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International Journal of Pharmaceutics 155 (1997) 219–229

international journal of pharmaceutics

Examination of drug solubility, polymer types, hydrodynamics and loading dose on drug release behavior from a triple-layer asymmetric configuration delivery system

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Received 5 December 1996; received in revised form 15 May 1997; accepted 28 May 1997

Abstract

The significance of factors such as drug solubility, polymer molecular weight, drug loading and hydrodynamic conditions on drug release from a swellable triple layer asymmetric configuration delivery system is investigated. Poly(ethylene oxide) (PEO) of various molecular weights and hydroxypropylmethyl cellulose (HPMC) were major polymeric constituents of the delivery system. Theophylline, propranolol hydrochloride and diltiazem hydrochloride with water solubilities of <1, 5 and $>50\%$, respectively, were used as drug models. The triple-layer delivery system was produced by compressing particulate systems on a laboratory Carver press with a 10-mm diameter punch and die. Results show that due to the geometry, system design and maintenance of constant surface area linear release kinetics are achievable. Increase in drug solubility expedites drug release rate and shortens duration of release; while increase in polymer molecular weight results in reduction of release rate and prolongation of release period. Drug loading does not seem to affect the release behavior significantly even though a freely water-soluble drug such as diltiazem hydrochloride was employed. In addition, with an increase in stirring rate there was a corresponding increase in release rate, while linearity of release profile remained unaltered. Results further indicate that, as long as surface area is controlled, front synchronization is not a prerequisite for achieving zero-order release kinetics. Moreover, from a pharmaceutical perspective, the complex behavior of release mechanisms for different drugs in relation to matrix erosion, polymer swelling capacity and system design is explained. © 1997 Elsevier Science B.V.

Keywords: Poly(ethylene oxide) PEO; Swelling/erosion; Zero-order kinetics; Triple-layer tablet; Drug diffusion; Controlled drug release; Hydrodynamic effects; HPMC; Release and drug solubility; Drug loading

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PII S0378-5173(97)00164-6

1. Introduction

In the past two decades, significant advances in controlled release technology have been accomplished and their applications in the development of pharmaceutical medicine is very popular. Numerous methodologies, devices and innovations have been utilized and investigated in order to achieve zero-order kinetics over a prolonged time period. The basic mechanism of drug liberation from such systems is governed by swelling/erosion, dissolution/diffusion, osmosis, ion-exchange, polymer coating/membrane barrier, specific geometries and surface modifications (Kydonieus, 1992). It appears that in controlled release discipline, simple and practical formulations for drugs of different physicochemical characteristics are in demand and remain a challenge for pharmaceutical scientists.

In terms of formulation, monolithic matrix systems (tablets) are most widely used for ease of administration and low cost of manufacturing. However, simple matrix systems are incapable of attaining zero-order release due to the inherent limitations that the area of diffusing surfaces decreases and diffusion path length increases as time progresses (Higuchi, 1963; Lee, 1980). Any matrix system that is intended for constant drug delivery must circumvent the said limitations. For instance, incorporation of hydrophilic and swellable polymers into tablet matrix has been demonstrated to alter the release kinetics from square root of time to non-Fickian (Lapidus and Lordi, 1968). Generally, drug release from hydrophilic swellable tablet matrices involves the penetration of water into the matrix, relaxation of polymer chains and diffusion of drug through the swollen gel layer (Hopfenberg and Hsu, 1978; Harland et al., 1988). In the past, various geometrical and compositional modifications of monolithic matrices have provided linear and quasi-linear release kinetics (Paul, 1985; Fassihi, 1988; Colombo et al., 1989, 1990; Devi et al., 1989; Conte et al., 1993, 1994; Danckwerts, 1994; Fassihi and Ritschel, 1993; Fassihi and Yang, 1996). Geomatrix delivery system design is an example of a commercially successful hydrophilic system which is based on symmetrical three-layered tablet geometry (Colombo et al., 1989).

Recently, the asymmetric configuration drug delivery system based on disproportional swellable/erodible triple-layered tablet technology, providing constant drug release over long period of time, was described (Yang and Fassihi, 1996, 1997). The swellable/erodible polymer used was poly(ethylene oxide), a linear water-soluble resin available over a wide range of molecular weights. It was shown that drug release from such a system exhibited zero-order kinetics and was independent of variation in dissolution media pH and compression force (Yang and Fassihi, 1996). To explore the flexibility of the designed system and shed more light on drug release behavior, factors likely to affect drug transport from this system, namely, molecular weight of polymer, drug solubility, drug loading, polymer type, and hydrodynamic conditions, are further investigated and presented in this study.

2. Materials and methods

2.1. Materials

Poly(ethylene oxide) (PEO, Polyox® WSR) NFs with average molecular weight of 1×10^6, 2×10^6, 4×10^6, 7×10^6 (corresponding Polyox® WSR grades are WSR N-12K, WSR N-60K, WSR-301, and WSR-303, respectively) were received from Union Carbide Corp. (Danbury, CT). Hydroxypropylmethyl cellulose (HPMC, Methocel K4M) was supplied by Dow Chemical Company (Midland, MI). Theophylline anhydrous and magnesium stearate USP were purchased from Amend Co. (Irving, NJ). Diltiazem hydrochloride and propranolol hydrochloride were purchased from Sigma Chemical Co. (St. Louis. MO). Other excipients were of USP or NF grades. All materials were used as received.

2.2. Tablet manufacturing

The formulation composition of asymmetric configuration delivery system is listed in Table 1. All ingredients were passed through a # 20 US standard sieve, the particulate system for each layer was blended in a cube-mixer for 15 min.

Table 1
Formulation composition

Layer	Total weight (mg)	Components[a,b]	Formulation (%, w/w)	
			I	II
1	200	PEO $M_W = 7 \times 10^6$	60	60
		HPMC K4M	20	20
		Anhydrous Lactose	20	20
2	300	PEO	—	50
		HPMC K4M	35	—
		Active agent	50	50
		Anhydrous lactose	15	—
3	50	Anhydrous lactose	50	50
		PEO, $M_W = 1 \times 10^6$	50	50

[a] 0.1% w/w magnesium stearate was used as lubricant in each layer.
[b] Active agent is theophylline, or diltiazem hydrochloride, or propranolol hydrochloride.

Magnesium stearate (0.1%) was added and further mixed for 5 min. The tablets were produced using a Carver laboratory press (Model C, Fred S Carver Inc., Wabash, IN) with a 10-mm diameter flat-faced tooling. The powder mix of each layer was transferred into the die manually, the first and second layer were compressed up to 900 lb and, finally, after addition of the third layer the total die content (i.e., 530 mg) was compressed to 5000 lb. The full compression cycle of 1 min was used in each case. A detailed compaction study for this system under conditions similar to a high-speed rotary press has been recently reported (Yang et al., 1997). Results of this study demonstrated that tablets of good tensile strengths with no lamination can be easily produced. In the present study, the amount of active drug in the final tablets was constant for all drug models (i.e., 100 mg). To study the effect of loading dose on drug release an additional batch of tablets containing 150 mg diltiazem hydrochloride per tablet was also manufactured. The amount of other components in the middle layer were reduced accordingly.

2.3. Drug release study

The in vitro release studies were conducted in accordance with USP 23 apparatus II procedure (VK 7000, Vankel Industries, Inc., Edison, NJ) at 37°C in 900 ml 0.1 HCl solution. The paddle speed was 50 rpm unless otherwise stated. The amounts of theophylline, propranolol hydrochloride and diltiazem hydrochloride released were measured using an HP 8451A Diode Array Spectrophotometer at 272, 292 and 240 nm, respectively.

2.4. Polymer matrix erosion

To evaluate the effect of polymer dissolution on drug release kinetics, pure polymer compacts of HPMC and PEO were prepared and placed in the dissolution apparatus for dissolution test in the same manner as described above. Individual swollen tablets were removed at preselected time intervals and dried at 60°C to constant weight under vacuum, and the weight loss due to dissolution/erosion was calculated.

3. Results and discussion

The principle of asymmetric configuration delivery system was described in detail in the previous reports (Yang and Fassihi, 1996). In brief, it consists of three layers of particulate systems directly compressed together. The middle layer shielded by external layers on both sides is the drug deposit core. The external layers have different thicknesses and are designed to initially delay the hydration rate of the middle layer and restrict

the early drug release by diffusion only through cylindrical side surfaces of the tablet. Furthermore, the external layers are preprogrammed to erode away at different rates. As dissolution process proceeds, the external layers will disappear gradually at disproportionate rates, creating more surface area for drug diffusion, thus counterbalancing the reduction of diffusing surface area due to the erosion as well as the increase in diffusional path-length due to continuous system swelling. Accordingly, the dependence of release kinetics on diffusion process was minimized, and zero-order kinetics prevailed. The dynamics of dissolution process for this system is schematically illustrated in Fig. 1. It should be noted that during the time period between swelling and system hydration and the completion of erosion of the third layer, a certain amount of drug may be diffused through the barrier layers, in addition to the amount released from the lateral sides.

3.1. Determination of release kinetics

Determination of actual release process and derivation of a mass-balance equation for a complex geometry and associated morphological dynamics is the subject of a different study. It is, however, appropriate to determine the release kinetics according to the following expression (Ritger and Peppas, 1987):

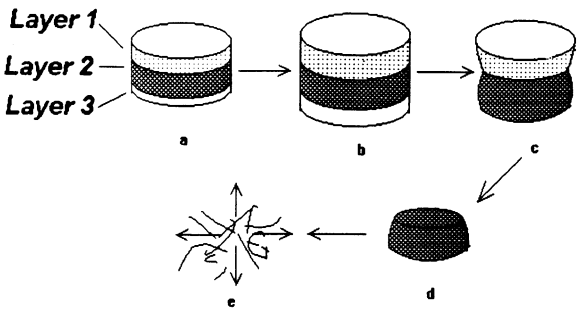

Fig. 1. Schematic dissolution behavior of asymmetric configuration drug delivery system. (a) Initial morphology of the triple layer tablet; (b) the tablet swells after introduction into dissolution medium; (c) system erosion and the complete disappearance of the third layer at approximately 5 h; (d) the first and middle layers disengaged gradually; (e) further erosion leading to complete solubilization.

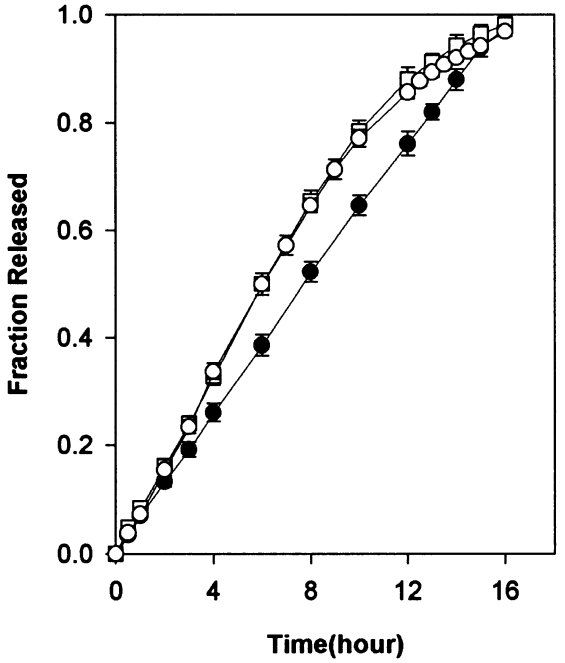

Fig. 2. Effect of drug solubility on the release characteristics of drug from the designed system (Formulation I): ●, theophylline (solubility, $<1\%$; $n=8$); ○, propranolol·HCl (solubility, 5%; $n=5$); □, diltiazem·HCl (solubility, $>50\%$; $n=5$); bars represents standard error of mean.

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t/M_∞ is the fraction of drug released, k is a constant, n is a diffusional exponent describing the operating release mechanism which in a case of cylinder ranges from 0.45 (Fickian release) to 0.89 (representing Case-II transport) for $M_t/M_\infty \leq 60\%$ of the drug release. Fig. 2 shows the release profiles of theophylline, propranolol·HCl, and diltiazem·HCl. The n values calculated from data fitting for theophylline, propranolol·HCl, and diltiazem HCl are 0.98, 1.02, and 0.90, respectively, indicating that drug release from the designed system follows zero-order kinetics in all cases. The linear regression analysis of release data (fraction released versus time) was performed. The correlation coefficient (r^2) for theophylline, diltiazem·HCl and propranolol·HCl was 1.0 in each case, which confirms the linearity of the release data.

3.2. Effect of drug solubility

Fig. 2 also serves to illustrate the effect of drug solubility on the release characteristics from the designed system. It is evident that the solubility of the drug affects both the release rate and release pattern significantly. As the solubility of the drug increases from $< 1\%$ (in the case of theophylline) to 5% (for propranolol·HCl), the drug release rate also increases. For example, average release rate increased from 0.10 mg/min in case of theophylline to an average of 0.132 mg/min for propranolol·HCl. This can be explained on the basis that the swelling/erosion process of polymer matrix controls drug release behavior. It is reported that polymer swelling occurs as a result of osmotic stress exerted at the advancing glassy core/rubbery gel (Windle, 1985). When drug solubility increases, the enhanced osmotic stress accelerates water penetration into matrix, resulting in a higher degree of polymer swelling and formation of more microcavities. Therefore gel strength weakens and more rapid gel erosion follows at the gel/dissolution medium front. In a more precise way, the enhanced osmotic stress due to more soluble drug expedites polymer dissolution and consequently drug release. Furthermore, the diffusivity of the drug in swollen gel increases when solubility increases. The diffusion of propranolol·HCl through swollen gel contributes profoundly to the greater release rate as compared with theophylline. However when the solubility increases by more than 10-fold (i.e., from 5% for propranolol·HCl to $> 50\%$ for diltiazem·HCl), release rates for both drugs are identical. This suggests that drug solubility affects release rate up to a certain extent, beyond which the drug release from the matrix system is independent of drug solubility, consistent with the literature reports (Harland et al., 1988). It is also noted that the duration of linearity for both drugs is shortened to about 70% from more than 90% in the case of theophylline. The incorporation of more soluble drug in the matrix results in rapid water penetration into, and greater hydration of the polymer matrix, thus rapidly exhausting the glassy core and suppressing the existence of a constant gel-layer thickness towards completion of release time. When the glassy core of matrix disappears, drug concentration becomes unsaturated, diffusion prevails, and consequently release rate tails off and anomalous release behavior is observed.

3.3. Effect of PEO molecular weight on drug release

The effect of PEO molecular weight (MW:1×10^6; 2×10^6; 4×10^6) in the middle layer on theophylline and diltiazem·HCl release is shown in Figs. 3 and 4. It is apparent that release rates of theophylline and diltiazem·HCl decreased and the duration of release was prolonged as PEO molecular weight increased. The linearity of the release profiles remained constant for theophylline (water solubility, $< 1\%$); however, in the case of diltiazem·HCl (solubility, $> 50\%$) release rates were constant up to $< 80\%$ released fraction, and then release profiles tailed off. It is known that drug release kinetics from PEO matrices are controlled by the polymer molecular weight (Apicella et al.,

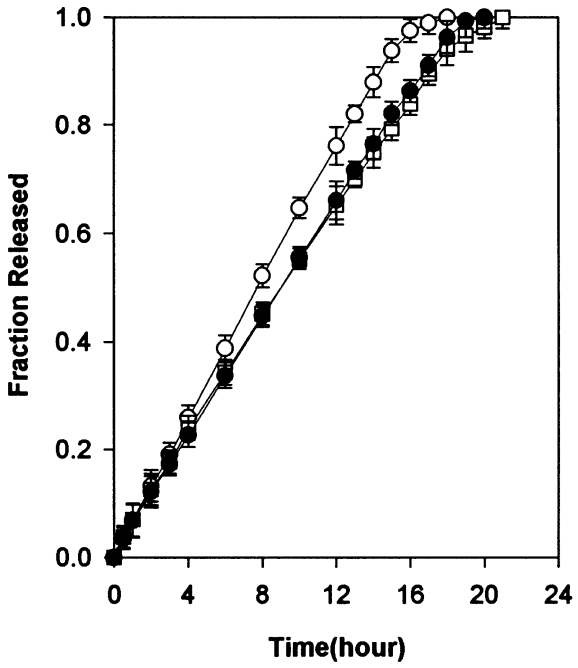

Fig. 3. Effect of PEO molecular weight on theophylline release characteristics from the designed system (Formulation I): ○, 1×10^6; ●, 2×10^6; □, 4×10^6, $n = 5$.

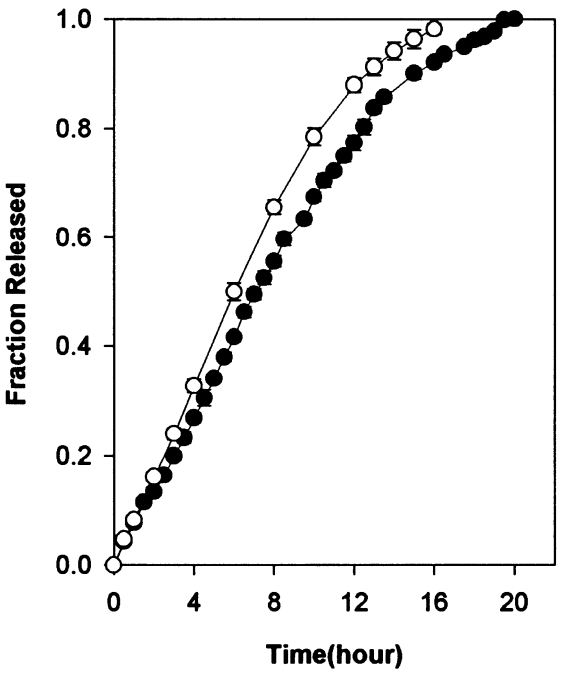

Fig. 4. Effect of PEO molecular weight on diltiazem·HCl release characteristics from the designed system (Formulation I): ○, 1×10^6; ●, 4×10^6, $n = 5$. Standard error of mean is shown except in those cases where they are smaller than the symbol.

1993; Kim, 1995). For example, simultaneous swelling and erosion governs drug release from low-molecular weight (MW 2×10^6) PEO matrices via front synchronization, leading to linear release kinetics. In contrast swelling can be the rate-controlling step in drug release from high-molecular weight PEO matrices. Mechanistically, polymer dissolution (erosion) takes place in three steps, (i) solvent penetration into the polymeric matrix, (ii) polymer swelling and chain entanglement, and (iii) true polymer dissolution as threshold disentanglement value is attained. Basically, as water penetrates into the polymer matrix, it enhances polymer chain mobility which will eventually disentangle at the advancing front, separating the gel layer from the erosion/dissolution front (Narasimhan and Peppas, 1997). Polymer chain activity and concentration at swollen gel/solvent front have to reach the necessary disentanglement threshold value before the true dissolution occurs (Lee and Peppas, 1987). It is, however, well established that polymer chain entanglement and attainment of threshold value depend on the nature of polymer and its molecular weight as well as concentration, solvent effect, and external mass transfer (Doi and Edwards, 1986). For the polymers having identical chemical structure, under identical hydrodynamic conditions, polymer dissolution rate and gel thickness usually vary as a function of the molecular weight of the polymer. Increase in polymer molecular weight results in the deceleration of polymer dissolution rate and augmentation of gel thickness. All such factors account for the reduction of release rate. Also, it should be noted that the swelling velocity of high-molecular weight poly(ethylene oxide) (Polyox® WSR-301) is far greater than its erosion rate. Continuous swelling leads to increase in gel thickness and retardation of drug release, with possible deviation from linearity. Therefore diffusion of drug through the swollen gel region and drug solubility play a decisive role in drug release modulation from high-molecular weight polymer matrices.

It is particularly noteworthy to observe that release of both theophylline and diltiazem·HCl from the present delivery system were linear up to 100 ($r^2 = 1.0$) and 80% ($r^2 = 1.0$) of total drug fraction released, respectively. Thus, it appears that in this particular geometrical design front synchronization is not necessarily a prerequisite for zero-order release kinetics, and that diffusing surface area available for drug diffusion plays a more important role. Furthermore, it may be suggested that the surface area of the matrix system is either maintained approximately constant (for low-molecular weight PEO) or it is proportionally increased to counterbalance the increase in gel thickness and tortuosity (for high-molecular weight PEO) by the preprogrammed differential erosion rate of external layers.

3.4. Drug loading

A controlled release dosage form of highly soluble drugs is much desired since many of them play leading roles in clinical drug therapy (Khan, 1995). To investigate the drug loading effect on

the release profiles, a lightly water-soluble drug (diltiazem·HCl) was chosen as a model drug. It is known that freely water-soluble drugs are difficult to formulate for two reasons. Firstly, system susceptibility to possible 'dose dumping', and secondly, maintenance of linearity in drug release. As shown in Fig. 5, the release rate of diltiazem·HCl did not change significantly as loading dose increased from 33.34 to 50%, and both release profiles were almost superimposed. This may suggest that the penetration of water into the matrix is not greatly enhanced by the incorporation of a larger dose of diltiazem·HCl, and water uptake by the matrix is dependent on the polymer and system design rather than the drug. It is known that the state of water in swollen polymeric matrices falls into two categories: bound water and free water (Johari, 1991). Bound water refers to the water that combines with polymer chains, while free water appears to retain its original characteristics and play a role in drug solubilization and mass transfer within the gel microstructure. Since drug loading in the present work is well above the drug solubility within the swollen/gelled polymer matrix, variation in drug loading is not likely to produce significant changes in release rate. This particular aspect (i.e., drug loading up to 50% of matrix core) and the similarity of release profiles for different loadings are highly significant and the system design offers great potential for controlled delivery of other soluble drugs.

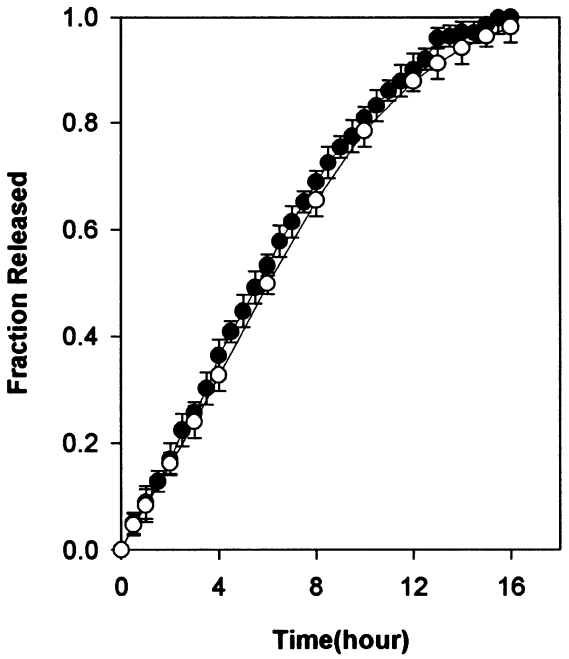

Fig. 5. Effect of diltiazem·HCl loading dose on its release profiles from Formulation I. ●, 50%; ○, 33.4%, $n = 5$.

3.5. Hydrodynamic conditions

Under well-controlled studies, the in vitro dissolution testing of oral solid dosage forms may be used as a surrogate for in vivo studies (Federal Register, 1995). The hydrodynamic conditions recommended by officially specified stirring speed, namely, 50 rpm and 100 rpm for the paddle method, may not necessarily simulate the actual hydrodynamic intensity encountered in vivo. In addition, the hydrodynamic conditions in vivo comprise not only the GI secretions and available biological fluid, but mechanical force due to propulsion, grinding, retropulsion and GI motility (Drewe and Guitard, 1993; Katori et al., 1995). Thus with delivery systems that undergo swelling and erosion, stressed hydrodynamics in dissolution studies may provide greater insight into system performance. It is also important to note that several studies have shown that the hydrodynamic intensity created at lower stirring speed (< 50 rpm) may mimic in vivo situation more closely (Katori et al., 1995; Shameem et al., 1995).

Figs. 6 and 7 illustrate the effect of stirring speed on theophylline release from the designed system for PEO polymer molecular weights of 1×10^6 and 4×10^6, respectively. The examined stirring speeds were 10, 50 and 100 rpm, respectively. As expected the release rate of theophylline was enhanced as stirring speed increased from 10 to 100 rpm, hence the polymer dissolution rate and external mass transfer increased with hydrodynamic stress (Ueberriter, 1967). Apparently when stirring speed is excessive the stagnant boundary layer effect is no longer the rate-limiting step in drug transport. In addition, at a certain point, a maximum turbulence threshold will be reached, beyond which greater turbulence and/or

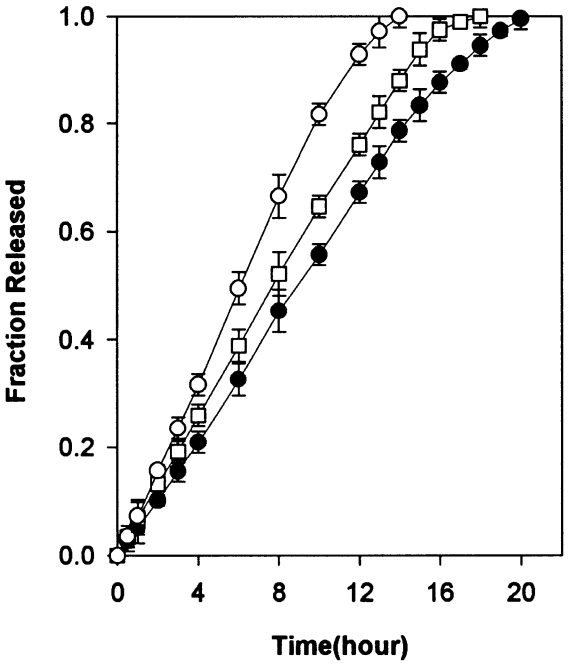

Fig. 6. Effect of stirring speed during dissolution process on theophylline release characteristics from the designed system (Formulation I): ●, 10 rpm; □, 50 rpm; ○, 100 rpm, $n = 5$. PEO molecular weight is 1×10^6.

fluid flow creates little or no variation in the transport process, resulting in indistinguishable release profiles.

3.6. Comparison of HPMC with PEO

Hydroxypropylmethyl cellulose (HPMC) is probably the most commonly used film former for tablet film coating and is also extensively utilized in fabrication of oral sustained/controlled release dosage forms due to its non-toxic and non-ionic nature, excellent compression properties and good capacity to accommodate high levels of drug loading (Alderman, 1984). Drug release from the HPMC matrix has been shown to be a swelling-controlled diffusion process with little erosion, and predominantly follows square root of time and sometimes anomalous kinetics depending on the processing techniques, viscosity and molecular weight of HPMC (Pham and Lee, 1994). In this study, a comparison between HPMC and PEO was carried out regarding their dissolution behavior, swelling capacity and subsequent effects on drug release from the designed system. Fig. 8 represents diltiazem·HCl release from the designed system where PEO and HPMC are the rate-controlling polymers. As shown in Fig. 8, the release rates of diltiazem·HCl from both low- and high-molecular weight PEO matrix tablets were faster and the duration of release shorter when compared with release from HPMC tablets, although the percentage of HPMC content in the middle layer was much lower than that of PEO. In order to explain the cause of such differences in release rates, pure compacts of each polymer were produced and subjected to dissolution studies. Fig. 9 shows the erosion profile of pure HPMC and PEO matrices made by direct compression of each polymer in a lubricated die in the absence of drug. Initially, the erosion rate of HPMC and PEO are similar. However, as dissolution progresses, the differences in erosion rates become significant. The overall erosion rate of PEO is faster than that of HPMC, and also the erosion

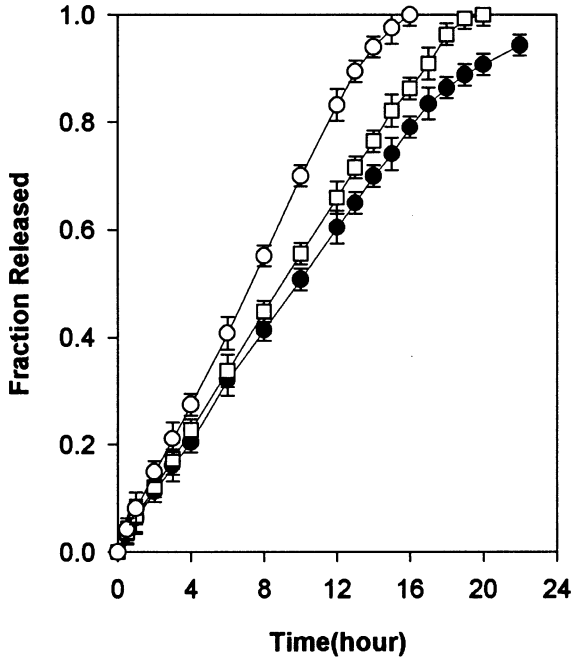

Fig. 7. Effect of stirring speed during dissolution process on theophylline release characteristics from the designed system (Formulation I): ●, 10 rpm; □, 50 rpm; ○, 100 rpm, $n = 5$. PEO molecular weight is 4×10^6.

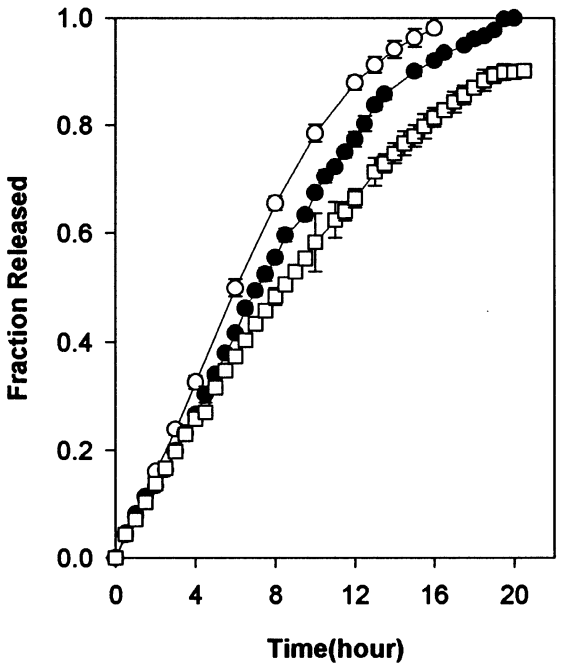

Fig. 8. Influence of HPMC and PEO on diltiazem·HCl release characteristics from the designed system. ○, Polyox® WSR N-12K, $n = 5$; ●, Polyox® WSR-301, $n = 4$; □, HPMC K4M, $n = 4$; bars represent standard error of mean.

rate of PEO is inversely proportional to its molecular weight. The swelling volume of pure compacts of PEO and HPMC in deionized water at 37°C was also evaluated according to the reported method (Kim and Fassihi, 1997). The normalized volume changes of the compact are presented in Fig. 10. It is apparent that Polyox® WSR-301 (MW: 4×10^6) exhibits the highest degree of swelling due to the rapid water penetration, and HPMC K4M and Polyox® WSR N-12K (MW: 1×10^6) have comparable extent of swelling. This is in agreement with the observation that high-molecular weight PEO mainly swells and low-molecular weight PEO swells and erodes (Apicella et al., 1993; Kim, 1995). A higher degree of PEO swelling may provide greater free volume, higher drug diffusivity in the swollen polymer and consequently faster release as shown in Fig. 8.

4. Conclusion

The present investigation shows the robustness of the asymmetric configuration delivery system. The designed system provides significant flexibility in modulation of release kinetics for drugs of different solubility. It can also accommodate variable drug loading and polymers of different characteristics. The results further indicate that drug release from an asymmetric configuration delivery system is influenced by polymer molecular weight, drug solubility, and hydrodynamic conditions. High drug solubility, low-molecular weight polymer and intense hydrodynamic conditions would accelerate release rate and shorten duration of drug release. In general, drug release from PEO matrices is more rapid and more complete when compared with release from HPMC matrices. This study also demonstrated that zero-order release kinetics are easily achievable as long as the surface area of the system is carefully modulated.

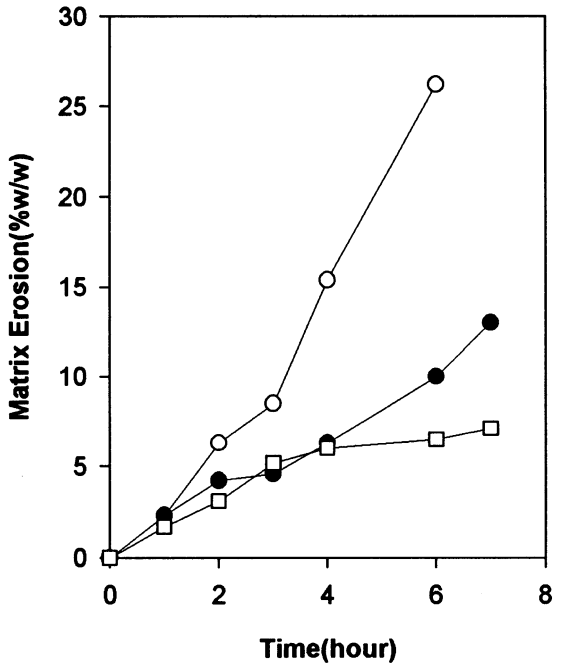

Fig. 9. Comparison of the matrix erosion with time for HPMC and PEO matrices in deionized water. Tablets were produced under identical conditions. ○, Polyox® WSR N-12K; ●, Polyox® WSR-301; □, HPMC K4M.

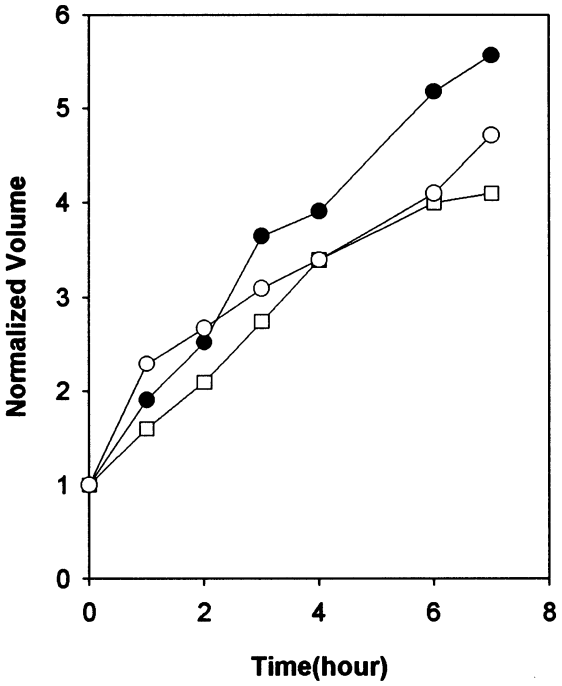

Fig. 10. Comparison of the normalized volume changes for pure HPMC and PEO matrices in deionized water at 37°C. Tablets were produced under identical conditions. ○, Polyox® WSR N-12K; ●, Polyox® WSR-301; □, HPMC K4M.

Since the triple-layer tablet production technology (three-layer rotary press) is currently available, the present delivery system offers potential in the development of oral dosage forms for achieving zero-order controlled release, pulsed release and slow-rapid or rapid-slow release products.

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