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Novel Approach to Zero Order Drug Delivery via Hydrogel for Diltiazem Hydrochloride

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Hydrogel matrix tablets of diltiazerm hydrochloride was formulated using hydroxypropyl methyl cellulose and sodium carboxy methylcellulose with the aim to attain a near zero order release. *In vitro* dissolution studies were carried out using USP Type 2 dissolution test apparatus. The release followed a typical Higuchian pattern. When an optimum mixture of hydroxypropyl methyl cellulose and sodium carboxy methylcellulose was used as the matrix material, the drug release followed zero order rate. The mechanism of diffusion was explained by the Peppas equation. The effect of the formulation was found by recording the electrocardiogram in isoprenaline-induced tachycardia conducted in mongrel dogs, which showed inhibition for 10 h.

Controlled release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidences of adverse drug reactions. Ideally, a controlled release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio[1]. One of the least complicated approaches is to form a tablet in which drug is embedded in matrix core of the polymer[2].

Hydrogels are used as controlled release devices for delivery of water soluble drugs[3-4]. Various types of polymers used as hydrophilic matrices and their modeling aspects have been reviewed[5,6]. Dilitiazem hydrochloride is a calcium channel blocker and has a short elimination half life, which makes it as a suitable candidate to be delivered at a controlled rate[7].

In the present study, controlled release tablets of diltiazem hydrochloride using, hydroxypropyl methyl cellulose (HPMC) and sodium carboxy methylcellulose (SCMC) as polymers were prepared. The swelling kinetics, *in vitro* and *in vivo* studies were carried out for the same.

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MATERIALS AND METHODS

Diltiazem hydrochloride was a gift sample from M/s. Anglo-French Pharmaceuticals, Bangalore. HPMC (viscosity 40 poise) and SCMC (high viscosity grade), magnesium stearate and talc were procured from M/s. Loba Chemie, Mumbai. All other chemicals and reagents used were of analytical grade. Mongrel dogs were obtained from the Laboratory Animal House, Veterinary College, University of Agricultural Sciences, Hebbal, Bangalore. The dog study was carried out in April 1998, at which time studies using mongrel dogs were permitted.

Preparation of tablets:

The drug and the excipients were sieved through sieve No. 100. Diltiazem hydrochloride (90 mg), the polymers in different ratios (Table 1) and the excipients were blended using a mortar and pestle. The polymers selected also served the purpose of binding. The powder mixture was granulated using distilled water and then passed through sieve No. 16. The granules were dried at 60° for 1 h in a hot air oven. The dried granules were passed through sieve No. 24/32. The granules were evaluated for angle of repose, bulk density and loss on drying. The results are given in Table 1. The prepared granules were mixed uniformly with 2% magnesium stearate and 3% talc, which were used as lubricant and glident respectively. The granules were compressed by

TABLE 1: COMPOSITION AND PHYSICAL EVALUATION OF GRANULES.

Formulation	Drug: Polymer Ratio	Angle of repose (°)	Bulk density (g/cc)	Loss on drying (%)
A_1	1:1	37.56	0.40	2.71
A_2	1:2	36.13	0.50	1.96
A_3	1:3	36.72	0.50	1.90
B_1	1:1	41.66	0.33	2.01
B_2	1:2	38.79	0.34	2.10
B_3	1:3	40.26	0.32	2.03
C_1	1:1:1	43.28	0.35	2.15

A_1, A_2, A_3, are hydrogels formulated using drug:HPMC ratio of 1:1, 1:2 and 1:3, Whereas B_1, B_2, B_3, contains drug:SCMC in the ratio of 1:1,1:2 and 1:3. C_3, contains a combination of drug, HPMC and SCMC in the ratio of 1:1:1. prepared by wet granulation method.

using cadmach tablet compression machine using 10 mm punch. The hardness was adjusted to 3-4 kg/cm^2.

Drug content:

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 90 mg of diltiazem hydrochloride was transferred into a 100 ml volumetric flask and extracted with distilled water. Then 1 ml of the filtered solution was diluted to 50 ml with distilled water and absorbance was measured at 236 nm. The drug content is as shown in Table 2.

Mass degree of swelling:

Each tablet was allowed to equilibrate with 100 ml of water for 5 h. The tablets were removed, blotted using tissue paper and weighed. The mass degree of swelling (Q) was calculated using the formula[8], Q = Mass of the swollen gel/mass of the dry polymer. The results are given in Table 2.

TABLE 2: DRUG CONTENT AND SWELLING DEGREE OF HYDROGELS.

Formulation	Drug Content (mg±S.D.)	Swelling degree (Q)
A_1	89.90±1.31	7.95
A_2	89.90±1.48	6.11
A_3	90.09±1.84	5.11
B_1	89.60±1.20	6.38
B_2	91.04±0.68	5.60
B_3	90.60±1.07	5.25
C_1	91.43±1.15	5.45

A_1, A_2, A_3, are hydrogels formulated using drug:HPMC ratio of 1:1, 1:2 and 1:3, Whereas B_1, B_2,B_3, contains drug:SCMC in the ratio of 1:1,1:2 and 1:3. C_3, contains a combination of drug, HPMC and SCMC in the ratio of 1:1:1. prepared by wet granulation method.

***In vitro* release study:**

In vitro release rate studies were carried out using USP dissolution apparatus Type-2[9,10]. Nine hundred milliliters of distilled water was used as the dissolution medium. Temperature was maintained at 37±1°. The paddle speed was controlled at 100 rpm. One tablet was placed in the dissolution medium. Samples (5 ml) were collected every 1 h and filtered, diluted up to 10 ml with distilled water and absorbance was measured at 236 nm. *In vitro* release study was also carried out on a 90 mg sustained release marketed product (M).

Fig. 1 explains the dissolution profile of the formulations and marketed product and fig. 2 gives the Higuchi's plot. Zero order release equation, Kosmeyer and Peppas equations were utilized to prove the zero order release. Higuchi's equation explains the diffusion controlled release rate. The correlation co-efficient and determination co efficient are given in Table 3.

Permeability:

It is a useful parameter to study hydrogel drug delivery. Since the drug is dispersed in the hydrogel, the slope of plot of Mt. Versus t1/2 will yield D, the drug diffusion coefficient, where Mt is the amount released[11] at time 't'. Table 4 gives the drug diffusion co-efficient.

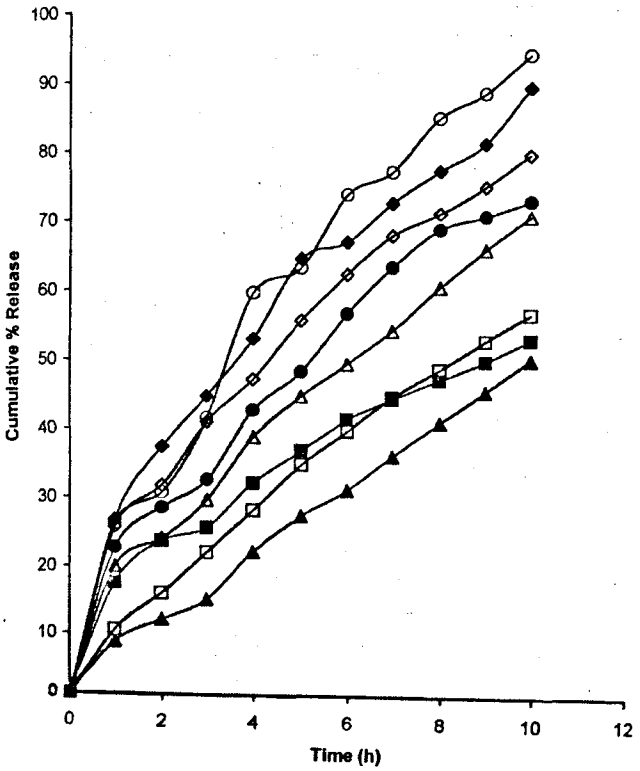

Fig 1: Dissolution profile of the formulation.

Release of diltiazem hydrochloride from various hydrogel formulations made up of drug:HPMC ratios of, 1:1 (A_1, -◆-), 1:2 (A_2, -◇-), 1:3 (A_3, -■-), drug:SCMC ratios of 1:1 (B_1, -△-),1:2 (B_2,-□-), 1:3 (B_3, -▲-), drug : HPMC:SCMC ratio of 1:1:1 (C_1,-●-) and Marketed product (M, -o-) was studied.

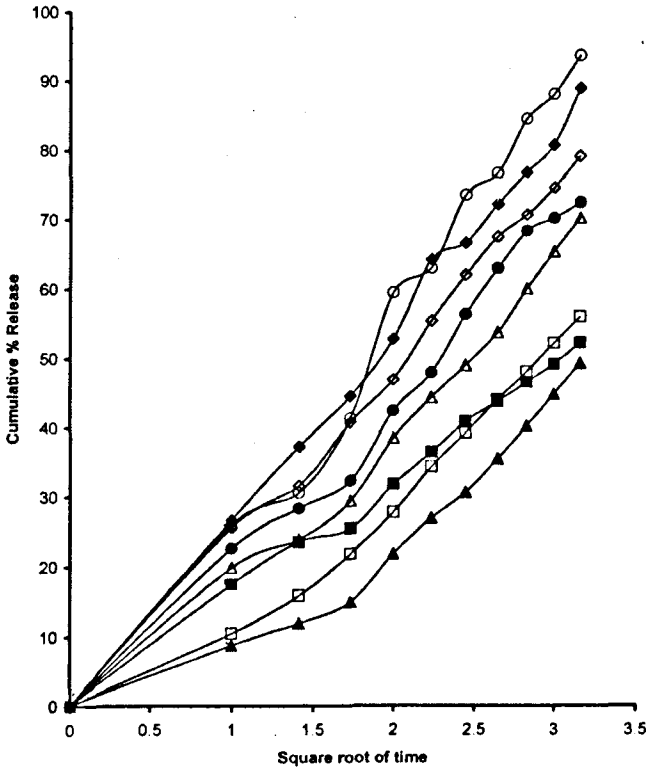

Fig 2: Higuchi's Plot.

Release of diltiazem hydrochloride from various hydrogel formulations made up of drug:HPMC ratios of, 1:1 (A_1, -◆-), 1:2 (A_2, -◇-), 1:3 (A_3, -■-), drug:SCMC ratios of 1:1 (B_1, -△-),1:2 (B_2,-□-), 1:3 (B_3, -▲-), drug : HPMC:SCMC ratio of 1:1:1 (C_1,-●-) and Marketed product (M, -o-) was studied.

TABLE 3: DISSOLUTION KINETICS OF DILTIAZEM HYDROCHLORIDE.

Formulation	Zero Order Equation		Higuchi's Equation	
	r	r^2	r	r^2
A_1	0.9870	0.9740	0.9956	0.9914
A_2	0.9946	0.9892	0.9943	0.9886
A_3	0.9920	0.9840	0.9954	0.9909
B_1	0.9960	0.9920	0.9882	0.9766
B_2	0.9979	0.9958	0.9944	0.9889
B_3	0.9936	0.9872	0.9818	0.9640
C_1	0.9967	0.9954	0.9918	0.9838
M	0.9850	0.9700	0.9850	0.9710

A_1, A_2, A_3, are hydrogels formulated using drug:HPMC ratio of 1:1, 1:2 and 1:3, Whereas B_1, B_2, B_3, contains drug:SCMC in the ratio of 1:1,1:2 and 1:3. C_3, contains a combination of drug, HPMC and SCMC in the ratio of 1:1:1. prepared by wet granulation method. M is the marketed product containing diltiazem hydrochloride.

TABLE 4: PERMEABILITY AND MECHANISM OF DIFFUSION.

Formulation	Drug Diffussion Coefficient-D	Value of n	Mechanism of Diffusion
A_1	25.41	0.582	Non-Fickian
A_2	23.50	0.622	Non-Fickian
A_3	14.86	0.777	Non-Fickian
B_1	22.20	0.749	Non-Fickian
B_2	19.96	1.005	Supper case II Fragment
B_3	17.82	1.180	Supper case II Fragment
C_1	21.24	0.814	Non-Fickian

A_1, A_2, A_3, are hydrogels formulated using drug:HPMC ratio of 1:1, 1:2 and 1:3, Whereas B_1, B_2, B_3, contains drug:SCMC in the ratio of 1:1,1:2 and 1:3. C_3, contains a combination of drug, HPMC and SCMC in the ratio of 1:1:1. prepared by wet granulation method.

Mechanism of diffusion:

For studying the mechanism of drug release from these tablets, the dissolution data was fitted to the equation of Korsmeyer and Peppas[12] $Mt/M\infty = Kt^n$, where $Mt/M\infty$ is the fractional drug released in time t and K is the constant incorporating structural and geometric characteristics of controlled release device, and n is the diffusional release exponent indicative of release mechanism. For Fickian diffusion n=0.5; for Non Fickian diffusion 0.5<n<I and for super case II, n=1 or >1. The results are given in Table 4.

***In vivo* studies:**

Two healthy adult mongrel dogs weighing 10 kg were used. They were kept in fasting condition for 12 h before the experiment. One dog was given plain tablet and the other was given C_1 formulation. ECG was recorded in the following sequence[13]. Normal heart rate of the dog was recorded keeping the chart speed as 2.5 mm/sec. Isoprenaline 3 µg/kg was given intravenously for inducing tachycardia and the heart rate was recorded. The plain tablet and C_1 was given to the dogs orally and after 1 h the heart rate was recorded. Thereafter the heart rate was recorded every 3 h up to 10 h each time administering isoprenaline intravenously.

RESULTS AND DISCUSSIONS

Seven formulations containing different drug polymer ratios were prepared by wet granulation method. The granules were compressed using cadmach single punch machine by adjusting the hardness to 3-4 kg/cm^2. The drug content was found to be within the limits. The swelling degree was found to be maximum for A_1 (7.95). This may be due to high swelling capacity of polymer indicating that release may be maximum from this formulation. In other formulations swelling degree was ranging from 5-7.95. C_1 had a swelling degree of only 5.45, which has a combination of HPMC and SCMC. Gel viscosity at the periphery increases owing to the high degree of cross-linking between HPMC, which is non-ionic, and SCMC, which is ionic in nature.

The release rate was found to be decreasing as the concentration of polymer increased. This may be due to the reason that the swelling degree is less because of the higher concentration of polymer. In C_1 the cumulative percentage drug release was about 70%. The release rate of the marketed product (M) was found to be around 94% after 10 h. The drug releases from all the formulation gives a near zero order release as shown in fig. 1.

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 rate of these process are equal, the diffusion path length for the drug remains constant and zero-order release is obtained.

Different equations and kinetic models have been used to describe the release kinetics from the tablet. All the formulation followed Highuchi's equation proving that the release is by diffusion mechanism. For studying the mechanism of drug release from the tablet the dissolution data was fitted into Korsmeyer and Peppas equation. A_1, A_2, A_3, B_1 and C_1 has value greater than 0.5 and less than 1 and they follow non-Fickian diffusion, in B_2 and B_3 n>1 and follows super case II transport. Non-Fickian diffusion is also called

as anomalous transport where diffusion and relaxation occur at comparable rates and thus interacting complex fashions. Case II transport is a special case of Non-Fickian transport and is distinguished by the development of solvent front that moves at a relaxation controlled constant velocity. Here relaxation occurs at an observable rate in the glassy part of the swelling gel but the rate is much slower than diffusion in the rubbery state. The drug diffusion coefficient D was found to be decreasing with increase in polymer ratio.

In vivo studies carried out in mongrel dogs showed a normal heart rate of 120-150 beats/min before the experiment. When isoprenaline was injected at a concentration of 3 µg/kg body weight of the dog, the heart rate was found to be 250-300 beats/min. For plain tablet and C_1 formulation the heart rate was 120-150 beats/min after 1 h and in C_1 treated dog there was inhibition continuously up to 10 h. Maximum inhibition of tachycardia for plain tablet after 1 h was 50-90% and lasted for 4 h. 59-90% inhibition of tachycardia was observed with C_1 formulation for 10 h. Maintenance of tachycardia over 10 h period indicates that this drug hydrogel combination may help in producing controlled release over the period and thus reducing the frequency of dosing. Therefore hydrogel matrices in appropriate proportions are suitable for formulating controlled release tablets to have zero order release for water soluble drugs like diltiazem hydrochloride.

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