing 0.5% (v/v) of 36% aqueous formaldehyde solution as a preservative. The hydrodynamics of the receptor fluid was maintained by stirring the fluid at 600 rpm with a star head magnetic bead.

Samples (10 ml) were withdrawn at predetermined time intervals, the remaining fluid in the cell was drained off, rinsed thrice quickly with 3 ml × 5 ml of fresh buffer and filled with fresh receptor medium (maintained at 37 °C) and the experiment was recommenced. All experiments were carried out at least in three replicates.

For release studies, the same procedure as described as above was followed, but without the skin sample. PBS was used as receptor medium and sink condition was maintained by replacing the fluid at every sampling interval with fresh receptor medium (maintained at 37 °C). All experiments were carried out in triplicate.

2.4. Analysis of BPL

Analysis of BPL in the skin permeation samples was carried out by the method reported by LeBrun et al., 1989. The samples (10 ml) were collected into 30 ml capacity screw capped vials with Teflon lined caps. The pH of each sample was adjusted to 12.5 with 4N NaOH. To this 5 ml of dichloromethane was added; the BPL content of samples were extracted into dichloromethane by shaking for 30 min on a rotary shaker. The samples were centrifuged; dichloromethane layer was separated and dehydrated with anhydrous sodium sulphate. The UV absorption of dichloromethane layer was determined at λ_{max} of 285 nm. The concentration of samples was calculated from the slope of a pre-constructed calibration curve. The calibration samples were extracted by the procedure as described above and the UV absorbance was measured. The absorbance was linear in the range 5–100 μg/ml, with a slope of 0.0084 and a correlation coefficient of 0.99968.

2.5. Data analysis

The cumulative amount (mg/cm^2) of BPL permeated through skin was plotted as a function of time (h). The slope of the linear portion of the plot is presented as the flux (μg/cm^2/h). The flux data were subjected to one-way analysis of variance (ANOVA) followed by Tukey's post-test to determine the level of significance between various groups. The data were considered to be significant at $P < 0.05$.

3. Results and discussion

The development of once-a-day TDS for BPL requires an appropriate selection of reservoir materials and device components. Using the published data (Green et al., 1989; Wellstein et al., 1986) for effective therapeutic plasma concentration: $C_p = 2.4$ ng/ml; volume of distribution: $V_d = 375$ l; elimination rate from plasma: $K_{el} = 0.347\ h^{-1}$ and also assuming that area of applicable system: $A = 25\ cm^2$; the target delivery rate of BPL (K_0) is calculated (12.5 μg/cm^2/h) using the equation:

$$AK_0 = C_p V_d K_{el}$$

Bupranolol base possesses a favorable octanol-water partition coefficient (log K_p, 2.97) for transdermal delivery. The present study employed base form of drug as the base is about 15 times more permeable than the HCl salt (Cordes et al., 1988). In this study, reservoir-type TDS of BPL was prepared with different gel reservoirs (R1–R6), rate controlling membranes (PE, EVA, NYLON and CAN) and penetration enhancers. The drug was present in the gel in a dispersed state to provide maximum thermodynamic activity of the formulation. The drug content of the gel was found to be within ±5% of coefficient of variation of the total drug content of the gel.

3.1. Effect of different gel reservoirs and rate controlling membranes

The release profiles of TDS followed matrix diffusion kinetics, i.e., quantity released (Q) is proportional to square root of time ($t^{1/2}$), as shown in Table 2. The release rate of BPL from nonionic polymer gels (HPMC, HPC) was much higher than those from anionic polymer gels. The pH of the gels, except CMC gel was in the range of 7.4–7.8. The pK_a of BPL (9.49) indicates it was 99% ionized at this pH range, but the drug remained mostly in the suspended form. In the case of CMC, the pH of the gel was at 4.4 and addition of BPL raised the pH to approximately to 4.8. The retarded release of BPL by anionic polymers may be probably due to complexation of BPL with the polymers. Among the devices with nonionic polymer gels, R5-PE and R6-PE (HPC-M and HPC-H as gel reservoirs, respectively)

Table 2
Effect of different formulation variables on the release rates of Bupranolol from reservoirs-type TDS

Formulation variable	Formulation code	Release rate constant (mg/cm^2/h$^{1/2}$)	Correlation coefficient (r^2)
Effect of gelling agent	R1-PE	0.1380 ± 0.0134	0.9464
	R2-PE	0.1110 ± 0.0057	0.9843
	R3-PE	0.3544 ± 0.0100	0.9952
	R4-PE	0.0801 ± 0.0018	0.9967
	R5-PE	0.6259 ± 0.0211	0.9932
	R6-PE	0.5416 ± 0.0157	0.9973
Effect of Rate controlling membrane	R6-EVA	0.1787 ± 0.0056	0.9941
	R6-NYLON	0.2748 ± 0.0110	0.9904
	R6-CAN	0.6108 ± 0.0082	0.9989
Effect of penetration enhancers	R7-PE	0.6091 ± 0.0179	0.9974
	R8-PE	0.5571 ± 0.0131	0.9977
	R9-PE	0.5916 ± 0.0180	0.9976
	R10-PE	0.5498 ± 0.0147	0.9973
	R11-PE	0.5679 ± 0.0181	0.9979
	R12-PE	0.5363 ± 0.0150	0.9972

showed maximum release of BPL. The device R3-PE (HPMC as gel reservoir) showed relatively less release rate as compared to R5-PE or R6-PE. The devices containing anionic polymers (R1-PE, R2-PE and R4-PE) show minimal BPL release and the release rates of BPL by all these devices were approximately 5-fold lower than R6-PE.

The release of atenolol (Demou et al., 1994), timolol (O'Nell and Deasy, 1988) and propranolol (Takka et al., 2001) was also much lower due to anionic polymers as gelling agents. The retarded release with anionic polymer gels is presumably due to binding of ionized drug to the polyanion (O'Nell and Deasy, 1988). Bupranolol being a cationic drug, the amine groups of the drug are believed to interact with carbonyl groups of the anionic polymers and thereby the drug release is retarded from the anionic gel matrix.

Due to porous nature of the polyethylene membrane, it provides least resistance to the diffusion of drug molecules, as the permeation through the membrane is governed by the diffusion of drug molecules through the liquid retained in the pores of the membrane. The adhesive employed is highly permeable and provides less resistance to diffusion. Thus, the differences in the release profiles of various devices are attributed to the reservoir composition. The reservoir composition appears to be crucial in determining drug release, unlike nonporous membranes where partitioning and diffusion through continuum are likely to be more predominant.

From the results of the study, a gel formulation, which showed the highest drug release (HPC gel, R6) was selected and the effect of various rate-controlling membranes on the release of drug from this gel was studied. The release rates of R6-PE and R6-CAN were approximately 3-fold higher than R6-EVA. The device R6-EVA showed the lowest drug release and in this case the rate-limiting step is the diffusion through the polymeric membrane, which is much slower than the diffusion of drug through the gel matrix. In addition, poor permeation of BPL through EVA membrane might be due to the low vinylacetate content of the membrane (CoTran™-EVA with 9% vinylacetate). Similar results were reported for isosorbide dinitrate (Ocak and Agabeyoglu, 1999), timolol (O'Nell and Deasy, 1988), chlorpheniramine maleate (Andronis et al., 1995), levonorgestrel (Friend et al., 1988) and melatonin (Konsil et al., 1995) where low vinyl acetate content of the EVA membrane was the rate-determining factor for the drug release. Overall CoTran™-polyethylene membrane showed highest BPL release from the devices. This membrane was used in the TDS for studying the effect of different penetration enhancers on the release and skin permeation of BPL.

3.2. Effect of penetration enhancers

3.2.1. Release studies

The effect of various penetration enhancers on the release rates of BPL from TDS is presented in Table 2. There was no significant difference between the release rates of different formulations. It has been reported that the release of bendroflumethiazide through a microporous polypropylene membrane (Celgard 2400) from gel formulation follows matrix diffusion kinetics (Viegas et al., 1997). Similarly the release of testosterone from a gel formulation through microporous membrane was non-zero order (Mazer et al., 1992). In the present study, penetration enhancers did not change the release profile of BPL from the devices, as the differences in the release rates among formulations were not significant ($P > 0.05$).

3.2.2. Skin permeation studies

The effect of pyrrolidones as penetration enhancers on the permeation of BPL is presented in Fig. 2. Skin permeation of BPL from different formulations followed a 'Q versus t' relationship. Permeation rates of the devices R7-PE and R8-PE were about 3- and 1.5-fold higher than R6-PE ($P < 0.01$). PY (R7-PE) and MPY (R8-PE) both acted as penetration enhancers even at low concentrations. The penetration enhancing ability of pyrrolidones has been well established (Sasaki et al., 1995; Godwin et al., 1997; Yoneto et al., 1996). PY and MPY were used as enhancers in the reservoir TDS of bendroflumethiazide (Viegas et al., 1997) and zidovudine (Seki et al., 1991), respectively. These enhancers were employed at 20% (w/w) concentration along with co-enhancers such as propylene glycol (PG) or isopropyl myristate. In the present study, the enhancers were used at 5% (w/w) concentration in the gel and the drug was present in suspension form to ensure maximum thermodynamic activity. The results indicate that the reservoir TDS can be prepared by using pyrrolidones for enhanced delivery of BPL.

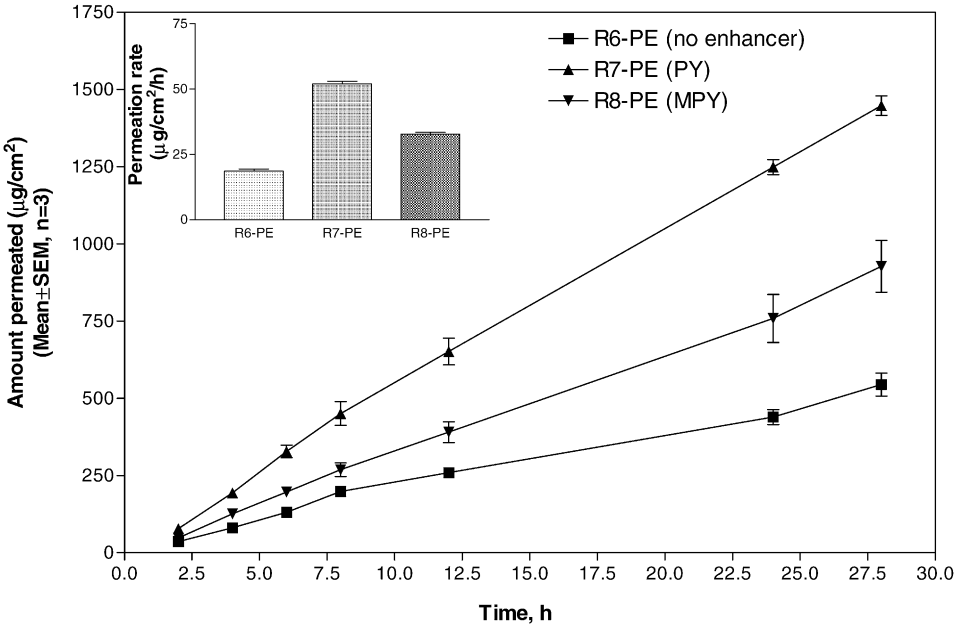

Fig. 2. Effect of PY and MPY on the skin permeation profiles of BPL from reservoir-type TDS.

The effect of PMβCD as a penetration enhancer on the permeation of BPL is presented in Fig. 3. The permeation rate of R9-PE containing PMβCD is about 2.5-fold higher than R6-PE ($P < 0.01$). A comparison of the device R9-PE with R10-PE indicates that the flux of R9-PE is 1.8 times higher than R10-PE ($P < 0.05$). In the device R9-PE, PMβCD was used at 10% (w/w) concentration as penetration enhancer; whereas in the case of R10-PE, an inclusion complex of BPL–PMβCD (in 1:1 molar ratio) was employed in the fabrication of TDS. From the results of saturation solubility studies it was observed that the solubility of BPL increased substantially by 10% (w/w) PMβCD, due to complex formation (Babu and Pandit, 2004). This increase is 1.5 times higher than the solubility of BPL–PMβCD inclusion complex. From the results it appears that it is not necessary to use inclusion complex, but simple addition of PMβCD to the formulation is sufficient to improve the permeability of BPL. The permeation of hydrocortisone was higher with an ointment or hydrogel containing hydrocortisone-HPβCD complex, than by adding HPβCD separately in the formulation (Preiss et al., 1994). In contrast the results of Loftsson et al., (1994) indicate that incorporation of HPβCD into an aqueous cream base containing hydrocortisone dramatically improved the flux through a synthetic membrane. The present study also indicates that the permeation of BPL can be increased by incorporation of PMβCD into a gel formulation. The higher permeation rate of R9-PE is due to higher amount of PMβCD in this formulation, which has greater solubilizing and skin permeation effect on BPL. This may be due to the combined effect of increased aqueous solubility of BPL and reduced barrier function of skin by PMβCD. Methylated βCDs are known to interact with stratum corneum components of rat skin and improve drug absorption (Larrucea et al., 2002). Methylated βCDs extract all the major lipid classes and proteins and reduce barrier function of skin (Vollmer et al., 1993, 1994). We reported recently the effect of pretreatment of rat skin with CDs on permeation of BPL (Babu and Pandit, 2004). Skin pretreatment with PMβCD at 10% (w/w) concentration increased the flux by 1.7-fold. Thus, PMβCD reduced the skin barrier function for BPL, probably by interacting with stratum corneum lipids.

The effect of propylene glycol (PG) as a penetration enhancer on the permeation of BPL is presented in Fig. 4. Inclusion of PG in devices R11-PE and R12-PE increased the permeation rate significantly versus

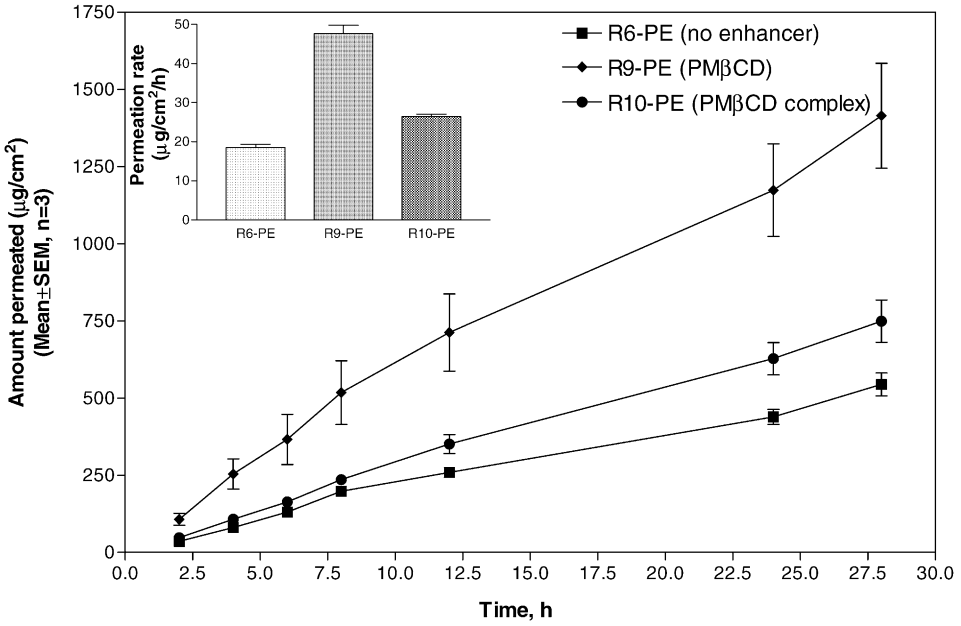

Fig. 3. Effect of PMβCD and PMβCD–BPL complex on the skin permeation profiles of BPL from reservoir-type TDS.

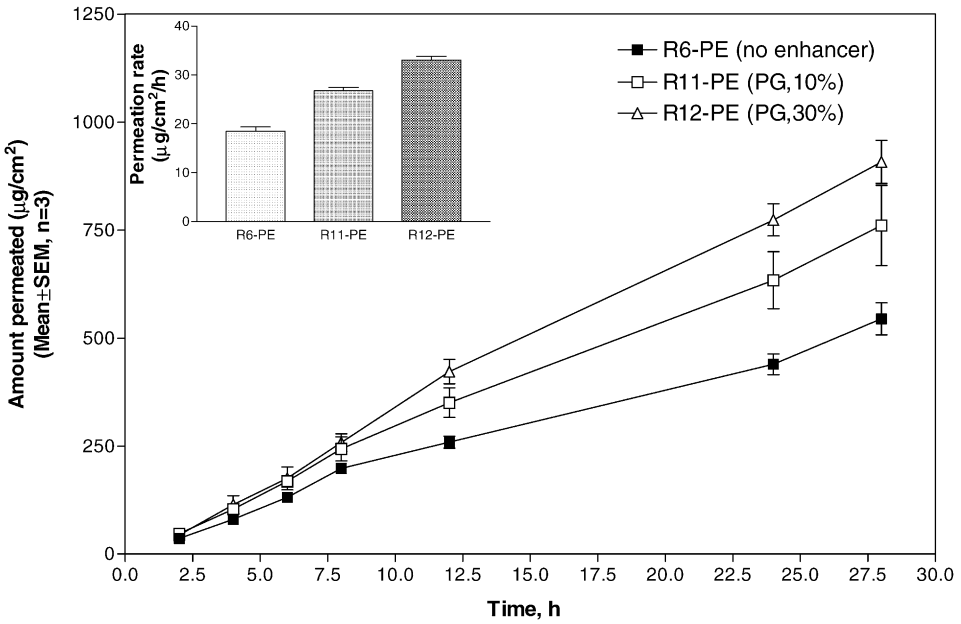

Fig. 4. Effect of PG on the skin permeation profiles of BPL from reservoir-type TDS.

R6-PE (no enhancer, $P < 0.05$). Increase in the PG concentration from 10% (R12-PE) to 30% (R13-PE) has no significant effect on the flux of BPL ($P > 0.05$). PG is 'generally recognized as safe' solvent and employed as a topical vehicle to improve the solubility of lipophilic drugs. PG shows penetration enhancement activity towards 5-fluorouracil (Rigg and Barry, 1990), progesterone (Valenta and Wedding, 1997) and estradiol (Goodman and Barry, 1988). In the present study PG at 30% (w/w) improved the permeation of BPL by 1.8-fold versus control as shown by flux data.

The results of the present study indicate that a TDS can be fabricated by using HPC gel reservoir and microporous polypropylene membrane. By employing PY or PMβCD as enhancers the flux of BPL could be enhanced 4–5 times above the target delivery rate. The adhesive CoTran-PGTA maintained its adhesive properties in the presence of penetration enhancers with no apparent change over 24 h. These experiments were performed using full thickness rat skin. Full thickness skin in vitro represents an artificially higher barrier to absorption of lipophilic compounds, relative to the same skin in vivo (Bronaugh and Stewart, 1984, 1986). This barrier in vitro is thought to arise from the lack of blood capillaries that are present in vivo to help clear low water soluble drugs. The in vitro permeation of BPL through dermatomed human skin was much higher than full thickness skin (Green et al., 1989). The data collected using full thickness rat skin indicate that it is possible to formulate transdermal patch by selecting appropriate reservoir materials and transdermal components. These results cannot be directly extrapolated to humans, as rodent skin is generally more permeable than human skin (Wester and Maibach, 1993, 1999), the target flux obtained for rat skin must be adjusted accordingly for humans.

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