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FORMULATION, IN-VITRO RELEASE AND THERAPEUTIC EFFECT OF HYDROGELS BASED CONTROLLED RELEASE TABLETS OF PROPRANOLOL HYDROCHLORIDE

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ABSTRACT

Matrix based controlled release tablets of Propranolol Hydrochloride (PHCL) were formulated using hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (sod. CMC) and their combinations. The in-vitro dissolution kinetics revealed a zero order release for selected drug, HPMC and sod. CMC combination. The selected formulation was evaluated in mongrel dog by recording the isoprenaline induced tachycardia and measuring the inhibition of tachycardia. The results showed the sustaining therapeutic effect of the formulation.

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INTRODUCTION

Controlled release (CR) dosage forms continue to draw attention in the search for improved patient compliance and decreased incidences of adverse drug reactions. Ideally, a CR dosage form will provide therapeutic concentrations of the drug in the blood that are maintained throughout the dosing interval with a reduction in the peak/nadir concentration ratio[1]. One of the least complicated approach to the manufacture of CR dosage form involves direct compression of the blends of the drug, release retardant polymer and the additives to form a tablet in which drug is embedded in the matrix core of the polymer[2].

Hydrogels have attracted considerable attention in recent years as controlled release devices for the delivery of water soluble drugs[3].

Lapidus and Lordi[4] have studied the drug release from compressed hydrophillic matrices. Recently, a number of studies have been carried out using hydrogels for oral CR dosage forms, highlighting its importance to control the release of drugs from dosage forms[5-10].

Propranolol Hydrochloride (PHCl) is a non-selective β-blocker antihypertensive drug. It has a short elimination half-life of 3h, which makes it a suitable candidate to be delivered at a controlled rate[11].

The purpose of this investigation is to formulate the controlled release tablets of PHCl using HPMC, sod. CMC and combinations and their evaluations for in-vitro release kinetics and therapeutic efficacy in mongrel dog.

MATERIALS

Propranolol Hydrochloride, HPMC and sod. CMC were received from IEL; Madras, Wilson Laboratories; Bombay and CDH; New Delhi, respectively. Potato starch, microcrystalline cellulose (MCC), dicalcium phosphate and talc were received from Sisco Research Laboratories; Bombay, Nu Chem; Bombay, and Hansa Chemical Works; Bombay, respectively. Other chemicals and reagents used were of analytical grade.

METHODS

Preparation of Tablets - The drug and the excipients were sieved through 80 mesh for preparation of matrix tablets. The calculated amount of the drug and hydrogels were blended and then compressed into tablets using Manesty E_2 single punch hand operated tablet machine using flat faced punches at a compression pressure of 16 tons psi. Batch specifications for the six batches of matrix tablets have been shown in Table 1. Each batch consisted of 20 tablets. Loading dose (4.26 mg/tablet) of the drug was blended with lactose granules and press coated the A_6 batch tablet for in-vivo study. Drug content was determined following the method of I.P. 1985 for PHCl.

TABLE 1

Batch Specification and Drug Content of Tablets

S.N.	Batch	Drug : Polymer(s) ratio	Drug content/Tablet (mg)
1.	Plain Tablets	-	39.98
2.	A_1	Drug:HPMC, 1:5	40.00
3.	A_2	Drug:HPMC, 1:3.5	40.00
4.	A_3	Drug:Sod.CMC, 1:4	40.20
5.	A_4	Drug:Sod.CMC, 1:6	40.20
6.	A_5	Drug:HPMC:Sod.CMC, 1:2:5	40.60
7.	A_6	Drug:HPMC:Sod.CMC, 1:0.5:3	40.00

Plain tablets were prepared for comparison with CR tablets, for evaluating the therapeutic efficacy in dogs. Each tablet contained drug (40 mg), dicalcium phosphate (53 mg), MCC (4 mg), magnesium stearate (2 mg) and talc (1 mg). The drug was mixed with the excipients and directly compressed into tablets of 100 mg in Manesty E_2 single punch hand operated tablet machine at a compression pressure of 12 tons psi.

In-vitro Dissolution Studies - Dissolution tests were carried out in 'VEEGO TABLET DISSOLUTION TEST APPARATUS' [MODEL VDA - 1, (USP XIX), BOMBAY] containing 500 ml of dissolution fluid, phosphate buffer pH 7.4, maintained at $37 \pm 1^{o}C$.

Each tablet (plain/CR) was placed in the glass vessel containing the buffer and the paddle was lowered into the dissolution medium 3 cm above the bottom and rotated at 50 rpm. Five millilitre aliquots were drawn through a PVC tube fitted with glass wool at one end, at one hour intervals for a period of eight hours and same amount of fresh dissolution fluid was added to replace the amount withdrawn. The drug concentration was determined by measuring the absorbance at 290 nm in a Beckman 24-UV Spectrophotometer.

In-vivo Studies - Therapeutic efficacy of the formulation was tested in mongrel dog by measuring the inhibition of

isoprenaline induced tachycardia over 8 h[12]. This inhibition can be quantified and used as a measure of β-blockade which is closely related to propranolol levels. This was achieved by measuring the heart rate of the dog under different conditions using a 'STUDENT PHYSIOGRAPH' (BIO-DEVICES, INDIA).

Two healthy adult mongrel dogs weighing about 15 kg were used. The dogs were kept in fasting condition for 12 h before the experimentation. One was used for plain tablet evaluation and the other one for CR tablet.

The dogs were weighed and carefully chained down using a dog holder. The pulse transducer/sensor of the instrument was fixed to one of the left arms of the dog and the other end was connected to the coupler. Recordings were taken in the following sequence.

a) Normal heart rate of the dogs was recorded, keeping the chart speed at 2.5 mm/sec.

b) Isoprenaline, according to 3 μg/kg body weight of the dog was administered intraveinously, for inducing tachycardia and the heart rate was recorded.

c) Tablet (plain/CR) was given to the dog orally and after 1 h the heart rate was again recorded.

d) Thereafter the heart rate was recorded every 2 h up to 8 h each time administering isoprenaline (3 μg/kg body wt) intraveinously.

RESULT AND DISCUSSION

Different equations and kinetic models have been used to describe the release kinetics from tablets. Release rate constants, correlation coefficient and determination coefficient were calculated for zero order, first order and Higuchi equations. The results have been shown in Figs. 1-3 and Table 2.

In batches A_1 and A_2 where HPMC alone has been used, the pattern of release follows Higuchi equation[13] (Table 2). The mode of release approaches Fickian type (Fig. 3). This may be attributed to an increase in diffusional pathlength for the drug which in turn may be due to slower erosion rate of the rubbery layer and faster advancement of the swelling front into the glassy polymer. Higher the ratio of HPMC greater will be the retardation. Hence tablet of the batch A_1 shows greater retardation in release than batch A_2 (Fig. 2).

Tablets of batches A_3 and A_4, where sod.CMC alone has been used, exhibits the best correlation by the Higuchi equation, followed by first order[14] (Table 2). However, both the batches exhibited an appreciable increase in the release rate for the first few hours (Fig. 2). This may be attributed to the increase in the erosion rate of the polymer. Later, an increase in the diffusional pathlength, because of the polymer swelling, retards the rate of release.

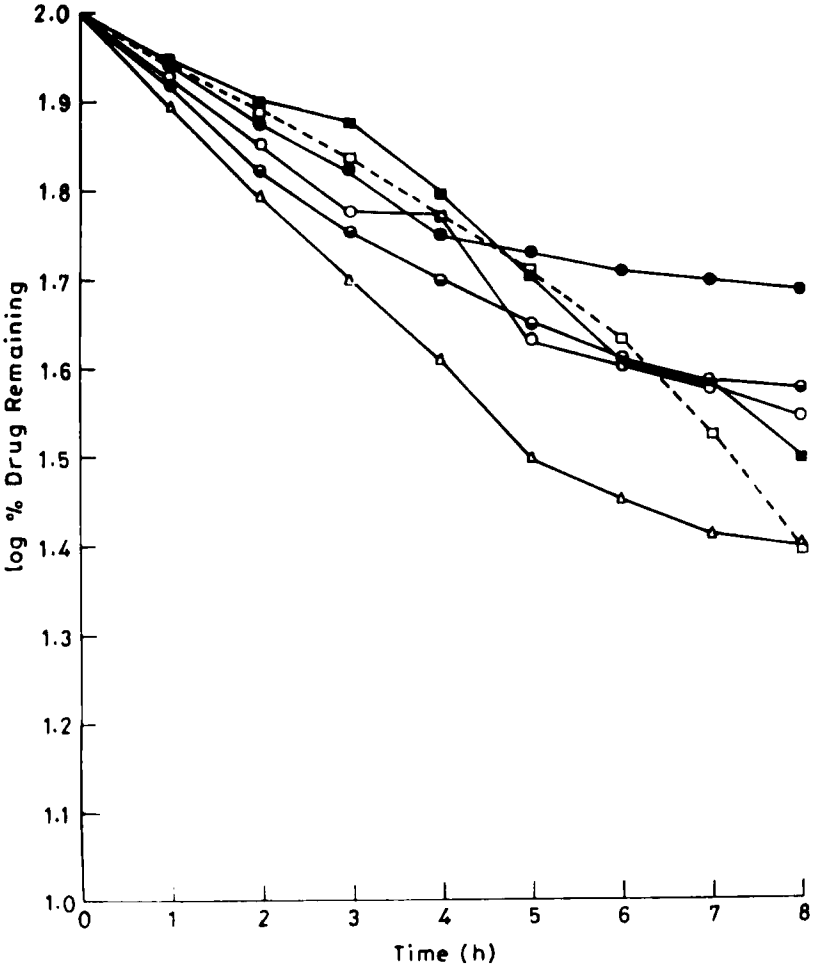

FIGURE 1

Plot of log% remaining vs time for matrix tablets of Propranolol Hydrochloride. Key: ● , A_1; ◒ , A_2; △ , A_3; ○ , A_4; ■ , A_5; □ , A_6.

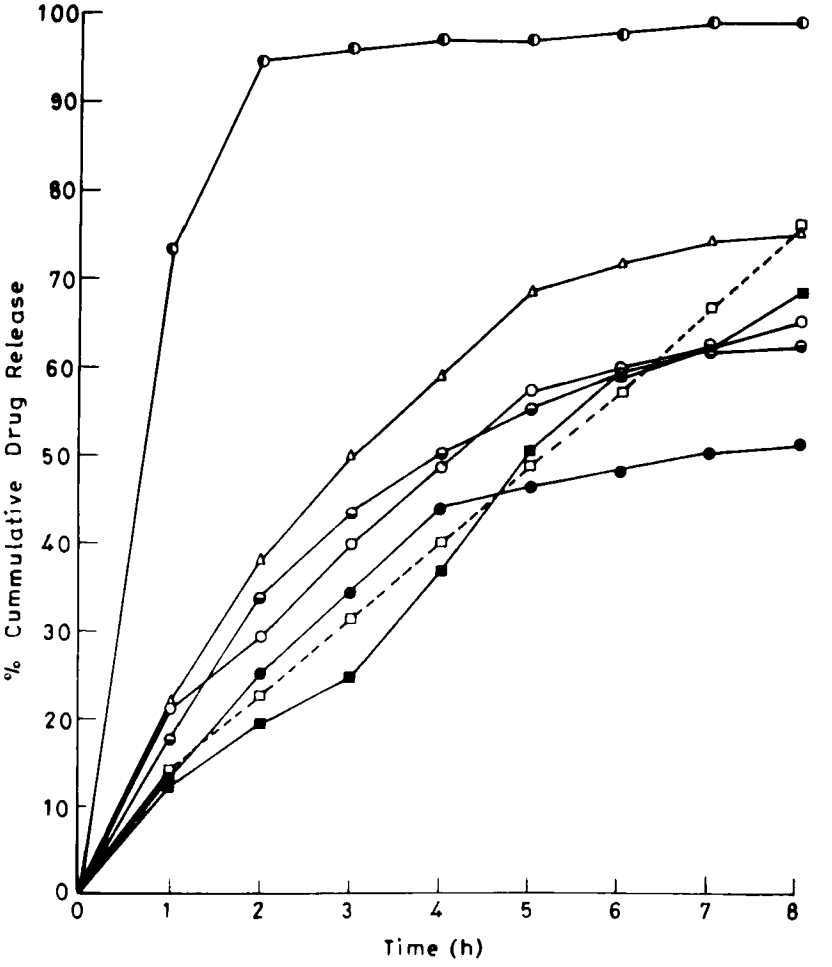

FIGURE 2

Plot of % cumulative drug release vs time for plain and matrix tablets of Propranolol Hydrochloride. Key: ●, A_1; ◒, A_2; Δ, A_3; ○, A_4; ■, A_5; □, A_6; ◐, Plain tablet.

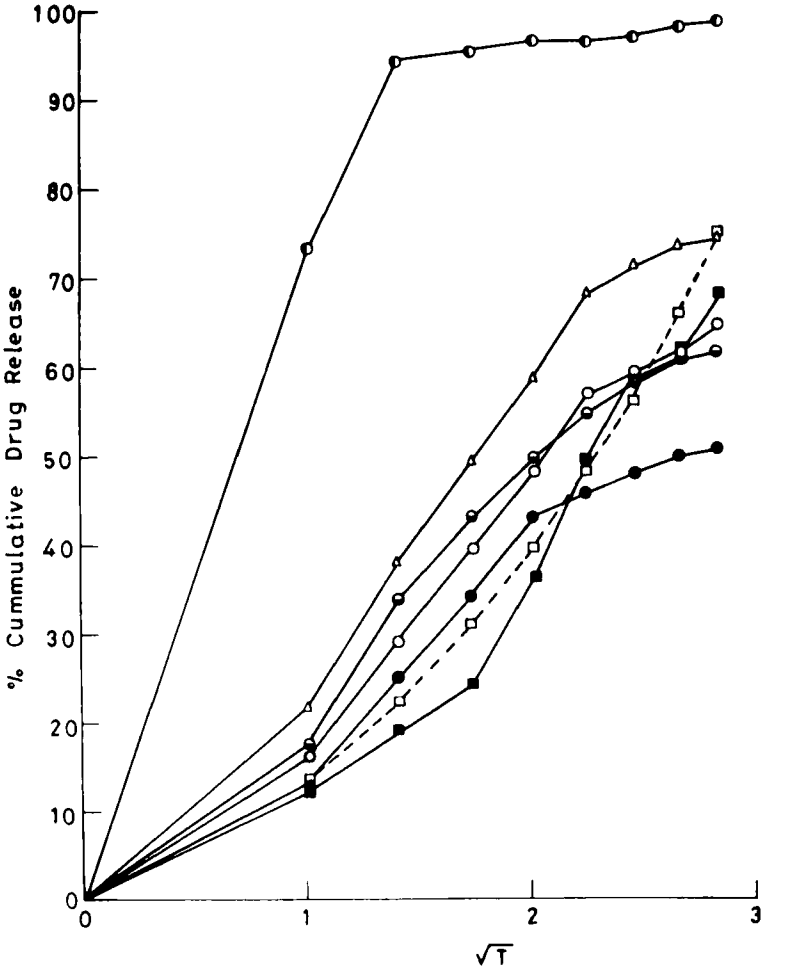

FIGURE 3

Plot of % cumulative drug release vs square root of time for plain and matrix tablets of Propranolol Hydrochloride. Key: ● , A_1; ◒ , A_2; Δ , A_3; ○ , A_4; ■ , A_5; □ , A_6; ◐ Plain tablet.

TABLE 2

Dissolution kinetics of Propranolol Hydrochloride from Tablets in Phosphate Buffer pH 7.4

Kinetics		Batches					
		A_1	A_2	A_3	A_4	A_5	A_6
First	K_1	-0.0354	-0.0475	-0.0738	-0.0549	-0.0671	-0.0746
order	r^2	0.8976	0.9375	0.9537	0.9620	0.9774	0.9677
	r	0.9474	0.9682	0.9766	0.9808	0.9886	0.9837
Zero	K_o	5.2014	5.9742	7.4599	6.8375	8.6182	8.7451
order	r^2	0.8582	0.8795	0.8936	0.9173	0.9776	0.9999
	r	0.9264	0.9378	0.9453	0.9578	0.9887	0.9995
Higuchi	K_h	0.2540	0.2534	0.2540	0.2540	0.2540	0.2540
equation	r^2	0.9810	0.9804	0.9810	0.9810	0.9810	0.9810
	r	0.9905	0.9901	0.9905	0.9905	0.9905	0.9905

K_1 = first order dissolution rate constant; K_o = zero order dissolution rate constant; K_h = Higuchi equation dissolution rate constant; r = correlation coefficient; r^2 = determination coefficient.

Tablets of the batch A_5 also exhibit a release pattern following Higuchi equation. However, tablets of the batch A_6 which also contains mixture combination of HPMC and sod-CMC gives a zero order release (Fig. 2). The best correlation was obtained for zero order release (r =.9995) followed by Higuchi equation (r = 0.9905) and first order release (r = 0.9837). This non-Fickian release pattern may be attributed to the following factors :

(i) Gel viscosity at the periphery increases owing to the high degree of cross-linking between HPMC (non-ionic in nature) and sod-CMC (ionic in nature). The increase is synergistic.

(ii) An increase in the viscosity at the periphery consequently leads to decrease in the rate of advancement of the swelling front into the glassy matrix, which ultimately causes slow diffusion of the drug.

(iii) During the release of the drug from the matrix, two processes go on simultaneously. The first one being advancement of swelling front into the glassy polymer, and the second one is the attrition of the rubbery state polymer, i.e., the gel at the periphery which is devoid of the drug. When the rates of these two processes are equal, the diffusional pathlength for the drug remains constant and zero order release is obtained.

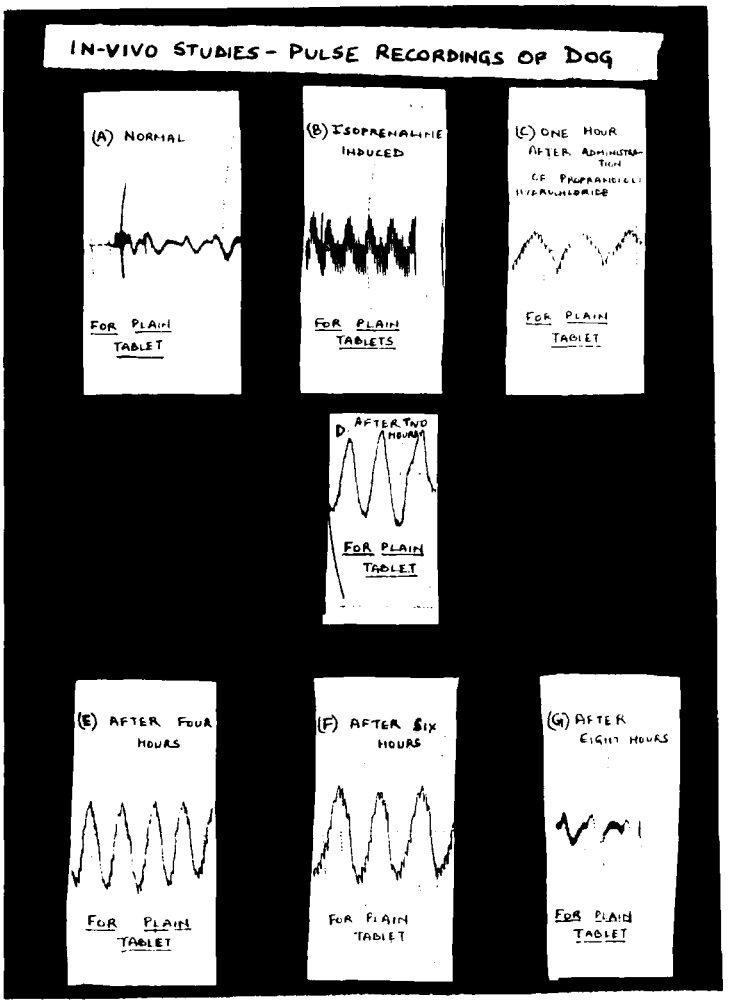

FIGURE 4

Physiograph pulse recordings for plain tablet of Propranolol Hydrochloride.

(iv) Ratio of the total gum to the drug and also the ratio between the hydrogels in the tablet is very important. This is the reason why only a particular drug-polymer ratio gives a zero order release.

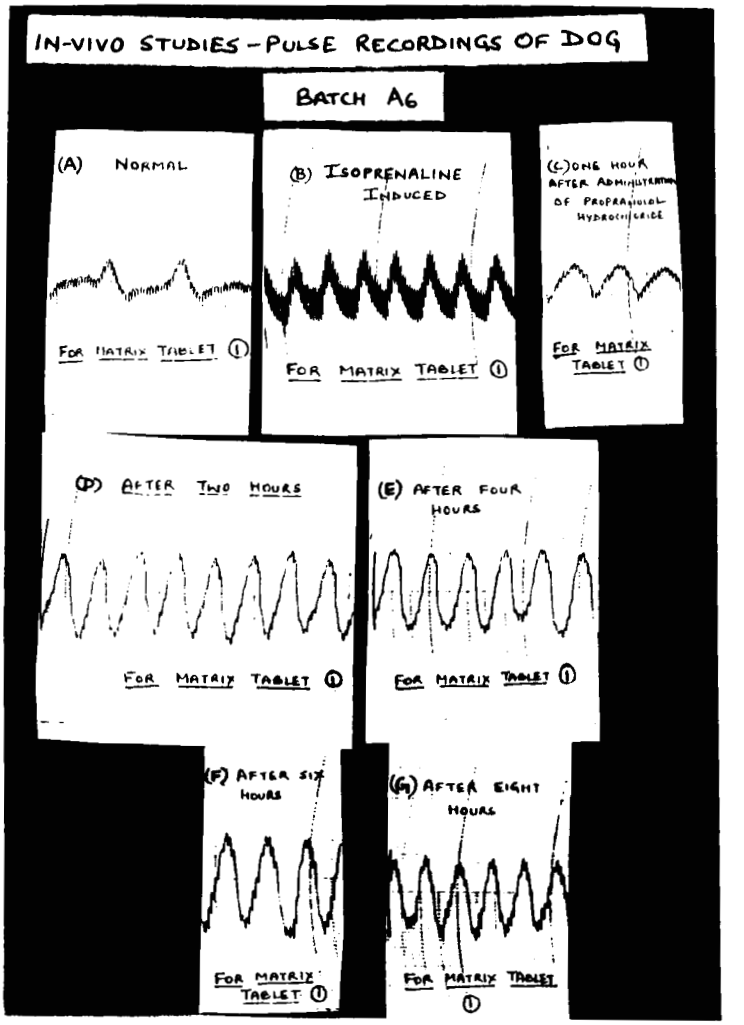

FIGURE 5

Physiograph pulse recordings for matrix tablet (batch A_6) of Propranolol Hydrochloride.

The zero order release pattern from hydrogel matrices has also been observed by other workers[8,9,15].

The plain tablet releases nearly 95% of the drug within two hours.

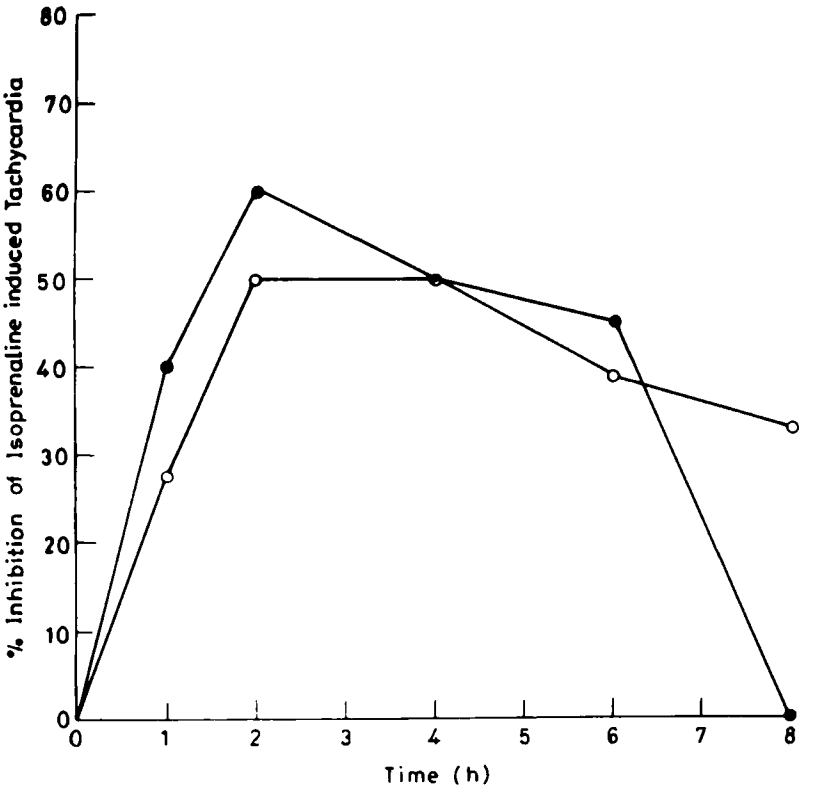

FIGURE 6

Plot of % inhibition of isoprenaline induced tachycardia vs time for plain and matrix tablet (batch A_6).
Key: ● , Plain tablet; O , A_6.

In-vivo studies carried out in mongrel dog showed a maximum inhibition of 60% up to 2 h for plain tablet (Fig. 6). By the end of eighth hour heart rate came back to normal. The batch A_6 showed 50% inhibition of tachycardia after 2 h, which was maintained up to 4 h (Fig. 6). At the end of eighth hour 33% inhibition of tachycardia was observed. Pulse recordings of the plain and CR tablet have been shown in Figs. 4 and 5 , respectively.

Maintainence of tachycardia over the period of 8 h indicates that this drug hydrogel combination may help in producing sustained action over the period and thus reduce the frequency of dosing.

CONCLUSION

Hydrogel matrices in appropriate proportion are suitable for formulating CR tablets to have zero order release and sustaining therapeutic effect of water soluble drugs like propranolol hydrochloride.

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