In vitro Parameters Evaluation of Theophylline Release from the Hydrogels of α-PVA/NaCl/H2O System

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Abstract: In order to study the effect of in vitro parameters on the theophylline release from the hydrogel system of anactive-PVA/NaCl/H2O, in vitro parameters such as agitators, rotation speed, release medium and release temperature were evaluated. Theophylline release was studied for a period of 750 min using paddle and propeller agitator, rotation speed (25, 50, 100 and 150 rpm), release medium (simulated fluids pH 1.2, 7.5 and phosphate buffer pH 8.5 with 0.05 M at 37°C) and release temperatures (27, 37 and 47°C). SEM and DSC studies were performed to evaluate the surface morphology and heat capacity as well as melting temperatures of the hydrogels affected by various simulated fluids and phosphate buffer. A regular Fickian diffusion was found (Higuchi Model) for first 60 to 70% release. A faster release rate was found in paddle rotation than that of propeller one. Among the release medium comparatively high release rate in extremely low pH (1.2) and near about same release rate in distilled water, pH 7.5 and pH 8.5 were found. DSC thermogram of these treated xerogels showed low melting temperature as well as high heat capacity of pH 1.2 sample than that of others. Rotation speed had a little effect on release rate but the diffusion exponent. It decreased linearly with increasing rotation speed. On the other hand release rate increased proportionally to temperature where diffusion exponent decreased with increasing temperature in a parabolic fashion. Theophylline release behavior was regular Fickian diffusion (Higuchi Model) irrespective of in vitro conditions studied here. However release rate, diffusion exponent, kinetic constant and diffusion co-efficient vary with rotator type, rotation speed, release medium and temperature.

Key words: Diffusion exponent, diffusion co-efficient, kinetic constant, Fickian diffusion, release rate, hydrogel, theophylline, xerogel

INTRODUCTION

It is very difficult to simulate exactly the peristaltic movement of gastrointestinal (GI) tract in respective GI fluids. At present, there are no specific USP specifications for sustained release (SR) dosage forms (Nicholas, 1991). However, there is USP paddle method type II, basket method and beaker method for in vitro drug release correlations of conventional dosage form (e.g., tablet, capsule, both disintegrating and nondisintegrating). The apparent diffusion boundary layer and dissolution rate constant for various surfaces of compacts and at various locations in the USP paddle dissolution apparatus (Type II) were already reported (Healy et al., 2002). However, they concluded that a more exact description of the hydrodynamics would be necessary in order to precisely model drug dissolution in the paddle dissolution apparatus. Moreover drug release depends on the nature of retardant, drug solubility, drug-matrix interaction, drug loading and added diluents (Desai et al., 1966a-c).

In vitro release evaluation of an anti-inflammatory drug from a chemically cross-linked hydrogel (cross-linked with ethylene glycol diglycidyl ether) in simulated GI fluids (pH 1.68 and phosphate buffer saline pH 7.4) was reported by Pitarressi et al. (2001); Oliko-Kabir et al. (1998) reported another chemically cross-linked hydrogel of guar gum (cross-linked with glutaraldehyde) and described a bit of swelling properties in simulated GI fluids as well as drug release kinetics thereby. Most of the chemical cross-linking agents are toxic and sometimes carcinogenic. Where as

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physically cross-linked PVA hydrogels are non-toxic, non-carcinogenic, have good biocompatibility as well as desirable physical properties (Finch, 1992; Peppas and Stauffer, 1991).

Recently we have reported the properties of the hydrogels and films obtained from a-PVA/NaCl/H₂O system (Yamaura and Naito, 2002; Shaheen and Yamaura, 2002a, b, 2003; Dai et al., 2002). This system has got the high melting temperature (90-95°C), low gelation time and high gelling temperature. Due to high melting temperature of this hydrogel system made itself superiority in respect of dose dumping because it does not melt at body temperature (37°C) so no possibility of dose-dumping at all. Dose dumping is one of the great disadvantages of sustained-release dosage forms.

The present research aims to evaluate the fate of a hydrogel matrices derived from such a developed novel physically cross-linked hydrogel system like a-PVA/NaCl/H₂O from the viewpoint of theophylline release, when these like to be passed through GIT environment (gastric fluid, intestinal peristaltic movement and physiological temperature of gut).

Here we have evaluated the effect of in vitro parameters like agitators (paddle and propeller), rotation speed, dissolution medium and release temperature, on the theophylline release from the hydrogels of a-PVA/NaCl/H₂O system and tried to find out the effects of in vitro parameters from this hydrogels system.

**MATERIALS AND METHODS**

**Materials:** Atactic poly(vinyl alcohol) (a-PVA) was purchased from UNITIKA Chemical Ltd, as commercial grade (degree of polymerization: 1730, degree of saponification: 99.39 mol %). Theophylline was purchased from Wako Pure Chemical Industries Ltd. Absorbance of TH was measured at λmax: 274 nm using an UV-visible Recording Spectrophotometer, Shimadzu-160. Other instruments used in the experiments were: Toyama Dissolution Tester NTR-VS6, Eyela mazela Z rotator, Yamato Constant temperature water bath BK,53, Advantec Immersion Circulator and Eyela Digi. Thermopet NTT., Rigaku Thermo Plus DSC 8230, Yamato Neo-Cool Unit No. 803028 available in the department of kaisei engineering, Shinshu university, Japan.

**Methodology:** Theophylline (3%) hydrogels of a-PVA (7%)/NaCl (11%)/H₂O system were prepared by chilling at -20°C for 24 h (Shaheen and Yamaura, 2002a). The average diameter and thickness of the hydrogels matrix discs were 15 mm and 6.63±0.45 mm (CV 0.06), respectively. And the average loaded theophylline per matrix disc was calculated as 35.4±2.3 mg (CV 0.06).

Theophylline (TH) release was carried out by paddle method (USP type II) with a rotation of 25, 50, 100, 150 rpm and also by using a propeller of 25 mm diameter placed at 30 mm from the bottom of the vessel with a rotation of 100 rpm at 37°C in distilled water (DW). Three release temperatures (27, 37 and 47°C) were also considered to evaluate the temperature effect. The temperature interval was chosen ±10°C of physiological temperature (37°C). TH release was also studied in various simulated fluids without enzymes (pH 1.2 and pH 7.5) and also in phosphate buffer (pH 8.5) at 37°C to evaluate the release-medium effect. The compositions of these fluids are: Simulated gastric fluid without enzyme (SGF) pH 1.2 (NaCl 0.034 M, HCl 0.067 M), SGF pH 4.5 (K₂HPO₄ 0.1 M), SIF pH 7.5 (K₂HPO₄ 0.05 M, NaOH 0.04 M) and the phosphate buffer pH 8.5 (K₂HPO₄ 0.05 M, NaOH 0.05 M). Time to time withdrawn samples (5 mL) were analyzed by Spectrophotometer, Shimadzu UV-160 at λmax: 274 nm for TH concentration. Necessary volume was adjusted with the respective fluids. All the experiments were performed in triplicate and the mean values were taken as well as the coefficient of variation for the range.

The hydrogel of these treated fluids were freeze-dried and thereby xerogels were prepared for DSC studies. In DSC experiment, 2 mg samples were sealed in an aluminum pan corresponding with a control sample of Al₂O₃ in the same amount and also sealed in the pan. The samples were oscillated from 30 to 300°C with a heating rate of 20°C/min.

**RESULTS AND DISCUSSION**

**Effect of agitators:** Usually drug release followed by dissolution is performed in perfect sink conditions. To maintain sink condition agitators are used to replace the
diffused drug from the stagnant layer of the dosage form (Shargel 1993). In Fig. 1 and Table 1, two types of agitators’ (paddle and propeller) rotations were studied on the release rate (percent Higuchi) of theophylline from the hydrogels of α-PVA/NaCl/H2O system. Release rates were faster in paddle rotation (6.0% release/min10−6) than that of propeller (4.9% release/min10−6). When % cumulative release vs. square root of time was plotted straight lines were found up to asymptotic value, which indicated the Higuchi Matrix Dissolution Model (Higuchi, 1963). Release rates were found out from these plots. Usually propeller characteristically produces flow parallel to the axes of rotation whereas paddle rotation caused tangentially primarily and consequently, concentration gradients in axial and radial directions. Due to these flow properties and large surface area, release rate might be faster.

According to Korsmeyer–Peppas model (Korsmeyer et al., 1983; Peppas, 1985; Ritger and Peppas, 1987) the release pattern was regular Fickian diffusion \( n = 0.44, 0.465 \) for paddle and propeller, respectively), where \( n \) is diffusion exponent in:

\[
\frac{M}{M_0} = k t^n
\]  

(1)

In general, release rate varies considerably according to the type of agitators used, degree of laminar and turbulent flow in the system, shape and design of the stirrer and physicochemical properties of the solid (Nogami et al., 1969).

Here the physico-chemical properties of the hydrogels are completely different than that of solid dosage form. However, type of agitators influenced release rate markedly. And diffusion coefficient, \( d \) and kinetic constant, \( k \) values were comparatively lower in propeller agitator (Table 1). The diffusion coefficient, \( d \) was found out for 60% release of the early time approximation of Fick’s second law of diffusion according to following the equation (Baker and Lonsdale 1974):

\[
\frac{M}{M_0} = 4 (dt / \pi D)^{1/2}
\]  

(2)

![Fig. 2: Effect of rotation speeds (25, 50, 100 and 150 rpm) on theophylline release](image)

Where, \( d \) is the diffusion coefficient and \( l \) is the thickness of the hydrogel matrix and it is valid when \( 0 \leq M/M_0 \leq 0.6 \).

**Effect of Rotation Speed**: The effect of rotation speed on the rate of heterogeneous reactions led to the following empirical relationship between the rate of dissolution and the intensity of agitation (Hamed et al., 2000):

\[
K = a N^b
\]  

(3)

Where, \( N \) is the speed of agitation, \( k \) is the dissolution rate and \( a \) and \( b \) are constants. If the dissolution process is diffusion-controlled, the value of \( b \) should be 1 or close to 1 in accordance with the Nernst-Brummer film theory, which states that the film thickness is inversely proportional to the stirring speed. Here in case of hydrogel of above system, dissolution process is regular Fickian diffusion \( n = 0.433-0.465 \) but release rate is almost sluggishly increased with rotation speed (7.44, 7.75, 7.81 and 8.18% release/min10−6) for 25, 50,
Fig. 3: Inversely proportional relationship between diffusion exponent and rotation speed

Fig. 4: Effect of release mediums (distilled water, simulated fluids without enzyme and phosphate buffer pH 8.5) on theophylline release kinetics

100 and 150 rpm, respectively, calculated from the Fig. 2. When we consider the diffusion exponent $n$, it decreased apparently linear with increasing rotation speed (Fig. 3). It means that excessive rotation affects the Fickian diffusion process in this hydrogel system. However there is no remarkable change in diffusion coefficient, $d$ and kinetic constant, $k$ with increasing rotation speed (Table 1).

Effect of release medium: Generally simulated gastrointestinal fluids without enzyme (pH 1.2, pH 6.8 or pH 7.5) are used to evaluate the drug release. Here we have used simulated fluids without enzyme pH 1.2, pH 7.5, distilled water and phosphate buffer pH 8.5. Relatively high release rates (9.6% release/min$^{1/3}$ and 9.1% release/min$^{1/3}$) in extremely low pH 1.2 and also high pH 8.5, respectively were found, where those were almost the same (8.1% release/min$^{1/3}$ and 8.5% release/min$^{1/3}$) in DW and pH 7.5, respectively (Fig. 4). Up to the 60 to 70% release, the release pattern was Fickian diffusion in each case ($n = 0.445-0.455$, Table 1). But a high diffusion coefficient and also kinetic constant in pH 1.2 are the resultant effects of higher drug release (Table 1).

It has been reported that the strong acidic solution tends to disintegrate the tablets slightly faster than water and thereby may enhance the dissolution rate by increasing the effective surface area (Hamed et al., 2000). Here strong acidic fluid might deteriorate the hydrogels a little bit and thereby increasing an effective surface area than water, which causes the relatively little bit high release rate.

Thermal studies of the xerogels by DSC were described in Fig. 5 and 6. We already reported

Fig. 5: DSC thermogram of the xerogels, derived from the various simulated fluids, DW and phosphate buffer treated hydrogel of a-PVA/NaCl/H$_2$O System

Fig. 6: Heat capacity and melting temperature expression in corresponding with pH of the simulated fluids and phosphate buffer
evaluated the results were just vice versa, there was exceptional high heat capacity of the same (pH 1.2) and the others showed the same sluggish increase (Fig. 6). All these results explain that hydrogel of this system deteriorated markedly during the treatment of extremely low pH than that of other pH and the fate of these gels showed such characteristic thermal properties, which made it higher release rate. Heat capacity is directly related to degree of crystallinity of the gel (Peppas et al., 1997) and crystallinity affects both the intra and inter-molecular structure of the gel.

However, the diffusion exponent and total time up to asymptotic value of theophylline release were almost the same. It might be due to comparatively fewer stem and branch pores of these xerogels, though they are large enough than those of others. In this way theophylline release from this system has got regular Fickian diffusion (Higuchi Model) as well as the same total time of sustained release effect, irrespective of simulated fluids and phosphate buffer.

**Effect of release temperature:** Effect of release temperature on the hydrogels system of α-PVA/NaCl/H₂O system was evaluated in Fig. 7 and Table 1. It had been observed that comparatively higher release rate (8.6%release/min¹⁶) in higher release temperature (47°C) and vice versa in relatively lower temperature (7.75% release/min¹⁶ for 37°C and 6.5% release/min¹⁶ for 27°C) was found. Release rate proportionally increased with increasing temperature but diffusion exponent decreased with increasing temperature in a parabolic fashion (Fig. 8).

The effect of temperature variations of the dissolution medium depends mainly on the temperature/solubility curves of the drug and excipients in the formulations (Nogami et al., 1969; Carstensen et al., 1980). Horiike et al. (2000) reported the effect of temperature on the release of Brilliant Blue from the syndiotacticity-rich PVA hydrogel. They also reported Brilliant Blue release increased with increasing temperature and the degree of release is 27 < 37 < 47°C. Here also the degree of TH release from the hydrogel of α-PVA/NaCl/H₂O system followed the same pattern. High release rate might be due to the high drug solubility as well as the polymer solubility from the hydrogels at relatively high temperature. Since high temperature weakens the physical cross-linking originated from hydrogen bonding as well as van der Waals’ forces and hence drug release is more easy and fast. This also explains a lot in increased diffusion coefficient, $d$ and also kinetic constant, $k$ with increasing temperature (Table 1).
Release time up to asymptotic value: TH release was studied up to a total of 750 min. But an asymptotic value was obtained near about after 10.5 h in each case except the effect of temperature 47°C (Fig 1, 2, 4 and 7). In this temperature, the asymptotic is reached near about after 8.5 h.

CONCLUSION

In vitro parameters of dissolution were studied in respect of TH release from the hydrogels of a-PVA/NaCl/H2O system. The total sustaining time of TH release (except for the case of 47°C) and also the type of release, were the same (10.5 h, regular Fickian diffusion) irrespective of in vitro conditions studied here. Diffusion exponent decreased linearly with increasing rotation speed and that of parabolic fashion with increasing release-temperatures. Release rate was also linearly increased with release temperature.

Comparatively high release rate in simulated fluids of very low pH and high pH might be due to the deterioration of macromolecular network system. DSC studies accorded the deterioration of the hydrogels, while treated with these fluids. Such deterioration could not affect the diffusion process (regular Fickian diffusion, Higuchi Model) and total sustaining time (10.5 h) after all. Kinetic profiles (diffusion exponent, kinetic constant and diffusion coefficient) are influenced with the external parameters like agitator, rotation speed, release medium and temperature etc. Anyway, from the viewpoint of cost-effective manner, we can conclude it had better use DW for dissolution studies in case of this hydrogel system unless there is an investigative study needed specifically due to the corroding action of strong acidic and basic fluid. Moreover from the fates of this hydrogel system in various simulated fluids (without enzyme) it might predict the in vivo suitability of the hydrogel of a-PVA/NaCl/H2O system in GI fluids during its residence time. However further more investigative studies are necessary to confirm these suitability for in vivo compatibility.

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