J. Pharm. Pharmacol. 1996, 48: 367–370
Received May 30, 1995
Accepted October 30, 1995

Carboxymethylcellulose-sodium Based Transdermal Drug Delivery System for Propranolol

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Abstract

Propranolol, a β-adrenoceptor blocker, suffers from a high degree of first-pass metabolism resulting in very low bioavailability (<10%) following administration with conventional oral formulations. To circumvent this significant therapeutic hurdle, we formulated a carboxymethylcellulose-sodium (CMC-Na) based transdermal system for propranolol and evaluated the patch for its in-vitro and in-vivo performance.

In-vitro permeation studies using the excised hair-free rat skin model resulted in 66·54% permeation at the end of 24 h in a modified Franz diffusion cell. This zero-order permeation profile was characterized by a drug permeation rate of $52{\cdot}87 \pm 11{\cdot}63\ \mu g\ cm^{-2}\ h^{-1}$. Skin irritation studies in rats (n = 5), evaluated for flare-and-wheal with respect to a formalin control, indicated that the drug-containing patch evoked only a mild response over a 7-day period. Preliminary in-vivo studies in male albino rabbits (n = 3), indicated that plasma drug levels averaged $11{\cdot}75 \pm 3{\cdot}40\ ng\ mL^{-1}$ in a 24-h study period before patch removal.

Propranolol (±-1-isopropyl amino-3-(1-napthyloxy) propan-2-ol) is a β-adrenoceptor blocking agent that has been used extensively for the treatment of many cardiovascular diseases including arrhythmias, hypertension, and angina pectoris (Riddell et al 1987). However, like other β-blockers, the drug is subjected to a high degree of hepatic first-pass metabolism resulting in low oral bioavailability indicating the need for alternative drug delivery modes.

Transdermal delivery has been extensively investigated as a viable alternative to deliver such drugs with improved bioavailability. Many β-blockers have been a focus for transdermal delivery research over the recent years. We have previously shown that transdermal delivery of propranolol from hydroxypropylmethylcellulose matrices results in a significant improvement in bioavailability of the order of 20-fold (Krishna & Pandit 1993). In the current study, we have evaluated the use of carboxymethylcellulose-sodium salt (CMC-Na) as a drug reservoir for improved transdermal system characteristics.

Materials and Methods

Materials

Propranolol hydrochloride was obtained from Cipla Ltd., Bombay, India. Propranolol free base was produced from the salt, and its purity confirmed by TLC and melting point studies. CMC-Na and polyvinyl alcohol were purchased from Central Drug House (P) Ltd., Delhi, India. All solvents were of analytical grade and were obtained from Central Drug House (P) Ltd., Delhi, India and were used without further purification.

In-vitro drug analysis

Propranolol was assayed in samples obtained from in-vitro permeation experiments using spectrophotometry. Standard curves were generated in pH 7·4 phosphate buffer over a concentration range of $2–18\ \mu g\ mL^{-1}$ and absorbances read at a λ_{max} of 290 nm (r = 0·9997, intercept = 0·0038, slope = 0·0192) in a Beckman U-24 spectrophotometer (Beckman Instruments, Fullerton, CA, USA).

In-vivo drug analysis

Propranolol concentrations in plasma were analysed using the spectrofluorometric method of Shand et al (1970). Briefly, to 1·0 mL plasma, was added 0·25 mL 4 M sodium hydroxide. About 4 mL *n*-heptane (containing 1·5% isoamyl alcohol) was added and extracted for 10 min. The heptane layer was removed, and 5 mL 0·1 M hydrochloric acid added to it, and again mixed for 10 min. The acid layer was separated from the heptane layer, and the final acidic layer analysed for drug content in a LS-5 model Perkin Elmer spectrofluorometer (Perkin Elmer, Bucks, UK), at excitation and emission wavelengths of 290 nm and 345 nm using 0·1 M hydrochloric acid as blank. Calibration curves containing propranolol over a concentration range of $5–120\ ng\ mL^{-1}$ were generated in plasma (r = 0·999). The limit of quantitation was 2·5 ng in a 2-mL plasma sample (< 20% coefficient of variation).

Patch formulation

Polyvinyl alcohol (PVA) (3%) was used as the backing membrane. About 450 mg PVA was dissolved in 15 mL distilled water with slight warming. The resulting clear polymer solution was poured on a clean glass substrate and dried in a constant relative-humidity environment at 60°C for 6 h. The drug reservoir film was then cast over the backing layer. CMC-Na (600 mg) and propranolol (78 mg) were dissolved separately in 10 and 5 mL of warm distilled water, respectively, and combined at 45°C with constant stirring. The clear drug-polymer solution was spread over the backing layer carefully and oven dried at 45°C for 12 h. The rate-controlling membrane was drug-free CMC-Na

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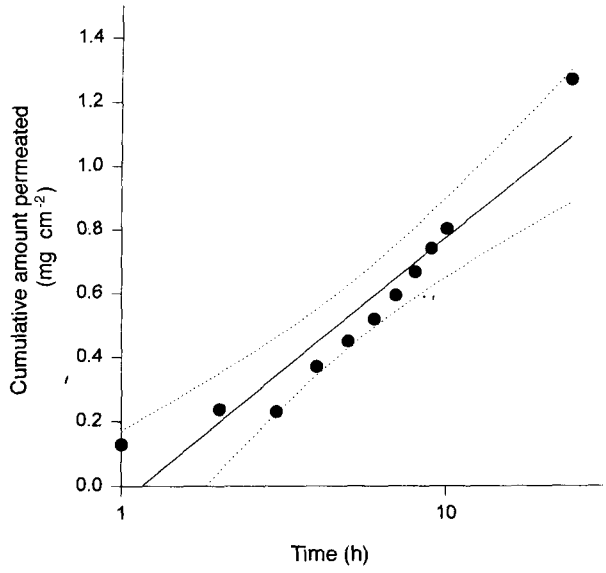

FIG. 1. In-vitro permeation profile from transdermal propranolol patch (9·443 mg/4·95 cm^2 patch) through excised hair-free rat skin (n = 3). Dotted lines represent 99% confidence interval for the fitted data points.

(4%) spread over the reservoir layer to a thickness of 0·6 mm to yield a 20 μm thick film, and oven dried at 45°C for 12 h. A peripheral adhesive (Leucoplast) was attached to the 2·5-cm diameter discs for in-vivo studies.

In-vitro permeation studies

A modified Franz diffusion cell was used for evaluating drug permeation profiles across excised skin. Hair from the abdominal region of a healthy albino rat was carefully removed and the skin excised. The dermal side of the skin was thoroughly cleaned of any adhering tissues and equilibrated for 1 h in pH 7·4 phosphate buffer. Transdermal discs (2·5 cm diameter) were placed in intimate contact with the stratum corneum side of the skin and placed in between two halves of the diffusion cell. The amount of drug permeated into the pH 7·4 phosphate buffer receptor solution was determined by removing 1 mL samples at hourly intervals for 10 h and then at 24 h. The withdrawn volume was promptly replaced with an equal volume of fresh prewarmed buffer, and absorbances read at 290 nm in a Beckman U-24 UV spectrophotometer.

Skin irritation

The patch was tested for its potential to cause skin irritation or sensitization in hair-free rats (n = 5). The method of Vlasses et al 1985 was followed with slight modification. The patch was applied onto the nude abdominal skin using a peripheral adhesive. Each site of patch application was rated with regard to flare-and-wheal. An aqueous solution of formalin (0·8%) was also applied as a standard irritant, and its effects compared with test. Animals were observed for any indication of irritation over a 7-day study period.

In-vivo studies

In-vivo studies were performed in healthy male albino rabbits (Zoological Emporium, Varanasi, India) weighing 1·2 ± 0·2 kg (n = 3). Each rabbit was fasted 24 h before patch application (6 mg/2·5 cm diameter discs) to the inner hair-free region of the pinna. Blood samples were collected from the central ear artery at 3, 6, 9, 24, 25, and 26 h. The samples at 25 and 26 h, were collected following patch removal at the end of 24 h. The samples, collected in heparinized tubes, were centrifuged and plasma stored at −20°C until assay.

Results and Discussion

In-vitro permeation studies

Zero-order permeation rates were observed (Fig. 1). Propranolol was observed to permeate across the hair-free rat skin at a constant rate of 52·87 ± 11·63 μg cm^{-2} h^{-1}, according to the Fick equation:

$$Q = \frac{(\partial.A.k)}{T} C.t \qquad (1)$$

where, Q is the cumulative amount of drug permeated through the membrane at time t, ∂ is the diffusivity, k the partition coefficient, A the effective surface area of the membrane, T the thickness of the membrane, and C the drug concentration.

The drug reservoir is a saturated system of the drug dispersed in the CMC-Na polymer. The rate-controlling membrane is a drug-free layer of CMC-Na. The concentration of the material in equilibrium with the inner surface of the surrounding membrane is assumed to be constant. Zero-order release is observed when the diffusional release of the drug (i.e. concentration gradient) is constant.

Using a CMC-Na based microporous polypropylene

Table 1. Studies on the transdermal delivery of β-blockers.

Drug	In-vitro flux (μg cm^{-2} h^{-1})	In-vivo plasma concn (ng mL^{-1})	Reference
Propranolol	52·87 ± 11·63 (rat)	11·75 ± 3·4 (rabbit)	This study
Timolol	–	13·3 ± 53·3 (man)	Vlasses et al 1985
Timolol	100 (rat)	–	Cargill et al 1986
Timolol	80 (mouse)	–	O'Neill & Deasy 1988
Propranolol	–	0·16–1·82 (man)	de Mey et al 1989b
Propranolol	–	9·3 ± 2·1 (rabbit)	Corbo et al 1990
Propranolol	–	15–20 (rabbit)	Krishna & Pandit 1993
Propranolol	34·75 (rat)	–	Krishna & Pandit 1994
Metoprolol	66·24 ± 7·18 (rat)	76·3 ± 10·3 (rat)	Ghosh et al 1995

N.B. The animal model used for each parameter is indicated within the parentheses.

Table 2. Skin irritation/sensitization evaluation of transdermal propranolol patch in hair-free rats (n = 5) (method of Vlasses et al 1985).

Rat No.	Transdermal propranolol patch		Formalin control	
	Erythema*	Oedema**	Erythema	Oedema
1	0	0	2	4
2	0	2	4	3
3	1	1	3	3
4	0	1	3	3
5	0	0	3	2
Mean score***	1·0 (mild)		6·0 (severe)	

*Erythema rating scale: 0—none, 1—slight, 2—well defined, 3—moderate, 4—eschar formation. **Oedema rating scale: 0—none, 1—slight, 2—well defined, 3—moderate, 4—severe. ***Rating based on: 1–2 (mild), 3–5 (moderate), and 6–8 (severe irritation).

membrane based transdermal system, O'Neill & Deasy (1988) observed a timolol flux across hairless mouse skin, of 80 $\mu g\,cm^{-2}\,h^{-1}$. This zero-order permeation profile is similar to our observations for propranolol in the present study across the excised hair-free rat skin. Table 1 summarizes the in-vitro permeation profiles and in-vivo plasma levels of some β-blockers delivered transdermally.

In general, hydrophilic drug reservoirs have been shown to exhibit greater, more favourable drug fluxes compared with lipophilic systems for timolol (O'Neill & Deasy 1988), and propranolol (Krishna & Pandit 1994). It would appear that these reservoirs would, therefore, provide optimal permeability characteristics for the drug.

Skin irritation studies

The prepared propranolol patch evoked only a mild response (Table 2), in marked contrast to the formalin-treated controls, which demonstrated severe irritation, in terms of flare-and-wheal. It appears that hydrophilic systems are well tolerated. Transdermal delivery of propranolol from a lipophilic system (de Mey et al 1989a,b) was not well tolerated in patch application studies in normal human subjects.

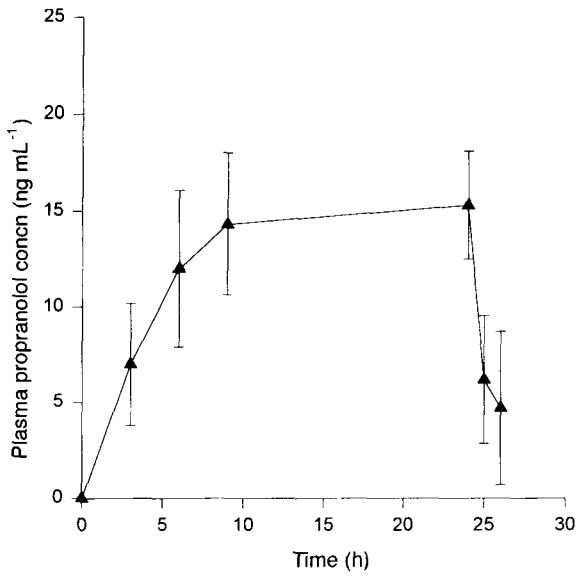

FIG. 2. Plasma propranolol concentration–time profile following transdermal application in rabbits (n = 3). Data are mean ± s.d.

In-vivo studies

In-vivo studies in rabbits (n = 3) indicated that plasma propranolol levels averaged 11·75 ± 3·40 ng mL^{-1} in a 24-h study period before patch removal (Fig. 2). These levels are only slightly lower than those reported for propranolol from HPMC matrices (Krishna & Pandit 1993). However, the relatively low plasma propranolol levels compared with conventional delivery models (oral, intravenous) could be attributed to the fact that propranolol is almost completely ionized during passage through the skin ($pH_{surface} = \sim 5{\cdot}0$; $pH_{lower} = \sim 7{\cdot}4$), and that passage through the hydrated pores in the skin might appear to be a predominant, although limited, pathway of drug permeation. Whether these low plasma propranolol levels following transdermal delivery of the drug are sufficient to cause significant β-receptor blockade remains to be established.

Our in-vivo levels in rabbits compare closely (Table 1) with that reported by Corbo et al (1990). In man, however, the maximum plasma propranolol level attainable is about 9·97 ng mL^{-1} (de Mey et al 1989b), with average steady-state concentrations being 0·16–1·82 ng mL^{-1} following transdermal application from a lipophilic reservoir. According to their study, these plasma levels were insufficient to cause significant β-receptor blockade.

Further, recent studies have demonstrated that propranolol is metabolized in human skin tissue, and that propranolol and its metabolites are retained in the skin (Ademola et al 1993). This would explain the low levels of the drug in plasma following transdermal delivery. This is also consistent with observations of partially improved propranolol bioavailability following patch application, i.e. 74·8% (Corbo et al 1990), and 64·48% (Krishna & Pandit 1993) in rabbits, where more than 25% of the drug is unaccounted for, leading us to speculate that the drug is either being retained in the skin or possibly being metabolized.

Acknowledgements

The authors would like to thank the Head, Molecular Biology Unit, Institute of Medical Sciences, Banaras Hindu University, Varanasi for the technical assistance provided for the spectrofluorometer facility. R. Krishna acknowledges the Junior Research Fellowship awarded by the University Grants Commission, New Delhi, India.

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