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EFFECT OF VISCOSITY INCREASING AGENT AND ELECTROLYTE CONCENTRATION ON THE RELEASE RATE OF THEOPHYLLINE FROM A HPMC BASED SUSTAINED RELEASE CAPSULES

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ABSTRACT

Sustained release (SR) granules (250-650μ) containing theophylline were prepared using hydroxypropyl methylcellulose (HPMC) as a rate retarding polymer. The effect of variable ionic strength and viscosity increasing agent on the theophylline release rate have been investigated. Irrespective of dissolution media the theophylline release kinetics was found to be dependent on square root of time. The Higuchian release rate (K) was found to increase exponentially with the increase in ionic strength of the dissolution fluid. An opposite effect was observed with the viscosity increasing agent sodium carboxy methyl cellulose (Na-CMC) in the dissolution fluid. The release rate decreased linearly with the increase of Na-CMC concentration in the dissolution fluid.

INTRODUCTION

Sustained release oral capsules are most conveniently prepared, but bioavailability of drugs from such capsules are affected by variations due to gastric emptying time[1]. The problem of gastric emptying time of single unit dosage form can be improved by using multiple unit dosages form (pellets) in hard gelatin capsules[2]. Therefore researchers have paid much interest towards the development of sustained release (SR) capsules containing various drugs[3–5]. Synthetic and semi-synthetic polymers are commonly used to prepare sustained release products[6]. Drug release from polymer matrices are controlled by several inter related mechanisms, such as, transport of dissolution fluid into the polymer bed, swelling of polymers at the surface, diffusion of drug through the water filled swelled gel layer, etc. Drug release from swellable matrices have been studied by several workers[7–9]. The effect of dissolution fluid characteristics on the release kinetics from hydrophilic polymers are not well studied. The aim of this work was to evaluate drug release mechanism from HPMC granular matrices in presence of viscosity imparting agent and electrolytes in the dissolution fluid.

MATERIALS

Hydroxypropyl methylcellulose, 50 cps (Shin-Etsu Chemical Co. Japan), Sodium carboxy methylcellulose (FMC Corporation), Polyethylene glycol-4000 (BDH), Theophylline anhydrous (BDH), NaCl (BDH). Other chemicals were of reagent grade.

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Table 1. Higuchi release rate constant and time for 50% release from SR theophylline capsules in dissolution media of different ionic strength.

I^{+} x 10^{-1}	K^{++} (% release $min^{-1/2}$)	r* (P<0.01)	t_{50}** (Hour)
00.0	7.00	0.991	1.55
0.85	7.20	0.991	1.50
1.70	7.50	0.987	1.35
3.40	8.60	0.987	1.09
5.10	10.25	0.993	0.94
6.80	12.75	0.990	0.73
10.20	16.75	0.981	0.45

+ I = Ionic strength of the dissolution fluid. ++ K = Higuchi release rate constant.
* r = Correlation coefficient. ** t_{50} = Time for 50% release.

METHODS

Preparation of capsules: Five gm of theophylline was mixed uniformly with 45 gm HPMC and 5 gm polyethylene glycol-4000. 10 ml of dichloromethane was used to prepare a wet mass and granulated using a sieve having aperture diameter of 750μ. These granules were air dried overnight and finally sieved. Granules of seive fraction between 250-650μ were filled into hard gelatin capsule shell no. 1 using a laboratory capsule filling apparatus.

Analysis of capsule: Average weight of the capsules was determined by weighing 20 capsules. Theophylline content of the capsules was determined by sprectrophotometric analysis at 270nm by using a Pye-Unicam SP3–800 spectrophotometer. The concentration of theophylline was calculated from a calibration curve. The experiment was done in triplicate.

Dissolution Studies: Dissolution studies were carried out according to USP XXII paddle method at 37°C and 50 rpm. Six vessel dissolution apparatus (Electrolab, India) was used for this purpose. Five ml of sample was withdrawn at a predetermined time interval from each vessel and 5 ml of the same dissolution fluid was replaced every time to maintain the sink condition. Different dissolution fluids containing increasing amounts of KCl were prepared to get ionic strength, 0.85, 1.70, 3.40, 5.10, 6.80, 10.20, $\times 10^{-1}$. Dissolution fluids containing increasing amounts of viscosity imparting agent (Na-CMC) were also prepared to get concentrations of 0.10, 0.15, 0.20, 0.30% w/v. The samples were assayed spectrophotometrically at 270 nm using a Pye-Unicam SP3–800 double beam spectrophotometer. Each batch of dissolution test was run in triplicate and average value was taken.

RESULTS AND DISCUSSION

Sustained release theophylline capsules containing granules (250–650μ) were prepared using HPMC as a rate retarding polymer. 10% polyethylene glycol 4000 (PEG–4) was used as plasticizer. Average fill wight was 503.05±3.71 mg/capsule. Theophylline content of the capsules was found to be 51.25±0.73 mg/capsule. Theophylline release rate was determined using dissolution media of different ionic strength. When percent theophylline release in different dissolution media was plotted against square root of time, straight line was obtained (Fig. 1) with good correlation coefficient r>0.98 (Table 1).

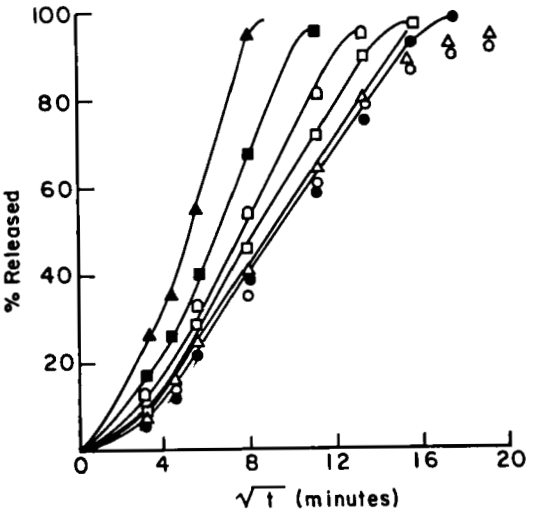

Figure 1. Higuchi plot of theophylline release from SR capsules in dissolution media of different ionic strength. Ionic strength X 10^{-1} ; ●, 0.85; △, 1.7; □, 3.4; ⌂, 5.1; ■, 6.8; ▲, 10.2; ○, triple distilled water.

Drug release from the hydrogel polymer matrices are controlled by several inter related mechanisms, such as, transport of dissolution fluid into the polymer bed, swelling of the polymer at the surface, diffusion of drug through the water filled swelled gel layer, etc. Concomitant erosion of the gel layer increases the diffusion rate of the core materials. Drug release from swellable matrices have been studied by several workers [8,9]. However, the square root of time dependent release mechanism from materials was originally proposed by Higuchi [10,11]. A simplified equation (1) is commonly used to quantify the square root of time dependent release rate.

$$Q = Kt^{1/2} \quad \text{---------- (1)}$$

where Q = the amount of drug release after time t and K = Higuchi release rate constant.

This experiment proved that the theophylline release from the HPMC granular matrices fits well with the square root of the time dependent release mechanism irrespective of the dissolution media used (Fig. 1). Similar Fickian release of benzocaine, sodium salicylate and benzoic acid from HPMC based compressed tablets have been reported[8].

The pH and ionic strength have certain effect on the tablet solubility containing ionizable drugs. It may also affect the hydration and swelling phenomenon of the hydrophilic polymers. It was assumed that the lower hydrodynamic activity of the dissolution fluid (due to the presence of ionic species) will retard water penetration into the HPMC/theophylline matrices and consequently lower the release rate. But this experiment showed a complete reversal of the process and there was an increase in the dissolution rate with increase in the ionic strength of the dissolution medium. Though dissolution medium of very high ionic strength (10.2×10^{-1}) was used at the extreme (normal buffers or biological fluids do not have such high ionic strength), this experiment has got significant value.

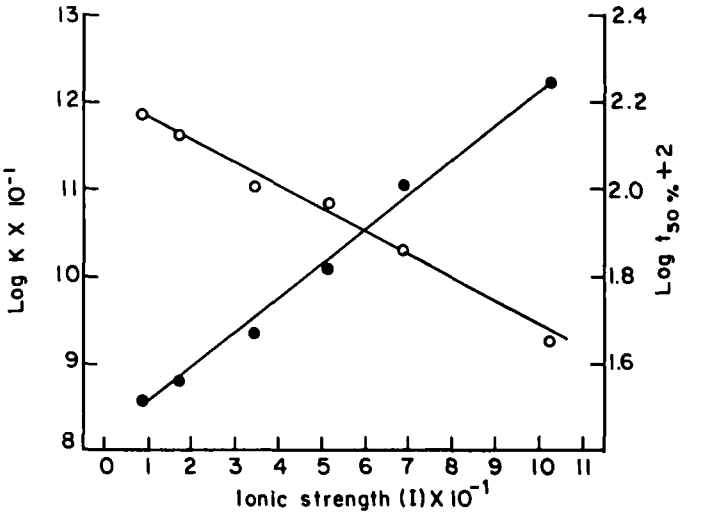

Figure 2. Effect of ionic strength (*I*) on the release rate constant (K) and the time for 50% release (t_{50}) from the SR theophylline capsules. ●, release rate; ○, t_{50},

Table 2. Higuchi release rate constant and time for 50% release from SR theophylline capsules in dissolution media containing Na-CMC.

Na-CMC+ (% w/v)	K++ (% release $min^{-1/2}$)	r* (P<0.01)	t_{50}** (Hour)
0.00	7.00	0.991	1.55
0.10	6.75	0.991	1.70
0.15	6.25	0.989	1.98
0.20	5.75	0.995	2.24
0.30	4.75	0.985	2.90

\+ Na–CMC = Concentration in the dissolution fluid ++ K = Higuchi release rate constant.
* r = Correlation coefficient. ** t_{50} = Time for 50% release.

Because formulations of inorganic salts or ionizable drugs will produce high ionic strength in the gel layer during hydration.

The increase in theophylline release with the increase in ionic strength may be attributable to several factors: (1) Increased ionic strength in the dissolution fluid increased erosion and dissolution of polymer chain from the surface. (2) Greater thermodynamic incompatibility with the increase in ionic strength may have caused rapid equilibrium with HPMC/theophylline system thereby causing raipid hydration and dissolution of the system. (3) High osmotic pressure created due to the presence of ionic species in the dissolution fluid may have caused rapid dissolution of the matrices. The high osmotic pressure outside the boundary layer of hydrogel may have pulled out water from the inner rubbery layer of the matrix. During this process of water extraction the loosely bound HPMC polymer at the rubbery layer was disrupted and caused rapid dissolution. All these factors combinedly may

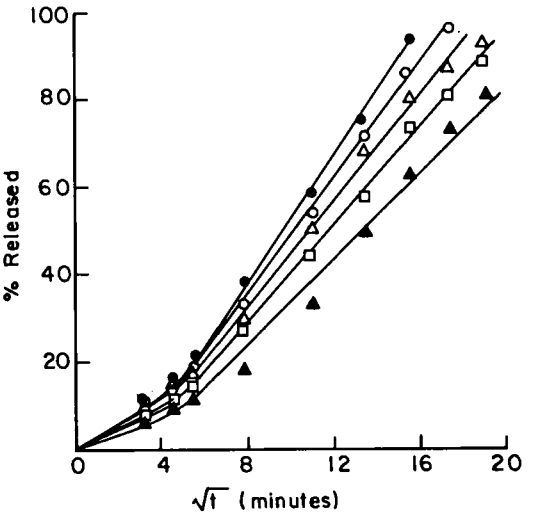

Figure 3. Higuchi plot of theophylline release from SR capsules at dissolution media of different concentrations of Na-CMC. Concentrations of Na-CMC: ○, 0.10; △, 0.15; □, 0.20; ▲, 0.30; ●, triple distilled water.

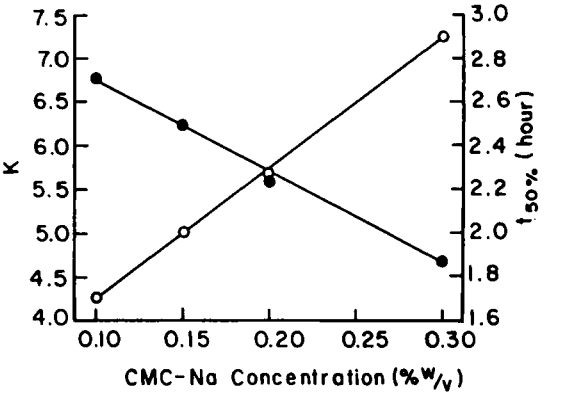

Figure 4. Effect of viscosity increasing agent (Na-CMC) on the release rate constant (K) and the time for 50% release (t_{50}) from the SR capsules. ●, release rate; ○, t_{50}.

have caused such rapid increase in the dissolution rate of theophylline with the increase in the ionic strength. When the release rate (K) of the capsule was plotted on log scale against the ionic strength of the dissolution fluid, a straight line was obtained (Fig. 2) indicating an exponential increase in the dissolution rate. Similarly when log of time for 50% theophylline release (t_{50}) was plotted against ionic strength, there was an exponential decrease in the t_{50} (Fig. 2). Recently other workers also reported significant effect of ionic strength on the dissolution rate of theophylline from sustained release tablets[12]. A parabolic curve was reported, where dissolution rate initially decreased and then increased with the increase in ionic strength.

Another investigation using different concentration of Na-CMC in the dissolution fluid showed opposite effect to those of ionic strength. Here the release rate of theophylline decreased with ithe ncrease in the viscosity of dissolution media (Table 2). The release mechanism followed the same Higuchian fashion (Fig. 3) with good straight line correlation (r>0. 985). Increase in the dissolution media viscosity by using Na-CMC reduced the hydrodynamic activity of the dissolution fluid and thereby decreased the rate of hydration of HPMC matrices. The formation of rubbery state at the boundary layer and consequent erosion of the hydrogel was lower in higher viscosity fluid, therefore release rate was also slower.

The decrease in the release rate as well as the increase in the t_{50} was linear with the increase in the Na-CMC concentration in the dissolution fluid (Fig. 4). In contrast, the ionic strength of the dissolution fluid caused exponential increase of the release rate (Fig. 2). In all cases the straight lines of Higuchi plot did not pass through the origin (Fig. 1 and 3) and extrapolation show negative intercept at the y-axis. This was due to time taken for dissolution of the outer hard gelatin shell and as well as time taken for initial hydration of the outer surface of the granules.

CONCLUSION

Polymer based sustained release matrix preparations are gaining importance over the traditional wax based formulations. The major problem lies with the *in-vitro* drug release properties and its correlation with the *in-vivo* release pattern. Because *in-vivo* conditions of stomach is different and it is difficult to simulate exact condition *in-vitro*. These experiments have shown that both the dissolution fluid viscosity and ionic strength affect *in-vitro* release rate. Therefore greater care should be taken during development of a HPMC based sustained release formulations.

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