A New Ternary Polymeric Matrix System for Controlled Drug Delivery of Highly Soluble Drugs: I. Diltiazem Hydrochloride

Hyunjo Kim[1] and Reza Fassihi[1,2]

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Purpose. The purpose of this study was to develop a new ternary polymeric matrix system that is easy to manufacture and that delivers a highly soluble drug over long periods of time.

Methods. Pectin, hydroxypropylmethylcellulose (HPMC), and diltiazem HCl granulated with gelatin at optimized ratios were blended at different loading doses and directly compressed. Swelling behavior, dissolution profiles and the effect of hydrodynamic stress on release kinetics were evaluated.

Results. Diltiazem release kinetics from the ternary polymeric system was dependent on the different swelling behavior of the polymers and varied with the drug loading dose and hydrodynamic conditions. Drug release followed either non-Fickian or Case II transport kinetics. The relative influence of diffusion and relaxational/dissolution effects on release profiles for different drug loadings was calculated by a non-linear regression approach. Photographs taken during swelling show that the anisotropic nature of the gel structure, drug loading dose, swelling capacity of polymers used, and the design of delivery system all play important roles in controlling the drug release and dissolution/erosion processes.

Conclusions. Zero-order delivery of diltiazem HCl from a simple tablet matrix was achieved. The ternary polymeric system developed in this study is suitable for controlled release of highly soluble drugs. It offers a number of advantages over existing systems, including ease of manufacturing and of release modulation, as well as reproducibility of release profiles under well defined hydrodynamic conditions. Our delivery system has the potential to fully release its drug content in a controlled manner over a long time period and to dissolve completely.

KEY WORDS: ternary polymeric system; highly soluble drugs; controlled drug delivery; pectin: HPMC; gelatin system; simple hydrophilic matrix; diltiazem hydrochloride.

INTRODUCTION

The use of single or multiple unit dosage forms as controlled drug delivery devices encompasses a wide range of technologies (1–5) and polymeric as well as nonpolymeric excipients. Controlled release delivery systems provide greater safety and efficacy for drugs in therapeutics than conventional dosage forms. Their purpose is to optimize the drug input rate into the systemic circulation in order to achieve a desirable and predictable pharmacodynamic response and pharmacokinetics as well as to improve patient compliance, minimize side effects, and maximize drug product efficacy. The use of controlled release products for chronic administration frequently is indicated. For example, calcium-channel blockers with a well established safety profile and therapeutic effectiveness, such as nifedipine, diltiazem and verapamil, (6–8) are extensively used in the management of angina and hypertension. Their worldwide sale exceeds 8 billion dollars (9). For delivery system design, physicochemical properties and intrinsic characteristics of the drug (e.g., high or low solubility, limited absorption, presystemic metabolism) may impose specific constraints during product development. To overcome such constraints and limitations, delivery system designs are diverse and often produce one of the following delivery-rate kinetics : first order (10), square or cubic root of time law (11,12), zero order (4,5), and non-Fickian diffusion including Case II transport (13–15).

Diltiazem is a benzothiazepine derivative with active metabolites. Its oral absorption is greater than 90%, its bioavailability ranges from 30 to 60% due to extensive variable first-pass metabolism, and its elimination half-life is 3–6 h. The protein binding is greater than 90% and it has a high clearance from plasma. The water solubility of diltiazem exceeds 50%. Daily doses of 120 to 360 mg are usually used for angina and hypertension. The drug was approved by the FDA in 1988, and is currently available as once-a-day dosage forms, such as Cardizem CD™ and Dilacor XR™. Cardizem CD consists of diltiazem drug particles coated with thin and thick polymeric membranes which become semipermeable upon exposure to aqueous fluid and provide extended drug release for 24 hours. Dilacor XR™ consists of 3 or 4 tablets in a capsule. Each tablet consists of three layers. The faster hydrating core layer contains 60 mg of the active drug. Two external layers sandwiched around the core limit drug release from the lateral side of a cylindrical shaped tablet. The tablet matrix is hydrophilic. Upon swelling, it results in continuous drug diffusion over a 24-hour period through the side wall of a constrained tortuous swollen structure. Both products deliver diltiazem for 24 hours and are effective in controlling mild-to-moderate hypertension, with low incidence of adverse effects and improved patient compliance.

The production of both formulations is complicated and cumbersome. Therefore a once-a-day, extended-release diltiazem tablet which consists of a simple matrix and which can be manufactured with high-speed tableting machines will represent significant advance. Such a tablet could also be used to deliver other highly soluble drugs.

In the past, many controlled-release systems for low or sparingly soluble drugs have been developed, but considerable difficulties have been experienced in the formulation of highly ionized and soluble drugs, especially at relatively high doses (e.g., >100 mg) (16,17). We recently reported the application of binary, hydrophilic polymeric matrix system for modulating the drug release rate. The tablet matrices were produced by direct compression, using various ratios of pectin:hydroxypropylmethylcellulose (HPMC) and sparingly soluble drugs (14,15). Both non-Fickian and Case II transport kinetics were easily achieved for periods of up to 24 hours by different combination of these two polymers.

The objectives of the present work were to develop a new simple matrix tablet based on pectin:HPMC:gelatin for the constant delivery of a highly soluble drug (e.g., diltiazem), and to evaluate the effect of the formulation variables and hydrodynamic stress on the drug release. The dissolution pro-

[1] Department of Pharmaceutical Sciences, School of Pharmacy, Temple University, 3307 N. Broad St., Philadelphia, Pennsylvania 19140.
[2] To whom correspondence should be addressed.

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files of our formulations were compared with that of a commercially available product (Dilacor XR™).

EXPERIMENTAL

Materials

Diltiazem hydrochloride was obtained from Sigma Chemicals (St. Louis, MO 63178). Granular gelatin type A and magnesium stearate both USP grades were obtained from AMEND Drug and Chemical Co. (Irvington, NJ). Pectin type 621 [designated as high methoxylated pectin citrus with a degree of methoxylation of 65–72%] obtained from Pectagel Co. (Great Neck, NY). Hydroxypropylmethylcellulose (HPMC) 2208 was supplied by Dow Chemicals as METHOCEL, K4M having nominal viscosity of 4,000 cps in water at 2% w/v level. All other chemicals were of reagent grade.

Methods

Granulation

The required quantities of diltiazem hydrochloride and gelatin (1:1 ratio) were sieved through a 40 mesh screen and blended in a cube mixer for 10 minutes. The powder blend was transferred into a mortar and ethanol was gradually added as a granulating agent with continuous mixing. The wet homogeneous mass was dried overnight in an air convection type oven at 30°C. The dried mass was sieved through a #20 mesh US-standard sieve and stored in air tight container for further use.

Tablet Preparations

Tablets containing the equivalent of 5, 10 and 20% w/w diltiazem powder and granules (using diltiazem hydrochloride:gelatin mixture) were blended together with a pectin:HPMC (1:2) mixture and directly compressed with a Carver press (Model C, FRED S. Carver Inc. 1569 Morris St. Wabash, IN 46992), using a 11 mm flat-faced punch and die. The pectin:HPMC (1:2) ratio was chosen as the optimum blend for its desirable swelling and erosion characteristics (14,15). Powder mixtures were blended in a cube mixer for 10 minutes. 1% w/w magnesium stearate was added to all formulations and mixed for an additional 5 minutes prior to compression. Tablets were compressed at 2,000 lbs unless otherwise stated, to give tablet hardness values of 10 Kp as determined by laboratory hardness tester (Erweka hardness tester, Model 2E, Schleuniger, CH-8033, Zurich). Each tablet weighed 500 mg. Tablets containing various drug loadings were prepared in a similar manner.

Dissolution Studies

Representative samples from each tablet batch were subjected to dissolution study in 900 ml deionized water at 37°C, using a USP 23 dissolution apparatus II (paddle method) at 50 rpm. The system was automated using an HP diode array UV spectrophotometer (Model 8452A) with continuous sampling, using a peristaltic pump (HP flow control, 89092A) and Mckinet software (HP 89532K Multicell Kinetics Software) for data analysis. Measurements were done at the wavelength of 238 nm. No interference due to the dissolved pectin, HPMC or gelatin was evident. Each experimental run on three tablet was done at least in duplicate. In addition, HPLC analysis of diltiazem samples according to the method described in USP 23 confirmed that no degradation products were formed during the entire dissolution period.

Matrix Erosion/Weight-Loss

In order to establish a correlation between drug fraction released and matrix erosion, individual tablets were removed during the dissolution studies at selected time intervals and carefully dried at 60°C under vacuum to a constant weight. The amount of drug released and the total matrix weight loss were calculated for each interval.

Tablet Hydration (Dimensional Changes)

Triplicate determinations of tablet hydration for the ternary polymeric combinations were performed by placing individual tablets on a perforated stainless steel platform in deionized 37°C water in transparent glass dishes. Axial and radial thicknesses and aspect ratios (diameter divided by the thickness) as well as changes in the volume ($V = \pi r^2 l$) of the tablets were measured over a 20-hour period. Normalized swelling thicknesses (swollen thickness divided by the original thickness) were measured, and photographs of tablet swelling at different time points were taken using an Olympus microscope (SZH 10, Japan) connected to a Kodak 8650 PC color printer.

RESULTS AND DISCUSSION

Once the basic pharmacodynamics and pharmacokinetics of a drug are characterized and understood, the goal of the controlled-release delivery systems is to provide desirable delivery patterns so that predictable plasma drug levels can be achieved. Among the physiological variables in the GI tract which may affect drug absorption are pH, gastrointestinal motility, luminal and brush border enzymes, antitransporter, the existence of enzyme gradients along the intestine, and variation in the absorbing capacity of the GI epithelia. In addition, the transit time of the delivery system and the presence of food, liquids, and complexing agents are likely to influence the absorption process. When designing a new delivery system, in addition to the above biopharmaceutical considerations and a recognition of the biochemical basis of membrane transport, the manufacturing difficulties and formulation factors need to be taken into consideration as well.

Some aspects of a new extended-release dosage form for highly soluble drugs developed in our laboratory will be presented. All dissolution studies were performed in deionized water (pH 7.0 $\pm$ 0.4 throughout the dissolution study) because we have shown (14,15) that matrix swelling was not influenced by variations in ionic strength and pH. This was attributed to the fact that the pectin (an anionic material) was highly methoxylated (degree of methoxylation $>$ 70%) and to the nonionic nature of HPMC. The latter polymer constituted more than 70% of the matrix composition. Type A gelatin within the pectin:HPMC matrix used in this study remained insensitive to variations in pH. In addition, diltiazem hydrochloride is freely soluble in water, and its release from this experimental formulation was not affected by the pH variation in the dissolution medium.

Kinetics of Drug Release from the Designed Ternary Polymeric Matrix System

Figure 1 shows the fraction of diltiazem hydrochloride released over a 21 hour period when the drug loading was 100 mg. There is an initial burst release (the first 17% are released during the first 100 minutes), followed by a relatively constant release rate of the remaining drug (equivalent to the loading dose). The swollen matrix gradually eroded away and completely dissolved toward the end of dissolution study. The drug release for the linear portion of the release curve is ascribed to swelling/erosion of the pectin/HPMC-based matrix tablet. In addition, the appearance of gelatin-drug particles with their own rate limiting gel-environment within the swollen boundary contributes toward this linearity by gradually dissolving into the matrix dissolution front (i.e., the water-gel interface) where the water content is high and gel structure is relatively weak. At the interface, as the polymer concentration decreases, the gel microstructure approaches the disentanglement threshold and continuously dissolves away (14,18). Consequently, the effect of an increasing diffusional pathlength on the drug release is counterbalanced by both swelling and erosion as well as by the appearance of gellified drug granules at the dissolution front. The resultant release is linear or non-Fickian. Schematics of the observed macroscopical changes associated with the matrix structure during the dissolution study and actual photographs are shown in Figures 2 and 3. The release mechanism and dynamics of the macroscopic and microscopic molecular changes associated with this polymeric matrix containing a highly water-soluble drug is complex, especially because more than one polymer is incorporated into the matrix. Hence, the investigation of the actual release kinetics/mechanism and the derivation of a mass balance equation pertaining to the moving boundary conditions depicted in Figures 2 and 3 are the subject of future study. It is, however, appropriate to analyze and interpret the release data in accordance with the commonly used classic exponential equations (19). In general, the kinetics of drug release from swellable hydrophilic matrices with an initial burst effect can be best described by the simple power law expression (20,21);

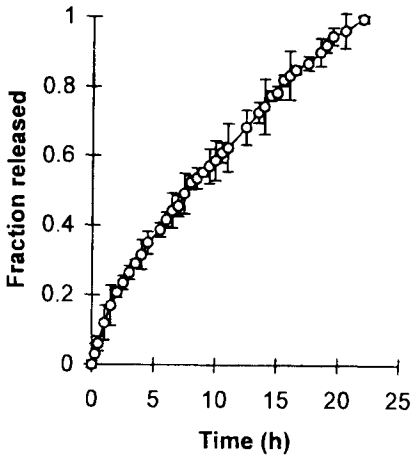

Fig. 1. Diltiazem hydrochloride release from the ternary polymeric hydrophilic tablet containing 100 mg drug, compressed at 2,000 lbs. (USP 23, paddle method, 50 rpm, 900 ml distilled water at 37°C, N = 3).

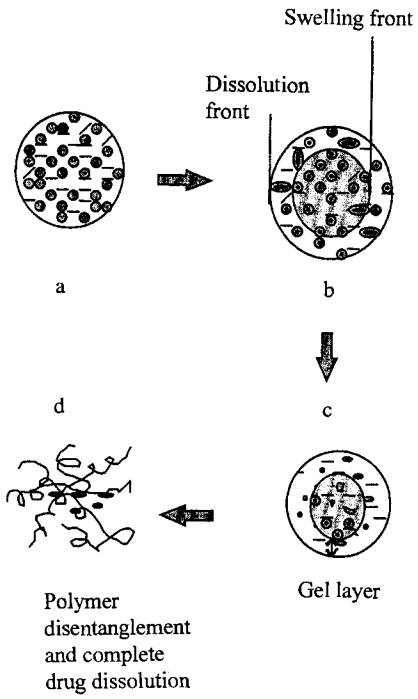

Fig. 2. Schematic representation of drug distribution (conditions: among drug particles and granulated drug) and matrix swelling during dissolution study. (a–b) Water diffuses into the matrix, reaching a threshold value when the glassy matrix undergoes a phase transition to the rubbery state, (b–c) drug is released from the swollen system, which gradually erodes away and finally competely dissolves (d).

$$M_t/M_\infty = kt^n + b \quad (1)$$

where M_t and M_∞ are the amount of drug released at time t and the total amount released (i.e., equivalent to the loading dose), k is the kinetic constant, the exponent n indicates the release mechanism and b, the y-axis intercept, represents the initial burst effect. In the absence of a burst effect, only kt^n on the right hand side of equation 1 was used for data analysis.

For a cylinder, values of $n = 0.45$ indicate Fickian drug release, $0.45 < n < 0.89$ indicate an anomalous (non-Fickian) release, whereas values of $n = 0.89$ indicate Case II transport kinetics (14,19). The calculated intercept b in Figure 1 was 0.17 and the fitting of the data was accomplished on the initial portion of the curve (i.e. $M_t/M_\infty \leq 60\%$, $r^2 = 0.998$, confidence limits $p = 0.95$). The n value obtained (within statistical error) after treating the release data according to equation 1 was 0.75, confirming that the release kinetics for the system containing 100 mg of a highly soluble drug such as diltiazem is anomalous (see Figure 1).

As anticipated for a swellable hydrophilic system containing different ratios of polymeric materials and a highly soluble drug, the release mechanism will be influenced by a number of parameters. These include but are not limited to: (i) the rate of fluid ingress into the matrix, (ii) the rate of matrix swelling and molecular diffusion of the drug through the swollen gel layer (Fickian diffusional release) into dissolution medium due to the chemical potential gradient, (iii) polymer relaxation and chain disentanglement which are usually associated with structural changes, stresses, phase transition from glassy to rubbery state, and increases in free volume, (iv) non-

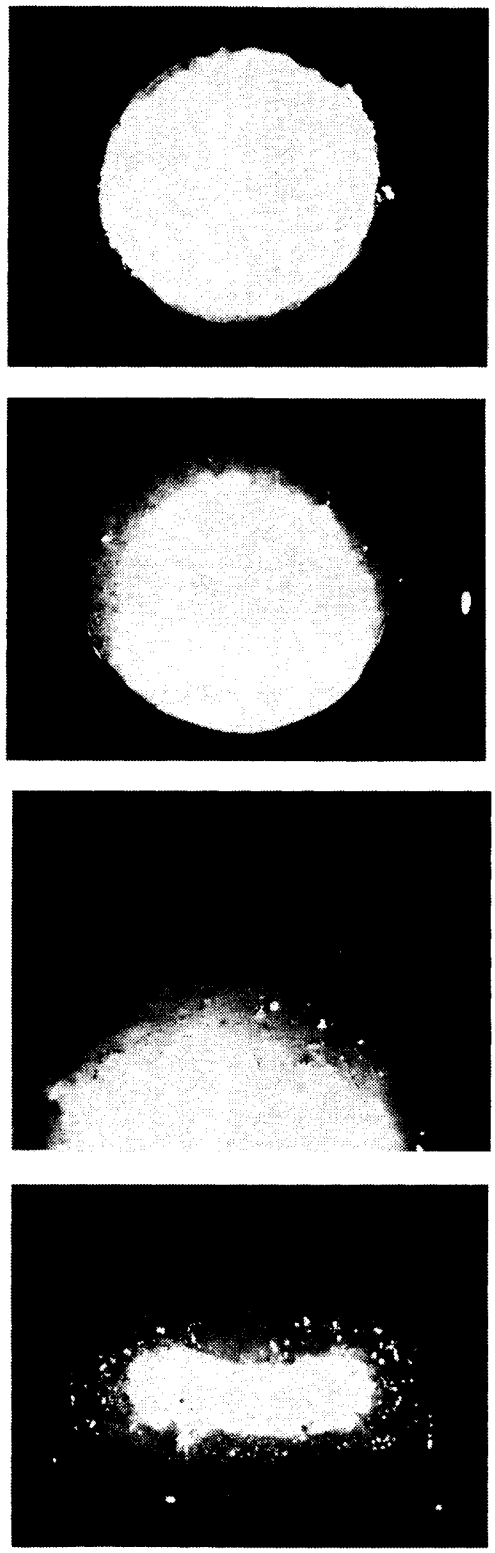

Fig. 3. Typical photographs of the ternary polymeric matrix system and its dimensional changes with swelling 1 hour (a) and 3 hours (b) after hydration. Both gel layer and glassy core as well as an anisotropic gel structure with various polymeric domains within the gel boundary are clearly evident in the magnified photographs (c) and tablet cross-section (d) taken 3 hours after hydration.

homogeneous gel microstructure and variation in the glass transition temperature (Tg) of the matrix components (i.e., HPMC, pectin and gelatin) as well as the existence of polymeric domains within the swollen gel, (v) processing techniques (i.e., direct compression, granulation and solvent effect) involved in tablet manufacturing, and (vi) dissolution/erosion and total disentanglement at the dissolution front. It should be noted that no transparent gel could be seen in this ternary combination. However, as the gel-layer thickness increased and swelling progressed, a more evenly hydrated region at the matrix dissolution front (i.e., water-gel interface) was formed (see Figure 3). On the contrary, where the concentrations of the polymer in the inner gel layer (i.e., close to the swelling front) is high, distinctive domains of uneven hydration related to pectin, HPMC and drug gelatin granules around the glassy core was macroscopically observed as shown in Figure 3. These observations suggest that drug transport process from the matrix is influenced by rate of fluid ingress and drug dissolution as well as by the swelling capacities of various polymeric domains within the matrix.

Figure 4a further demonstrates that the initial drug release (i.e., release in the first 10–12 hours) is predominantly diffusion controlled with no significant erosion, while the subsequent time release process is mainly erosion controlled. At the end of the dissolution study, the polymer chains in the swollen matrix were completely disentangled. Figure 4b illustrates that water uptake and swelling (volume changes) during the first 4 hours were extensive, reached a maximum after 2 hours, and then gradually decreased. Determination of volume changes beyond 5 hours could not be measured, accurately and data are therefore not included. Examination of Figures 4a and 4b indicates that matrix composition can accommodate the swelling due to water without significant chain disentanglement, erosion or polymer dissolution during the early portion of the release period. Similar observations for the drug release from HPMC matrices has been reported (22). The mechanism of drug release, dynamics of swelling and changes in matrix structure are influenced by drug loading as discussed in the following sections.

Influence of Drug Loading Dose on Release Behavior

500 mg-tablets containing diltiazem-gelatin granules equivalent to 5%, 12%, 20% and 24% diltiazem in an 1:2 pectin:HPMC blend were compressed at 2,000 lbs and subjected to dissolution studies. As shown in Figure 5, the release rate and the fraction of drug released is significantly influenced by the drug loading dose. The values of n depended on the loading dose, as did the amount of the drug released at 12 hours and the release rates. At a 5% loading dose n was 0.65, indicating that the drug release was mainly controlled by diffusional and to some extent by relaxation/dissolution (i.e., anomalous transport) (23–25):

$$M_t/M_\infty = k_1 t^{1/2} + k_2 t \qquad (2)$$

where M_t/M_∞ is the fraction of drug released in time t, k_1 and k_2 are constants describing diffusion-controlled and constant rate release, respectively. The k_1 and k_2 values obtained from non-linear regression curve fitting of release data are given in Table 1. At 5% drug loading, the k1/k2 ratio was 36.64, indicating that release was mainly controlled by the diffusion. At 12%

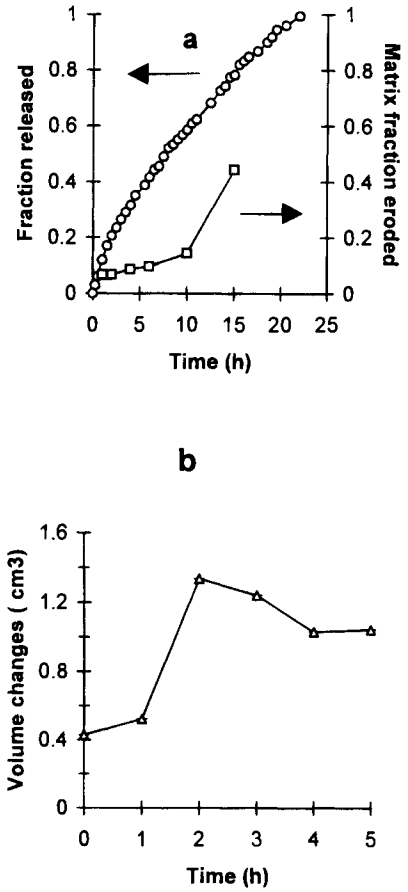

Fig. 4. (a) Relationship between the fraction of diltiazem hydrochloride released (N = 4) and the matrix fraction eroded when individual tablets were subjected to the dissolution process using USP 23, apparatus II, 50 rpm, with distilled water at 37°C. (b) Volume changes with time upon matrix exposure to distilled water at 37°C (N = 3, initial tablet diameter 11.0 ± 0.05 mm, thickness 4.5 ± 0.05 mm).

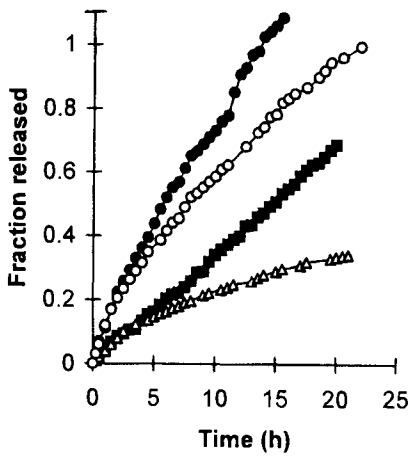

Fig. 5. Effect of diltiazem hydrochloride loading dose on release behavior from the hydrophilic matrix tablets compressed at 2,000 lbs. The tablets weighed 500 mg and the drug loading was 5% (△), 12% (■), 20% (○) and 24% (●). N = 3, SDs are not shown due to overlapping. (USP 23, paddle method, 50 rpm, 900 ml distilled water at 37°C).

Table 1. Release Constants Calculated from Dissolution Data of Diltiazem Matrices with Different Loading Doses[a]

Loading dose (%)	k1	k2	k1/k2	n[b]	$T_{50\%}$ (h)
5	0.00678	0.00084	36.64	0.65	—
12	0.00035	0.00579	0.06	0.95	15
20	0.015	0.00037	40.54	0.75	8
24	0.0194	0.00044	44.09	0.80	6

[a] k1 and k2 values were calculated by using non-linear regression on Sigma-Plot by means of equation 2 of the text.
[b] The n value was calculated by applying equation 1.

drug loading the n value was 0.95 and k1/k2 ratio was 0.06, indicating that the drug release was predominantly controlled by matrix swelling/dissolution, the so called Case II transport kinetics. At the higher loading doses of 20% and 24% the release behavior remained anomalous, with n values of 0.75 and 0.80, respectively. The $T_{50\%}$ (time for 50% drug release) values also show that the release rates increased with higher drug loadings. The $T_{50\%}$ was 15, 8 and 6 h for 12, 20 and 24% drug loading, respectively. Such diverse release behavior is related to the matrix composition, high drug solubility, and drug diffusion which causes greater channel formation in the swollen matrix at higher drug loadings. These factors promote complete drug release.

Influence of Hydrodynamic Stress on Drug Release Behavior

Figure 6 demonstrates the effect of paddle rotation speed on release behavior. The matrix tablets containing diltiazem-gelatin granules equivalent to 20% w/w diltiazem were subjected to various paddle rotation speed. As the paddle speed increased, drug release rates also increased. The n values calculated in accordance with equation 1 were 0.68, 0.75 and 0.78 for drug release at 25, 50 and 100 rpm, respectively. At the low paddle speed of 25 rpm, the drug release was predominantly controlled by diffusion/erosion (n = 0.68). At 100 rpm, the release mechanism remained anomalous with n = 0.78. Furthermore the mean dissolution time (MDT) determination was applied in order to analyze the influence of various paddle speed on the "closeness" of drug release profiles. The MDT was calculated (26) as

$$MDT = \sum_{i=1}^{n} \hat{t}_i \cdot M_t/M_\infty \qquad (3)$$

where M_t and M_∞ are the fraction of dose released in time $\hat{t}_i = (t_i + t_{i-1})/2$, and the total amount of drug released (i.e., equivalent to the loading dose). The calculated MDT-50% and MDT-70%, representing the time required to release 50% and 70% the total amount of the drug are shown in Figure 6b. As the paddle rotation speed increased $MDT_{50\%}$ and $MDT_{70\%}$ values decreased, indicating that more erosion and faster release rates have occurred.

Dynamics of Swelling in a Ternary Polymeric Matrix

The formation and growth of the hydrated surface gel layer was investigated for the ternary polymeric hydrophilic tablet matrices. Over 20 hours, this study was performed in deionized

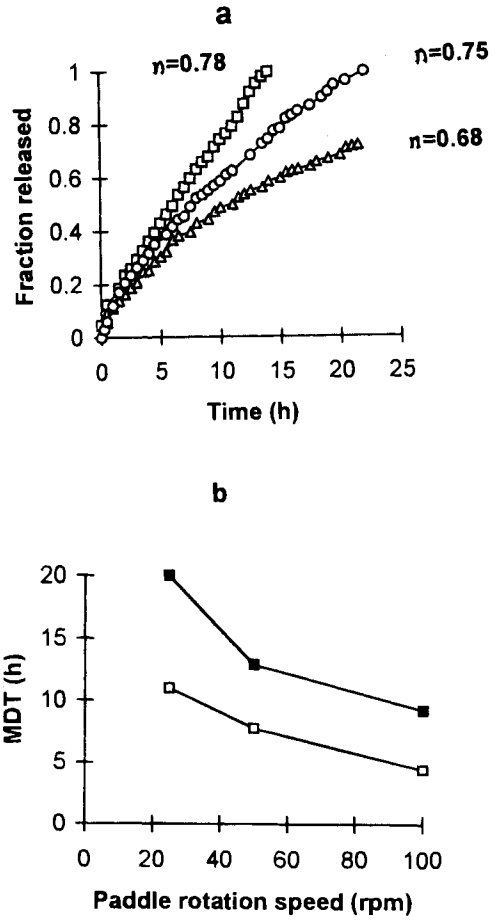

Fig. 6. (a) Effect of hydrodynamic stress on drug release from the hydrophilic matrix tablets compressed at 2,000 lbs. The tablets weighed 500 mg and the loading dose was 100 mg. Paddle speeds were 25 rpm (△), 50 rpm (○) and 100 rpm (□). N = 3, SDs are not shown due to overlapping. (USP 23, paddle method, 50 rpm, 900 ml distilled water). (b) Mean dissolution times (MDT) for different paddle speeds, $MDT_{50\%}$ = (□), $MDT_{70\%}$ = (■).

water at 37°C. All tablets became hydrated and their dimensions in both radial and axial directions changed continually. For example, the radial expansion relative to the original tablet diameter (which was 11 ± 0.05 mm) amounted to 36%, after 5 h of swelling while the axial expansion amounted to 100% of the original thickness of 4.5 ± 0.05 mm. The overall axial expansion after 20 h was much greater than the radial expansion namely, 150% vs 45%. These changes and the overall anisotropic swelling behaviour indicate that the pathlength for drug diffusion in both directions varied as a function of time. The implications of such preferential swelling on drug release kinetics require further study.

Comparative Evaluation of Dissolution Profiles Derived from Simple Ternary Polymeric System and a Commercially Available Three-Layered Tablet

Comparison of diltiazem release profiles obtained from a commercial product and from the ternary hydrophilic polymeric matrix is shown in Figure 7a. All tablets tested contained 60 mg of diltiazem hydrochloride. The release profiles are very similar in terms of linearity and drug fraction released (M_t/M_∞. ≤ 60%, r^2 = 0.999 confidence limit p = 0.95). The calculated n values of 1.00 for the commercial product and 0.95 for the present system indicate that the release kinetics in both cases are relaxational/erosion-dependent (Case II transport). The simple ternary matrix system shows a slight initial burst effect followed by linear release up to 70% of the loading dose. The mean dissolution times (MDTs), calculated for different time points using equation 3, are shown in Figure 7b. No significant differences in the dissolution profiles were found, based on the Student's t-test, with p > 0.05 at MDTs of 20, 30, 40, 50 and 60%.

CONCLUSIONS

This study deals with the design of a new simple matrix tablet which consists of pectin:HPMC:gelatin for the controlled delivery of diltiazem hydrochloride, a highly soluble drug. The high drug load of 20% produce anomalous release kinetics with

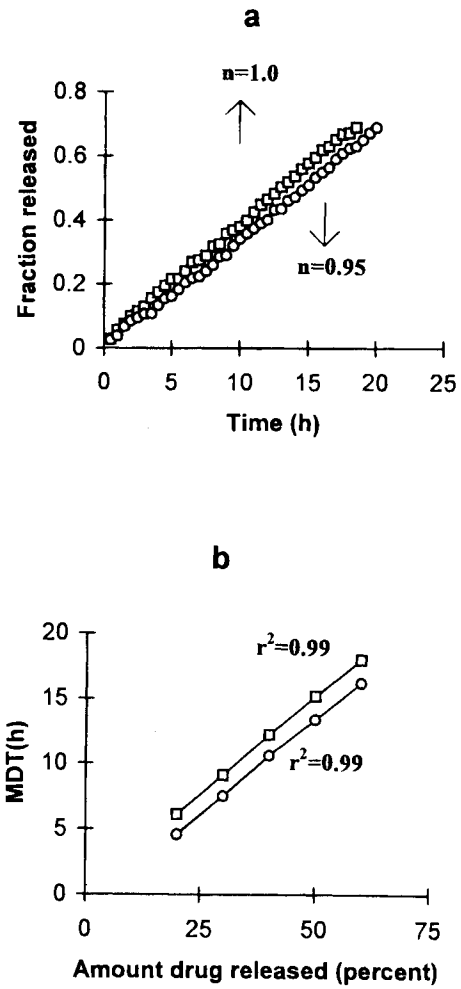

Fig. 7. (a) Comparison of diltiazem hydrochloride release from Dilacor™ XR(60 mg, □) and the ternary polymeric hydrophilic matrix tablets (loading dose: 60 mg, ○) compressed at 2,000 lbs. N = 3, SDs are not shown due to overlapping. (USP 23, paddle method, 50 rpm, 900 ml distilled water at 37°C). The n values were calculated from equation 1. (b) Comparison of percent MDT values at 20, 30, 40, 50 and 60% drug release for experimental tablet (○) and commercial product (□).

an initial burst effect. At the lower drug load of 12%, zero-order release was observed. The kinetics of drug release was principally based on diffusion, relaxation and erosion, depending on the drug loading dose. The release rate always increased with the drug loading dose. The overall release behavior was also influenced by the hydrodynamic stress. This latter effect indicates erosion-dependent drug release. Comparative dissolution study proved that our tablet provides release comparable to the commercial product up to 70%. Furthermore, our tablet is able to deliver highly soluble drugs and offers a number of advantages including ease of manufacturing and simple formulation compatible with conventional production technologies. The tablet dissolves completely and affords easily modulation of release kinetics.

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