J. Pharm. Pharmacol. 1990, 42: 720–722
Communicated December 5, 1989

COMMUNICATIONS

Design of a polyvinyl alcohol hydrogel containing phospholipid as controlled-release vehicle for rectal administration of (±)-propranolol HCl

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Abstract—Polyvinyl alcohol hydrogels which contained phospholipid, egg yolk lecithin or hydrogenated soya lecithin were designed as a transrectal delivery system for propranolol hydrochloride. The hydrogel preparations containing phospholipid were prepared by a low-temperature crystallization method. The release profile of propranolol from hydrogel preparations containing phospholipid complied with Fickian diffusion (Higuchi model). The release of propranolol from the hydrogel preparation decreased with higher contents of phospholipid (~2% w/w). In rats plasma concentrations of propranolol after rectal administration of hydrogel preparations containing phospholipid (1 and 2% w/w) were prolonged compared with those of rats receiving preparations without phospholipid.

The low bioavailabilities of some β-adrenoceptor antagonists such as propranolol from oral dosage forms have been attributed to extensive drug metabolism in the liver (Riddell et al 1987). A dosage form delivered by the rectal route could be advantageous for such a drug which undergoes first-pass metabolism after oral administration (De Boer et al 1982). We have previously reported that the rectal administration of propranolol HCl using polyvinyl alcohol (PVA) hydrogel improved the therapeutic effect, producing a higher bioavailability and more sustained action compared with a conventional suppository (Witepsol H-15) (Morimoto et al 1989a). The PVA hydrogel, prepared by the low temperature crystallization method, has a porous and three dimensional network structure and a high water content (Morimoto et al 1989a, b).

Propranolol is the most lipophilic of the β-adrenoceptor blocking drugs and partitions into the liposomal system (pH 7·4) (Betageri & Rogers 1987). In the present study, PVA hydrogel preparations containing dispersed phospholipid, egg yolk lecithin (EYL) or hydrogenated soya lecithin (HSL), were prepared to obtain a more uniform and prolonged action of propranolol HCl after rectal administration. In-vitro release characteristics of the drug from hydrogel containing phospholipid, and its plasma concentration after rectal administration to rats, were investigated.

Materials and methods

Materials. PVA (degree of saponification; 99·5 mol%, mean degree of polymerization; 1700) was from Unichica Ltd (Osaka, Japan) and (±)-propranolol HCl and egg yolk lecithin (EYL) were from Sigma Chemical Inc. (St. Louis, MO, USA). EYL and HSL (Nippon Fine Chemicals Co. Ltd, Osaka, Japan) were used as neutral phospholipids. Dicetyl phosphate (DCP; Sigma) was used as negatively charged phospholipid. All other chemicals were of reagent grade and were obtained commercially.

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Preparations. PVA hydrogels containing phospholipids were prepared by the low-temperature crystallization method. Briefly, PVA was dissolved in 1/15 M phosphate buffer (pH 7·0) at about 90°C, while the dissolved phospholipid (EYL or HSL), with or without DCP in chloroform, was pipetted into a round-bottomed flask. The chloroform was removed under nitrogen, using a rotary evaporator. To the dried lipid films, propranolol HCl solution (1/15 M phosphate buffer; pH 7·0) was added and the film hydrated by shaking at 37°C for EYL and at 70°C for HSL for 5 h. The resulting suspension and the PVA solutions were mixed at room temperature (20°C) and the final pH of the mixtures was adjusted to 7·0 with sodium phosphate. The mixtures were poured into plastic syringes (4·5 mm × 1·8 cm) for rectal administration in rats and into a suppository plastic mould (7·0 mm × 1·8 cm; 1 g preparation, Kanae Co, Osaka, Japan) for release tests. The hydrogels containing propranolol HCl were formed by freezing the mixtures at −20°C for 15 h to allow crystallization of PVA, followed by thawing at 5°C for 24 h. The hydrogel preparations were stored to inhibit aqueous evaporation at room temperature and were used within 2 weeks.

In a comparative study, propranolol HCl suppository was prepared with Witepsol H-15 (Dynamit Nobel, Witten, West Germany) using the fusion method and the drug was dissolved in isotonic buffer (pH 7·4) for oral administration.

Release tests. The release rate of propranolol HCl from the hydrogel (1 g) was investigated by the JP XI paddle method. The dissolution fluid (400 mL) was 1/15 M phosphate buffer (pH 7·4) maintained at 37°C. The hydrogel preparation was held at the bottom of the vessel in a stainless-steel wire mesh (sinker). The paddle was positioned approximately 2·5 cm from the bottom of the vessel and was rotated at 50 rev min^{-1}. A sample (2 mL) of dissolution fluid was removed at predetermined times and 2 mL of fresh fluid was added to the vessel to maintain the original volume. Propranolol HCl was assayed spectrophotometrically at 291 nm. Release-rate data were analysed on the basis of physical models (Fickian and non-Fickian drug release models) (Peppas 1985).

Rectal administrations in rats. Male Wistar rats, 260–320 g, were fasted for 17 h before the experiments. Following pentobarbitone Na (50 mg kg^{-1}) anaesthesia, hydrogel preparations were administered into the rat rectum, 2 cm above the anus. The dosage of the hydrogel preparation was 1·0 g kg^{-1} and the dose of drug was 10 mg kg^{-1}. For comparison, rectal administration of propranolol HCl suppository (Witepsol H-15) was also carried out. Blood samples (0·5 mL) were collected from the inguinal vein at 30 min and 1, 2, 4, 6, 8 and 10 h after administration, and plasma prepared. Plasma propranolol was determined by HPLC (Drummer et al 1981).

Data analysis. Plasma concentration-time curves were analysed by the program MULTI (Yamaoka et al 1981). The area under the plasma concentration-time curve (AUC) and the mean residence time (MRT) were calculated by the standard linear trapezoidal integration. Statistical significance was assessed by Student's *t*-test.

Results and discussion

Release tests. The in-vitro release tests of propranolol were carried out with hydrogel preparations containing phospholipids. Fig. 1A shows the releases of propranolol from hydrogel preparations containing the neutral phospholipid, EYL at 1% and 2% w/w (HSL results were similar). The release of propranolol from the hydrogel preparations was slower with higher concentrations of EYL. This result may be due to propranolol partitioning into phospholipid dispersed in hydrogels, since propranolol is a relatively lipophilic compound, i.e. its partition coefficient (log K_m) was 3·37 in an octanol/phosphate buffer system at pH 7·4 (Betageri & Rogers 1987).

Fig. 1B shows the release of propranolol from hydrogel preparations containing EYL and negatively charged phospholipid, DCP. Release was slower at higher concentrations of DCP. This result may be due to positively ionized molecules of propranolol interacting with negatively charged phospholipid, since propranolol is basic ($pK_a = 9·5$) (Riddell et al 1987).

The release rate from a polymeric hydrogel can be described by:

$$M_t/M_\infty = kt^n$$

where M_t/M_∞ is the fraction of drug released at time t, k is a constant characteristic of the hydrogel system and n is indicative of type of transport mechanism. The situation of $n = 1$ corresponds to zero-order release kinetics, $1 > n > 0·5$ corresponds to a non-Fickian diffusion model, and $n = 0·5$ corresponds to Fickian diffusion (Higuchi model) (Peppas 1985).

The kinetic parameters, n and k, for propranolol released from hydrogel preparations containing phospholipids were calculated from the slope and the intercept, respectively, of a plot of log (M_t/M_∞) versus log (time). These parameters are listed in Table 1. The n values found for propranolol approached 0·5 confirming Fickian diffusion.

Table 1. Kinetic parameters for releases of propranolol from PVA hydrogel preparations containing phospholipids.

	Release exponent n	Kinetic constant k (%·min^{-n})	Correlation coefficient r
Without phospholipids	0·486	7·691	0·999
1% EYL	0·450	6·411	0·998
2% EYL	0·467	5·333	0·999
1·8% EYL + 0·2% DCP	0·475	4·613	0·999
1% HSL	0·434	7·194	0·999
2% HSL	0·448	5·975	0·999
1·8% HSL + 0·2% DCP	0·435	5·062	0·998

Rectal administration. Fig. 2A shows the plasma concentrations of propranolol after rectal administration of hydrogel preparations containing the neutral phospholipid, EYL at 1% w/w and 2% w/w (HSL results were similar) and suppository (Witepsol H-15) in rats. The propranolol plasma concentrations obtained from hydrogel preparations were higher than that from the suppository. Furthermore, these propranolol plasma concentration profiles showed more prolonged actions with higher concentrations of EYL (and HSL) and were similar between EYL and HSL. This result corresponds with the release rate data for propranolol (Fig. 1).

Fig. 2B shows the plasma concentrations of propranolol after rectal administration of hydrogel preparations containing EYL

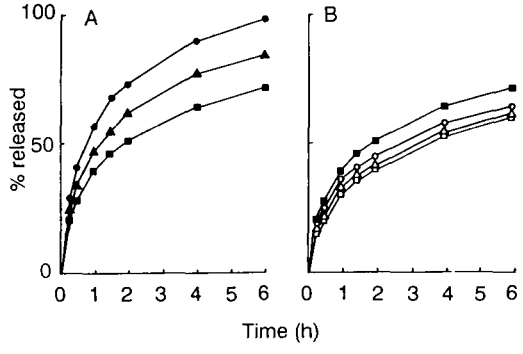

FIG. 1. A. Release profiles of propranolol from hydrogel preparations containing neutral phospholipid, egg yolk lecithin (EYL) at various concentrations. (●) in the absence of phospholipid, (▲) 1·0% w/w phospholipid, (■) 2·0% w/w phospholipid. B. Release profiles of propranolol from hydrogel preparations containing neutral phospholipid, EYL and a negatively charged phospholipid, dicetyl phosphate (DCP) at various concentrations. (■) 2% w/w EYL, (○) 1·9% w/w EYL and 0·1% w/w DCP, (△) 1·8% w/w EYL and 0·2% w/w DCP, (□) 1·6% w/w EYL and 0·4% w/w DCP. Each point represents the mean of 3 experiments.

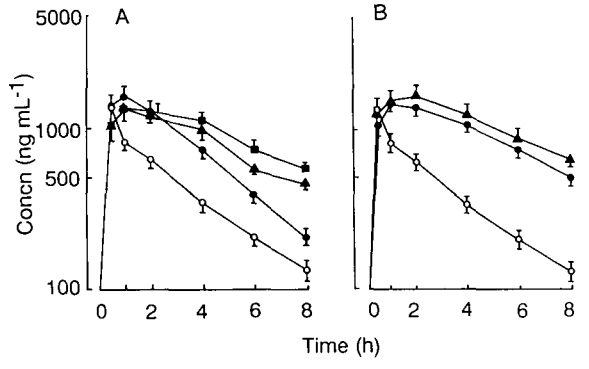

FIG. 2. A. Plasma concentrations of propranolol after rectal administration of hydrogel preparations containing phospholipid at various concentrations, and as a suppository, in rats. (●) in the absence of phospholipid, (▲) 1·0% w/w phospholipid, (■) 2·0% w/w phospholipid, (○) suppository (Witepsol H-15). B. Plasma concentrations of propranolol after rectal administration of hydrogel preparations containing neutral phospholipid, egg yolk lecithin (EYL), and a negatively charged phospholipid, dicetyl phosphate (DCP), and as a suppository, in rats. (●) 2% w/w neutral phospholipid, (▲) 1·8% w/w neutral phospholipid and 0·2% w/w DCP, (○) suppository (Witepsol H-15). Each point represents the mean ± s.e. of 4 animals.

Table 2. Bioavailability parameters after rectal administration of propranolol hydrogel preparations containing phospholipids in rats.

	t_{max} (h)	C_{max} ($\mu g\ m L^{-1}$)	[1]MRT (h)	AUC_0^{∞} ($\mu g\ h\ m L^{-1}$)	[2]BA (%)
10% PVA hydrogel (pH 7·0) without phospholipids	1·13±0·32	1·62±0·13	2·82±0·06	6·85±0·65	165·9±15·7
2% EYL	2·00±0·71	1·40±0·16	3·58±0·12**	10·82±0·40**	262·0±9·8
1·8% EYL+0·2% DCP	1·00±0·35	1·69±0·09	3·58±0·09***	14·44±1·30**	349·6±31·5
2% HSL	1·75±0·75	1·52±0·13	3·46±0·09***	10·95±0·72*	265·1±17·4
1·8% HSL+0·2% DCP	1·50±0·29	1·64±0·16	3·53±0·12**	14·17±1·52**	343·1±36·8
Suppository (Witepsol H-15)	0·75±0·14	1·39±0·17	2·65±0·04*	4·13±0·31*	100
Oral Administration	0·50±0	0·51±0·05	3·18±0·87	1·91±0·27*	46·2±6·5

MRT: mean residence time. [2]BA: relative bioavailability. The dose of propranolol HCl was 10 $mg\ kg^{-1}$. Each point represents the mean±s.e. of 4 animals. Statistically significant difference compared with PVA hydrogel without phospholipids. * $P<0·05$, ** $P<0·005$, *** $P<0·001$.

(1·8% w/w) and DCP (0·2% w/w) (HSL results were similar) in rats. The propranolol plasma concentration obtained from hydrogel preparations containing DCP, a negatively charged lipid, was slightly higher. However, this did not show more prolonged action than hydrogel preparations without DCP. This result does not correspond to the data of release rate for propranolol (Fig. 2B). The reason may be due to DCP enhancing the rectal absorption of propranolol.

The bioavailability after rectal administration of the propranolol HCl hydrogel preparations containing phospholipids in rats is are summarized in Table 2. Both AUC and MRT in hydrogel preparations were significantly greater than those of the conventional suppository. The AUC and MRT increased with addition of phospholipids (1% w/w and 2% w/w) to hydrogel preparations. Furthermore, the AUC of hydrogel preparations with the addition of DCP (0·2% w/w), increased compared with those of hydrogel preparations without DCP. However, these MRT values were not changed with the addition of DCP.

When the drug is absorbed in the lower rectum, it may enter the lower and middle rectal veins, and finally pass into the interior vena cava. It thereby bypasses the portal system and the liver (De Boer et al 1982). In our study, the bioavailability arising from rectal administration of a propranolol suppository increased the drug concentration by approximately 2·5 times compared with oral administration to rats. Furthermore, the bioavailability for rectal administration of the hydrogel preparation increased more than twice compared with that for rectal administration of the suppository. This is because the hydrogel preparation cannot spread in the rectal lumen as does the conventional suppository.

In conclusion, improved bioavailability of hepatic high-clearance and relatively lipophilic drugs, such as propranolol, should be obtained by rectal administration in PVA hydrogel preparations containing phospholipid.

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