JPP Journal of Pharmacy and Pharmacology

JPP 2003, 55: 1331–1337

Received March 19, 2003
Accepted June 30, 2003
DOI 10.1211/0022357021927
ISSN 0022-3573

Accessibility of solid core tablet for dissolution in an asymmetric triple-layer matrix system

Libo Yang and Reza Fassihi

Abstract

The importance of glassy matrix surface area to ensure constant drug release and the effect of barrier layer thickness on the duration of linear release in an asymmetric triple-layer tablet with zero-order release kinetics were investigated. Poly(ethylene oxide) of different molecular weights and hydroxypropylmethylcellulose K4M were the major polymeric constituents, and verapamil hydrochloride was used as a drug model. The contribution of diffusion and polymer relaxation towards drug release was evaluated based on drug release data using a non-linear regression analysis algorithm. The results demonstrated that application of barrier layers to the central core tablet enables polymer relaxation to be the predominant mechanism in controlling drug release and leads to the often desired zero-order release kinetics. The duration of linear release from the asymmetric triple-layer tablet depends on the barrier layer thickness and composition. It was further indicated that the magnitude of diffusion and polymer relaxation in controlling drug release is affected by the accessibility of the drug core tablet for dissolution, as well as the inherent swelling and erosion characteristics of the release rate-controlling polymer.

Introduction

Swellable hydrophilic matrices continue to be popular as the preferred drug delivery system for oral administration. Significant advances have been made with regard to understanding the mechanism of drug release from swellable matrices, characterization of the inherent swelling/erosion characteristics of the hydrophilic polymers (Bowtell et al 1994), and visualization and quantification of the delivery system performance in-vivo (Wilding et al 2001), greatly facilitating the design and development of such delivery systems. As a result, various modified-release products based on swellable hydrophilic matrices have been introduced onto the market. Drug release from a swellable hydrophilic matrix is a complex phenomenon, involving water or biological fluid penetration into the matrix, polymer chain relaxation and disentanglement, matrix geometry variation, and polymer gel dissolution/erosion (Hopfenberg & Hsu 1978; Harland et al 1988; Narasimhan & Peppas 1997). It is generally believed that concentration gradient-driven diffusion and polymer relaxation are the most important rate-limiting steps in regulating drug release from a swellable matrix, although the presence of drug and additional excipients may enhance or suppress the swelling pressure at the swelling front and thus modify the mechanical integrity of polymer gel depending on the solubility of the additives. Essentially, diffusion and polymer relaxation compete in controlling drug release, leading to the usually observed non-Fickian release kinetics.

The primary objective of developing a modified-release delivery system is to achieve optimum pharmacokinetics and pharmacodynamic response of the drug by modulating its input rate and profile. Accordingly, various drug delivery systems with constant, delayed, or pulsatile release profiles have been developed to address different pharmacological and pharmacodynamic demands. However, on many occasions, optimal therapeutic outcomes can be accomplished by maintaining constant drug plasma concentration over a prolonged period. This necessitates drug release of zero-order kinetics from the designed drug delivery system. As mentioned, drug release from a swellable hydrophilic matrix rarely exhibits zero-order kinetics unless an additional

Department of Pharmaceutical Sciences, Temple University School of Pharmacy, 3307 N. Broad Street, Philadelphia, PA 19140, USA

Libo Yang, Reza Fassihi

Current address: ICOS Corporation, 22021 20th Ave SE, Bothell, WA 98021, USA

Libo Yang

Correspondence: Libo Yang, ICOS Corporation, 22021 20th Ave SE, Bothell, WA 98021, USA.
E-mail: lyang@icos.com

controlling mechanism is incorporated into the matrix design. One aspect of research in the area of swellable hydrophilic matrices is to modify the geometry or the composition in order to obtain zero-order release kinetics. For example, it has been demonstrated that zero-order release kinetics is achievable using a binary polymeric matrix consisting of pectin and hydroxypropyl methylcellulose (HPMC) (Kim & Fassihi 1997a) or a ternary matrix composed of pectin, HPMC and gelatin (Kim & Fassihi 1997b), for both poorly and highly soluble drugs.

The geometrical modification of swellable hydrophilic matrices can be best described by layered tablet technology, which has been widely recognized as an effective approach to achieve constant drug release with extended duration (up to 24 h). The layered tablet was initially developed to incorporate two incompatible active substances into one dosage form (Buchwalter et al 1964), and later adapted for sustained release. The Geomatrix system is an example of a commercially successful layered hydrophilic matrix (Colombo et al 1989; Conte et al 1993, 1995). A layered tablet usually consists of a drug core layer covered with one or two impermeable/swellable barrier layers applied by compression. The barrier layers modulate the rate and extent of core layer hydration and shift the commonly observed non-Fickian release towards more favourable release kinetics including Case II transport (zero-order release). Overall, layered tablet technology shows the advantages of less sophisticated manufacturing (the layer-tablet rotary press has been available for a long time) and greater flexibility in obtaining different drug release profiles such as zero-order, bimodal, pulsatile and delayed release.

We have reported the development of a novel triple-layer tablet for constant drug release based on an asymmetric approach (Yang & Fassihi 1996; Fassihi & Yang 1998). A distinctive feature of this new system is that each layer differs in composition and thickness to ensure different swelling/erosion rates. The asymmetric design of the triple-layer tablet appears to be more rational in that the presence of barrier layers restricts drug release to the lateral sides of the matrix in the initial period, and the time-dependent sequential erosion of barrier layers permits drug release from planar sides at a later period of time to compensate for the reduction in release rate. The objectives of the present study were to provide a mechanistic analysis of drug release from asymmetric triple-layer tablets and to evaluate the significance of the accessibility of the central core tablet to dissolution medium in ensuring constant drug release. An attempt was also made to correlate the duration of linear release with barrier layer thickness. Verapamil hydrochloride was used as a drug model in this study.

Materials and Methods

Materials

HPMC (Methocel K4M) and poly(ethylene oxide) (PEO, Polyox WSR) with average molecular weights of 2×10^6 and 5×10^6 (corresponding Polyox WSR grades are N-60K and Coagulant, respectively) were from Dow Chemical Company (Midland, MI, USA). HPMC K4M has a nominal viscosity of 4000 cps in water at the 2% w/v level. Verapamil hydrochloride, which has a solubility of 8.3% in an acidic medium, was purchased from Sigma Chemical Co. (St Louis, MO, USA). Lactose monohydrate and magnesium stearate were provided by DMV International (Veghel, The Netherlands) and Mallinckrodt (St Louis, MO, USA), respectively. All materials were used as received.

Asymmetric triple-layer tablet fabrication

The formulation composition of the asymmetric triple-layer tablet for verapamil hydrochloride is given in Table 1. All ingredients were passed through a no. 20 US standard sieve and the mixture of each layer was blended in a cube-mixer for 15 min; 0.1% magnesium stearate was then added and mixed for a further 5 min. The tablets were produced using a Carver laboratory press (Model C; Carver Inc., Wabash, IN, USA) with 10 mm diameter flat-faced tooling. The powder mix of each layer was transferred into the die manually, the first and second

Table 1 Asymmetric triple-layer tablet formulation of verapamil hydrochloride.

Layer	Weight (mg)	Components[a]	Formulation 1	Formulation 2
1	200	Polyox WSR N-60K	40	40
		HPMC K4M	15	15
		Lactose	45	45
2	300	Polyox WSR-Coagulant	50	0
		HPMC K4M	0	35
		Verapamil HCl	33.3	33.3
		Lactose	16.7	31.7
3	100	Polyox WSR N-60K	50	50
		Lactose	50	50

[a] 0.1% w/w magnesium stearate was used as lubricant in each layer.

layer were precompressed up to 900 lb and, after addition of the third layer, the total die content was compressed to 5000 lb unless otherwise indicated, to obtain tablet hardness of ~10 kp as determined with an Erweka tablet hardness tester (Model 2E; Schleuniger, Zurich, Switzerland).

Drug release study

The in-vitro release studies were conducted in accordance with the USP 23 apparatus II procedure at 37 °C in 900 mL 0.1 M HCl solution. The paddle speed was 50 rev min^{-1}. The amount of verapamil hydrochloride released was measured using a HP 8451A diode array spectrophotometer at 230 nm, and Mckinet software (HP 89532K Multicell Kinetics Software) was used for data collection.

Evaluation of barrier layer thickness to delay drug release

To determine the efficiency of the barrier layer to prevent drug release from the planar base of the core tablet, a simple drug core tablet was produced by compressing 200 mg powder mixture of core layer (i.e. second layer) to 5000 lb in a 6-mm diameter tooling. The entire surface of the core tablet was then coated with layer 3 by compression in a 10-mm diameter tooling to achieve a barrier layer thickness of either 0.5 mm or 1.0 mm. During the process of compression coating, care was taken to ensure that the core tablet was positioned in the centre. Because the distance from the lateral surface of the core tablet and the edge of the compression-coated tablet is 2 mm, the onset of drug release from the compression-coated tablet can be concluded as drug release from the planar surface of the tablet. Dissolution studies were conducted in the same manner as described above.

Statistical analysis

The effects of different polymers as the rate-controlling component (i.e. polyethylene oxide and HPMC) and varying barrier layer thickness on verapamil release were evaluated by the Student's *t*-test. The extent of diffusion and polymer relaxation in controlling verapamil release kinetics from single layer core, double layer, and asymmetric triple layer tablets were analysed using a one-way analysis of variance. A post-hoc comparison of individual differences between the three designs was performed using Tukey's honestly significant difference test. Differences were considered significant at $P < 0.05$ in all cases.

Results and Discussion

Over recent decades, great efforts have been made to model the swelling and dissolution of polymers in general, and quantify the drug release process from swellable hydrophilic matrices in particular (Fan & Singh 1989). Because of the synchronous occurrence of numerous phenomena during dissolution of a swellable hydrophilic matrix, including water penetration, polymer chain relaxation, reptation and disentanglement, and drug diffusion, coupled with the complexity of the three-dimensional geometry of the matrix, the developed mathematical models are rather sophisticated and have to be solved by numerical algorithms or finite element methods (Paul & McSpadden 1976; Tu 1977; Harland et al 1988; Narasimhan & Peppas 1997; Siepmann et al 2002). This limits the routine application of these models in the process of product development. However, application of pseudo-steady state approximation has simplified some models to simple equations, which allows pharmaceutical scientists to improve the design of swellable hydrophilic matrices. For instance, the amount of drug released from a swellable hydrophilic matrix can be collectively expressed by the following equation (Harland et al 1988):

$$M_t/M_\infty = \alpha t^{1/2} + \beta t \quad (1)$$

where M_t/M_∞ is the fraction of drug released at time t, and α and β are constants denoting the magnitude of $t^{1/2}$-dependent diffusion and t-dependent polymer relaxation, respectively. The ratio of β to α is an indication of the prevailing mechanism. A similar approach had been used to characterize the solvent sorption behaviour of glassy polymers (Berens & Hopfenberg 1978). Both α and β are composite constants. In particular, β depends on both the drug and polymer volume fractions at moving boundaries and the mass transfer coefficient of the drug at the interface of the gel and dissolution medium (Harland et al 1988). This equation predicts mathematically that initial drug release (i.e. t is small) is controlled mainly by diffusion and, at later times, polymer relaxation becomes the dominant controlling component. Depending on the relative contribution of diffusion and polymer relaxation, drug release kinetics range from Fickian diffusion to limiting Case II transport. More often, the combination of comparable diffusion and polymer relaxation dominates the drug release process and non-Fickian release kinetics is observed.

Equation 1 also indicates that polymer relaxation becomes the controlling step and the rate of drug release becomes independent of time if the diffusional constant a is sufficiently small (i.e. $\beta >> \alpha$). In addition, earlier experimental observations and modelling showed that in a thermodynamically compatible polymer–solvent system, polymer relaxation is geometry independent, while the magnitude of diffusion varies directly with the dimensions of the system (Vrenta et al 1975; Berens & Hopfenberg 1978). Hence, the design of a swellable hydrophilic matrix with zero-order release would, in part, incorporate additional mechanisms to reduce the magnitude of diffusion in regulating drug release, especially in the first few hours.

Analysis of asymmetric triple-layer matrix system design

The principle of the asymmetric triple-layer tablet for zero-order release has been previously described (Yang & Fassihi 1996). In brief, it consists of a drug core layer

sandwiched with two different barrier layers. The barrier layers were designed to swell and erode away at differential rates. On exposure to dissolution medium, the tablet starts to swell as a result of the penetration of water, with the formation of a thin rubbery gel layer, and drug release through this thin gel layer is a rapid diffusion process. However, initial drug release occurred only from the lateral sides of the central drug core layer. The lateral side area constitutes a small portion of the total surface area of the core layer (e.g. the surface area of the lateral side is about 28% of the total surface area if the core layer is 2 mm thick and 10 mm in diameter). Gel layer thickness increases as dissolution progresses, retarding drug release and water penetration. Simultaneously, the barrier layers will be gradually removed through erosion after an induction period depending on composition and thickness. Erosion of the barrier layer yields additional surface area of the central drug core layer for water penetration into the glassy portion of the core tablet and for drug release, offsetting the reduction in release rate because of the increased gel thickness and/or the reduction of the matrix size from erosion. The minimal contribution of Fickian diffusion on initial drug release, together with simultaneous occurrence of barrier layer erosion, accounted for the observed zero-order release kinetics from the designed system. The dissolution process of this system is shown schematically in Figure 1. It should be noted that the first barrier layer could be either disengaged from the core layer (which is the case in this study) or cleared by erosion.

Verapamil release from the asymmetric triple-layer tablet

The release profiles of verapamil from the asymmetric triple-layer tablet with Polyox WSR-Coagulant (Formulation 1 in Table 1) and HPMC K4M (Formulation 2 in Table 1) as rate-controlling polymer in 0.1 M HCl solution over a 24-h period are shown in Figure 2. The release of verapamil, a highly water soluble drug (solubility 8.3% in 0.1 M HCl solution), was able to follow zero-order kinetics during the entire period of the dissolution study, with a slight burst effect. The linear regression of the fraction released versus time yielded a correlation coefficient (r^2) close to unity in both cases, confirming the linearity of verapamil release. Overall, high molecular weight PEO ($MW \geq 2 \times 10^6$) and HPMC swell substantially as a result of water ingress, with little erosion when subjected to dissolution (Apicella et al 1993; Pham & Lee 1994). Drug release from monolithic Polyox WSR-Coagulant and HPMC K4M matrices is primarily controlled by diffusion and follows non-Fickian kinetics. In this study, both Polyox WSR-Coagulant and HPMC K4M were used as rate-controlling components in the drug core layer, and verapamil release exhibited time-independent linear kinetics. The achievement of constant release is attributed to the involvement of successive barrier layer erosion (or disengagement). As shown in Figure 1, differential clearance of the barrier layers regulates the accessibility of the core layer exposed to the dissolution medium and creates additional surface area for drug diffusion and, more importantly, for water penetration into the glassy core to sustain the concentration gradient across the gel region, leading to constant release. Mechanistically, the zero-order release kinetics appear to be associated with the predominant controlling of polymer relaxation and negligible contribution of diffusion. The relative contribution of diffusion and polymer relaxation towards the extent of drug release kinetics is discussed in detail below.

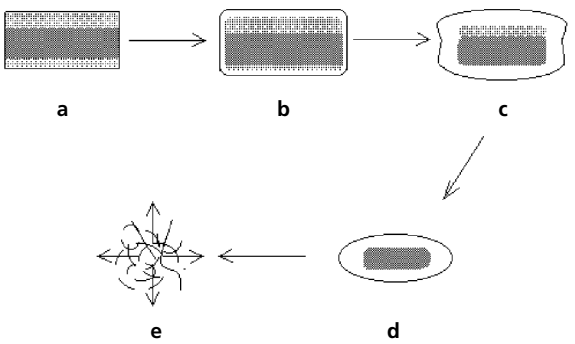

Figure 1 Schematic illustration of the dissolution process of an asymmetric triple-layer tablet. a. Initial morphology. b. Matrix swelling after introduction into dissolution medium with the formation of a thin gel layer. Drug release proceeds only at the lateral sides. c. Disappearance of the third layer and increment of gel layer thickness. d. Disengagement of the first layer from the central core allows drug to be released three-dimensionally. e. Complete system erosion. The shaded areas represent solid matrix and transparent areas represent the polymer gel.

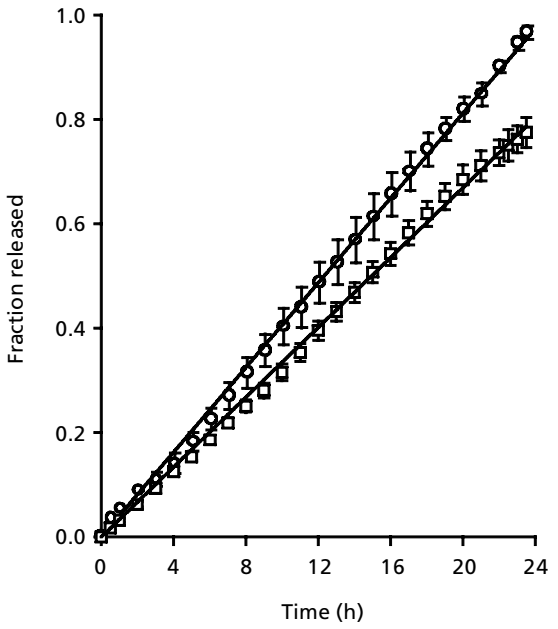

Figure 2 The fraction of verapamil hydrochloride released from the asymmetric triple-layer tablet with HPMC K4M (□) and Polyox WSR-Coagulant (○) as rate-controlling polymer in the core layer (n = 4, bars represent the s.e.m.).

From Figure 2, it is clear is that the release of verapamil proceeded significantly faster ($P < 0.05$) from the asymmetric triple-layer tablet with Polyox WSR-Coagulant as the rate-controlling polymer than from that with HPMC K4M as the rate-controlling polymer, although the amount of HPMC in the core layer was lower (35% HPMC K4M vs 50% Polyox WSR-Coagulant). The release rate, calculated by multiplying the slope of fraction released versus time with the total amount of loading dose, was 4.06 mg h^{-1} and 3.35 mg h^{-1} for Polyox WSR-Coagulant and HPMC K4M asymmetric triple-layer tablets, respectively. This is because PEO exhibits a greater degree of swelling/erosion than HPMC (Yang et al 1998).

Effect of barrier layer thickness on the release rate and duration of linear release

As discussed, the barrier layers modulate the relative contribution of diffusion and polymer relaxation to drug release, minimize the initial area of the central core tablet for interaction with dissolution medium and gradually increase the surface area of the core layer through erosion. The timing of barrier erosion and drug release from the planar side of the core tablet depends on the thickness as well as the composition of the barrier layer, which would have a profound effect on the release rate and duration of linear release. The effect of barrier layer thickness on the erosion lag time was investigated in this study by covering the entire surface of the drug core, by compression, with the powder mixture of layer 3. The barrier layer thickness was either 0.5 mm or 1.0 mm. The efficiency of the barrier layer to delay verapamil release is shown in Figure 3. Verapamil was released after a lag time of about 4 and 10 h, corresponding to the barrier layer thickness of 0.5 and 1.0 mm, respectively. The release profiles are comparable except for the discrepancy in lag time. This indicates that the erodible barrier layer only delays drug release prior to its complete hydration and subsequent erosion. The ability of the first barrier layer (200 mg) to delay verapamil release was also investigated in the same manner, and the results showed that it can prevent verapamil release for 24 h. As noted above, the first layer will be progressively disengaged from the core layer. The detachment of the first layer occurred well after the disappearance of the third layer, thus regulating drug release in sequence.

Figure 4 shows the release of verapamil from the asymmetric triple-layer tablet having a third layer thickness of either 0.5 mm or 1.0 mm with Polyox WSR-Coagulant as the rate-controlling polymer in the core layer, while the thickness of layers 1 and 2 remained unchanged. Different third layer thickness was achieved by using different amounts of layer 3 powder mixture; 0.5 mm is equivalent to 50 mg powder mixture, and 1.0 mm is equivalent to 100 mg powder mixture. The release profile was almost superimposed in the first 4 h, whereas acceleration in verapamil release occurred at about 4 h for tablets with a third layer thickness of 0.5 mm during the dissolution process. The timing of accelerated drug release corresponded to the onset of verapamil release from the planar base when the barrier layer thickness was 0.5 mm (see Figure 3). As a result, the duration of linear release lasted

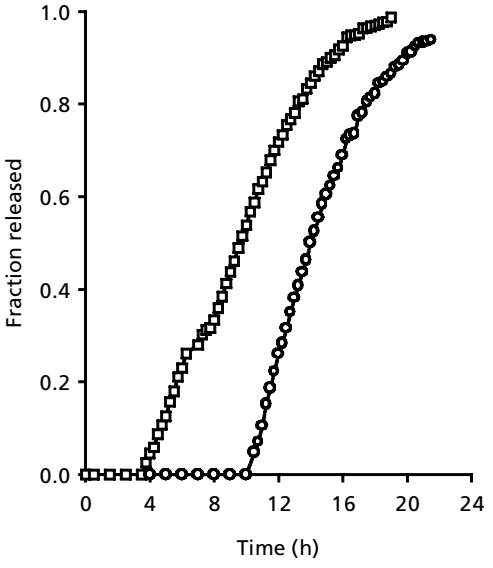

Figure 3 The efficiency of a barrier layer of different thickness to delay verapamil hydrochloride release (○, 1.0 mm; □, 0.5 mm, n = 3). The barrier layer was applied by compression-coating.

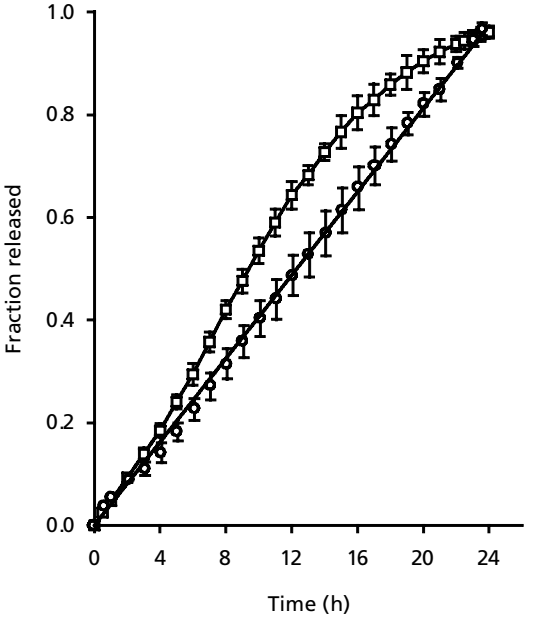

Figure 4 The effect of third layer thickness on verapamil hydrochloride release rate and the duration of linear release (○, 1.0 mm; □, 0.5 mm; n = 4, bars represent the s.e.m.).

for about 75% of the total drug loading. On the other hand, the third layer thickness of 1.0 mm could result in 90% verapamil delivery at a constant release rate over 24 h. This suggests that a third layer of 0.5 mm would hydrate and erode quickly, thus mainly preventing the initial burst effect, while with a thickness of 1.0 mm would delay solid core hydration more efficiently, leading to prolonged duration of linear release.

Accessibility of the tablet core to dissolution medium in the modulation of drug release kinetics

The importance of surface area in controlling drug release from matrix tablets has long been recognized, leading to the development of non-swellable special shaped devices such as pie-shape (Brooke & Washkuhn 1977) and hemisphere-shape (Hsieh et al 1983) for zero-order release. More recently, Colombo et al (1992) studied drug release from a series of swellable matrices prepared by varying the location of impermeable coatings on the cylindrical matrix (planar bases, lateral sides, or a combination) in an attempt to quantify the dependence of drug release kinetics on matrix surface area, which increases due to polymer swelling. It was concluded that the amount of drug released is linearly dependent on the releasing area of the matrix (Colombo et al 1992). It should be noted that the size of a swellable hydrophilic tablet would increase by several-fold due to polymer swelling during the dissolution process. The peripheral surface area of the swelling matrix for drug release would increase concomitantly. However, drug release from swellable monolithic tablets still follows non-Fickian kinetics as a result of continuous shrinkage of the glassy core, provided that neither in-situ chemical interaction between the drug and the excipients nor complexation between rate-controlling polymers occur within the gel during the dissolution. Therefore, it stands to reason that the area of solid tablet exposed to the dissolution medium is important for achieving constant release from a swellable hydrophilic matrix.

Figure 5 compares the overall verapamil release patterns from monolithic, double-layer and asymmetric triple-layer tablets with Polyox WSR-Coagulant as the rate-controlling polymer. As the barrier layer was applied to the planar base of the core tablet, drug release was suppressed, and the release kinetics was shifted from non-Fickian to zero-order. Verapamil release from the monolithic core tablet, as expected, showed non-Fickian kinetics, while zero-order release kinetics prevailed in the asymmetric triple-layer tablet. On the other hand, the core tablet with one planar face covered produced a biphasic release pattern, initial rapid release followed by relatively constant release. The release data from different matrices shown in Figure 5 were fitted to Equation 1 described previously by a non-linear regression analysis based on the Marquardt-Levenberg algorithm (Sigmaplot for Windows, version 4.0, 1997; Jandel Scientific, California, USA) to find the best fit of the data, and the corresponding values of α and β are given in Table 2. It is clear from Table 2 that the contribution of polymer relaxation becomes predominant in controlling verapamil release by application of the barrier layers. Drug release from the monolithic core tablet was regulated mainly by diffusion, although polymer relaxation was present ($\beta/\alpha = 0.08$); as one planar side of the core tablet was coated by compression, the magnitude of polymer

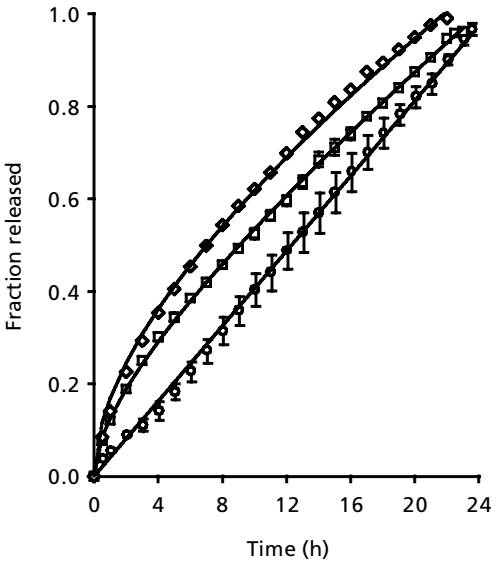

Figure 5 Comparison of verapamil hydrochloride release from monolithic (◊), double-layer (□), and asymmetric triple-layer tablets (○) (n = 4, bars represent the s.e.m.).

Table 2 Diffusion and relaxation contribution to verapamil hydrochloride release from different matrices.

Matrix	α	β	β/α
Monolithic matrix	$0.156 \pm 0.48\%$	$0.0125 \pm 0.12\%$	0.08
Double-layer matrix	$0.105 \pm 0.18\%$	$0.02 \pm 0.04\%$	0.2
Triple-layer matrix	1.14×10^{-10}	$4.06 \times 10^{-2} \pm 0.12\%$	3.56×10^{8}

Values of α and β were calculated via a non-linear regression algorithm by Equation 1. Significant differences ($P < 0.05$) were found between α, β and β/α values of different matrices based on a one-way analysis of variance.

relaxation significantly increased ($\beta/\alpha = 0.2$). Polymer relaxation contributed predominantly towards the kinetics of drug release ($\beta/\alpha = 3.56 \times 10^8$) when both planar sides of the monolithic core tablet were covered with time-dependent erodible barrier layers. The results show that the relative magnitude of diffusion and polymer relaxation towards drug release from a polymer matrix can be altered by controlling the dimensions of the polymer matrix exposed to the dissolution medium.

Conclusion

The present study demonstrated that the barrier layers in the asymmetric triple-layer tablet regulate the accessibility of the drug core tablet to the dissolution medium by sequential erosion, thus, making the contribution of polymer relaxation predominant in controlling verapamil release kinetics. The duration of linear release depends on the timing of the barrier erosion, which is governed by the thickness and composition of the barrier layer. The results further indicate that the magnitude of diffusion and polymer relaxation in controlling drug release are affected by the geometry of the polymeric matrix as well as the inherent characteristics of the rate-controlling polymer.

References

Apicella, A., Cappello, B., Del Nobile, M. A., La Rontonda, M. I., Mensitieri, G., Nicolais, L. (1993) Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. *Biomaterials* **14**: 83–91

Berens, A. R., Hopfenberg, H. B. (1978) Diffusion and relaxation in glassy polymer powders: 2. Separation of diffusion and relaxation parameters. *Polymer* **19**: 489–496

Bowtell, R., Sharp, J. C., Peters, A., Mansfield, P., Rajabi-Siahboomi, A. R., Davies, M. C., Melia, C. D. (1994) NMR microscopy of hydrating hydrophilic matrix pharmaceutical tablets. *Magn. Reson. Imaging* **12**: 361–364

Brooke, D., Washkuhn, R. J. (1977) Zero-order drug delivery system. Theory and preliminary testing. *J. Pharm. Sci.* **66**: 159–162

Buchwalter, F., Granatek, A., DeMurio, M. (1964) US Patent 3,121,044

Colombo, P., La Manna, A., Conte, U. (1989) System for the controlled-rate release of active substance. US Patent 4,839,177

Colombo, P., Catellani, P. L., Peppas, N. A., Maggi, L., Conte, U. (1992) Swelling characteristics of hydrophilic matrices for controlled release: new dimensionless number to describe the swelling and release behavior. *Int. J. Pharm.* **88**: 99–109

Conte, U., Maggi, L., Colombo, P., La Manna, A. (1993) Multi-layered hydrophilic matrices as constant release devices (Geomatrix systems). *J. Control. Release* **26**: 39–47

Conte, U., La Manna, A., Colombo, P. (1995) Tablets with controlled-rate release of active substances. US Patent 5,422,123

Fan, L. T., Singh, S. K. (1989) *Controlled release, a quantitative treatment*. Springer-Verlag, New York

Fassihi, R., Yang, L. (1998) Controlled release drug delivery system. US patent 5,783,212

Harland, R. S., Gazzaniga, A., Sangalli, M. E., Colombo, P., Peppas, N. A. (1988) Drug/polymer matrix swelling and dissolution. *Pharm. Res.* **5**: 488–494

Hopfenberg, H. B., Hsu, K. C. (1978) Swelling-controlled, constant rate delivery systems. *Polym. Eng. Sci.* **18**: 1186–1191

Hsieh, D. S. T., Rhine, W. D., Langer, R. (1983) Zero-order controlled-release polymeric matrices for micro- and macromolecules. *J. Pharm. Sci.* **72**: 17–22

Kim, H., Fassihi, R. (1997a) Application of a binary polymer system in drug release rate modulation. 1. Characterization of release mechanism. *J. Pharm. Sci.* **86**: 316–322

Kim, H., Fassihi, R. (1997b) A new ternary polymeric matrix system for controlled drug delivery of highly soluble drugs: I. Diltiazem hydrochloride. *Pharm. Res.* **14**: 1415–1421

Narasimhan, B., Peppas, N. A. (1997) Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier. *J. Pharm. Sci.* **86**: 297–304

Paul, D. R., McSpadden, S. K. (1976) Diffusional release of a solute from a polymeric matrix. *J. Membr. Sci.* **1**: 33–48

Pham, A. T., Lee, P. I. (1994) Probing the mechanisms of drug release from hydroxypropylmethyl cellulose matrices. *Pharm. Res.* **11**: 1379–1384

Siepmann, J., Streubel, A., Peppas, N. A. (2002) Understanding and predicting drug delivery from hydrophilic matrix tablets using the "sequential layer" model. *Pharm. Res.* **19**: 306–314

Tu, Y.-O. (1977) A multi-phase Stefan problem describing the swelling and the dissolution of glassy polymer. *Q. Appl. Math.* **35**: 269–285

Yang, L., Fassihi, R. (1996) Zero-order release kinetics from a self-correcting floatable asymmetric configuration drug delivery system. *J. Pharm. Sci.* **85**: 170–173

Yang, L., Johnson, B., Fassihi, R. (1998) Determination of continuous changes in the gel layer thickness of poly(ethylene oxide) and HPMC tablets undergoing hydration: a texture analysis study. *Pharm. Res.* **15**: 1902–1906

Vrenta, J. S., Jarzebski, C. M., Duda, J. L. (1975) A Deborah number for diffusion in polymer-solvent systems. *AIChE J.* **21**: 894–901

Wilding, I. R., Coupe, A. J., Davis, S. S. (2001) The role of gamma-scintigraphy in oral drug delivery. *Adv. Drug. Deliv. Rev.* **46**: 103–124