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A Ternary Polymeric Matrix System for Controlled Drug Delivery of Highly Soluble Drug with High Drug Loading : Diltiazem Hydrochloride

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염산 딜티아젬의 방출을 제어하기 위한 삼중 폴리머 매트릭스 시스템

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ABSTRACT–The purpose of this study was to use a ternary polymeric matrix system for high drug loading of a highly soluble drug for controlled release delivery. The controlled drug delivery of diltiazem HCl (solubility > 50% in water at 25°C) with high loading dose (the final loading dose of drug was 34%) from a ternary polymeric matrix (gelatin, pectin, HPMC) was successfully accomplished. This simple monolithic system with 240 mg drug loading provided near zero-order release over a 24 hour-period by which time the system was completely dissolved. The release kinetics of diltiazem HCl tablet with high loading dose from the designed ternary polymeric system was dependent on the ratios of HPMC : pectin binary mixture. The release rate increased as pectin : HPMC ratio were increased. Swelling behavior of the ternary system and the ionic interaction of formulation components with cationic diltiazem molecule appear to control drug diffusion and the release kinetics. Comparable release profiles between commercial product and the designed system were obtained. The binding study between gelatin with diltiazem HCl showed the presence of two binding sites for drug interaction with subsequent controlled diffusion upon swelling. This designed delivery system is easy to manufacture and drug release behavior is highly reproducible and offers advantages over the existing commercial product.

Keywords–Ternary polymeric matrix, Diltiazem HCl, Controllrd release system, Swelling, Comparable release profile, Binding study.

Controlled release once-a-day dosage regimens are highly desirable in general, and especially for the treatment of chronic disease conditions. Diltiazem hydrochloride [1,2] used in this work as a model drug is a calcium channel blocker and a potent dilator of coronary arteries and has been shown to increase exercise tolerance in man. [3-5] In a therapeutic sense the goal of any drug delivery is to provide a therapeutic amount of drug to the proper site in the body and maintain an optimum drug concentration over a desired time period. Thus, it is possible 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.

To manufacture controlled release delivery system experimental designs have to be scientifically and rationally sound for achieving specific release kinetics. Variety of polymeric as well as nonpolymeric excipients are often utilized in con -junction with a range of technologies. The importance of the determination of small molecule-macromolecule interaction (binding) is therefore of interest to investigate the behavior of the compounds in pharmaceutical formulations which can affect drug liberation.

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). This study was, therefore, undertaken to evaluate a ternary polymeric matrix system containing a cationic drug, gelatin, and pectin for high drug loading of a highly soluble drug for controlled release delivery and characterize the ionic interaction between components with special emphasis on the effects of pH.

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Experimental

Materials

Diltiazem hydrochloride was obtained from Sigma Chemicals (St. Louis, MO 63178). Granular gelatin type B 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). Potassium chloride from Fisher Chemical (Fair Lawn, NJ) and potassium phosphate from AMEND were used for phosphate buffer solution. 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 V-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.

Preparations of matrix tablets – Tablets containing diltiazem powder and granules (using diltiazem hydrochloride : gelatin mixture=1:1) were blended together with a pectin: HPMC mixture or only pure HPMC 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 composition of diltiazem hydrochloride matrix tablets was shown in Table I. Powder mixtures were blended in a V-mixer for 10 minutes. 1% w/w magnesium stearate was sieved by aperture diameter net of 500 mesh, added to all formulations and mixed for an additional 5 minutes prior to compression. Tablets were compressed at 5,000 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).

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.

Curve-fitting method by mathmatical model – All data were analyzed by Statgraphics Version 5.0 (Statistical Graphics Corporation, Rockville, MD). All drug release data were fitted into various kinetic model by this program using a nonlinear regression with the Marquardt algorithm. This analysis program includes curve-fitting a polynomial model to the data, test of fit, and calculation of the model parameters.

Equilibrium dialysis method for determination of the amount of drugs bound to pectin and gelatin – Cellulose tubings (MW cutoff : 12,000 to 14,000) containing 10 ml of 0.5% pectin in distilled water and in phosphate buffer solution (pH 7.0, unless otherwise stated) was immersed in 30 ml of distilled water and phosphate buffer solution of a drug in a 50 ml tube, at 37°C. The initial concentration of drugs was usually 3.0×10^{-4} to 3.0×10^{-2} M. The tubes were shaken at 37°C. After 24 hours, a time sufficient to attain equilibrium, drug concentrations in the tubes were determined and the amount of drug bound to pectin and gelatin was calculated. The volume of the solution inside the dialysis tube did not change. The drugs were assayed by the ultraviolet (UV) absorption method using a HP diode array spectrophotom eter. A blank for pectin and gelatin in distilled water or phosphate buffer was included.

Table I–*Various Formulations of Swellable Diltiazem Hydrochloride Controlled Matrix Tablets*

Formulation	Ingredients (mg)					Total tablet weight (mg)
	Diltiazem HCl	Gelatin	Pectin	HPMC	Mg stearate	
A	240	240	110	109	1	700
B	240	240	75	144	1	700
C	240	240	-	219	1	700
D	240	-	219	1	460	700

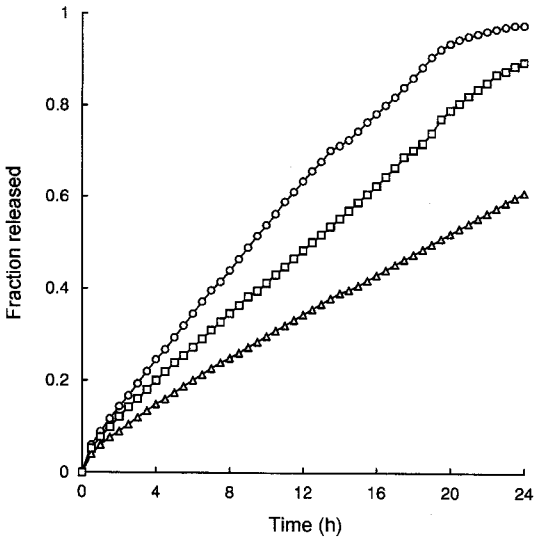


Figure 1–Dissolution profiles of diltiazem hydrochloride in phosphate buffer soln (pH 4.5) at 37°C using USP 23 apparatus II at 50 rpm (n=3). Key : (○) formulation A; (□) formulation B; (△) formulation C; (▲) formulation D in Table II.

Results and Discussion

Dissolution profiles from the designed matrix system

The release profiles of diltiazem hydrochloride from the tested formulations in deionized water are shown in Figure 1. Mathematical models have been used to describe drug release behavior for which the swelling property of the system is possible. Peppas et al. introduced exponential models (equation 1, 2) to analyze drug release from swellable polymeric devices with various geometric shapes :

$$\frac{M_t}{M_\infty} = Kt^n \quad (1)$$

$$\frac{M_t}{M_\infty} = K_1t^n + K_2t^{2n} \quad (2)$$

where M_t/M_∞ is the fractional release of drug, t is the release time, K is a constant incorporating structural and geometric characteristics of the controlled device (i.e., k_1 and k_2 denote diffusion and relaxation contributions), and n is the diffusional release exponent indicative of mechanism of release. It is shown that the value of n is 0.5 for Fickian transport and >0.5 and <1.0 for non-Fickian transport and 1 for zero-order (Case-II transport). When the value of n approaches 1.0, phenomenologically one may conclude that the release is approaching zero-order. The values of K, n and coefficient of correlation, r^2 shown in Table II following linear regression of dissolution data correspond to 60% dissolution data. Formulations A, B, and C are all approaching zero-order release kinetics, however, formulation D obeys a non-Fickian kinetics.

Curve-fitting by mathmatical model

To compare the release kinetics curve-fitting program was applied and all drug release parameters are shown in Table II. For the comparison purposes the mean square error (MSE), correlation coefficient (R^2), and the Akaike Information Criterion (AIC) were used.

$$AIC = N_d \ln SSR + 2P \quad (3)$$

Where N_d is the number of data points, SSR is the sum of residual squares, and P is number of parameters. The lowest

Table II–*Various Values from Dissolution Data of Different Formulations in Swellable Diltiazem Hydrochloride Controlled Matrix Tablets by Using Model Curve Fitting*

Formulations	Model	k_1	k_2	n	R^2	MSE	AIC	RSD
A	1	0.093	-	0.953	0.999	1.18×10^5	-79.98	2.186×10^{-3}
	2	0.093	0.30	0.937	0.999	1.18×10^5	-79.98	2.187×10^{-3}
	3	0.066	-	-	0.974	6.99×10^4	-44.67	0.024
B	1	0.066	-	1.040	0.996	1.69×10^5	-56.03	1.121×10^{-2}
	2	0.066	0.44	1.026	0.996	1.69×10^5	-56.03	1.122×10^{-2}
	3	0.047	-	-	0.980	6.10×10^4	-45.9	0.021
C	1	0.047	-	0.95	0.998	6.83×10^5	-74.4	7.114×10^{-3}
	2	0.047	0.49	0.99	0.998	6.83×10^5	-74.4	7.113×10^{-3}
	3	0.027	-	-	0.963	1.07×10^4	-14.57	0.028
D	1	0.074	-	0.847	0.999	2.20×10^5	-64.2	4.061×10^{-3}
	2	0.073	0.027	0.834	0.999	2.20×10^5	-64.2	4.060×10^3
	3	0.036	-	-	0.927	1.98×10^4	-40.71	0.039

Note ; 1. k_1t^n
2. $k_1t^n + k_2t^{2n}$
3. $1-(1-k_1t)^2$

AIC value correspond to the most appropriate model. As can be seen in Table II, AIC values are same in both model 1 and model 2 for every case. In order to allow comparison between models, RSD values were compared. The smallest value correspond to the most appropriate.

Zero-order release from designed hydrophilic matrix tablets

When a mixture of HPMC and pectin (2:1) was used as a matrix the value of n in the formulation B (up to 60% release) was approaching 1.0 indicating that the release mechanism follows zero-order kinetics. To elucidate the extent of zero-order release, the data corresponding to 100% release were also fitted to the above equation and confirmed that the release is in accordance to zero-order kinetics.

There is trend between formulation A, B, and C in terms of the release rate depending on the ratio of HPMC/pectin. As the ratio of pectin to HPMC increases the release rate is increased in controlled manner, which reported in previous work.

The mechanism of drug release and dynamics of matrix swelling

Schematics of the observed micro-environmental changes of granules associated with the matrix structure during the dissolution study is shown in Figure 2a and 2b.

When water is penetrated into the matrix during the dissolution study, granulated drug particles in the designed matrix absorbed water on their surface. In the micro-environment around granules, the swelling boundary of each granule is created under hydration while the outer matrix is constantly of swelling. Therefore, drug is most likely released from such matrix by continuous molecular interaction, association/dissociation, and transport.

Influence of pH on release of diltiazem hydrochloride from the designed matrix dosage forms

Figure 3 shows the dissolution profiles of diltiazem hydrochloride at pH 1.7, 4.5, deionized water, and 6.5 under pH-stat conditions and under continuous pH changes in water without any adjustment of pH. Results are shown in Figure 3 and Figure 4. The designed system at all different pH media appears to release drug in a controlled manner.

The ionic interaction between drugs and polymers which results in the changes of binding constant and release behavior is expected to be greatly influenced by the pH and ionic strength of the releasing medium. However, the designed matrix system is not sensitive to pH difference except for pH 1.7 because of hydrolysis and in physiological ionic strength 0.1 M of dissolution medium there is no change in drug release profile (unpublished data).

Binding Properties of Diltiazem hydrochloride to pectin and gelatin as determined by the equilibrium dialysis method.

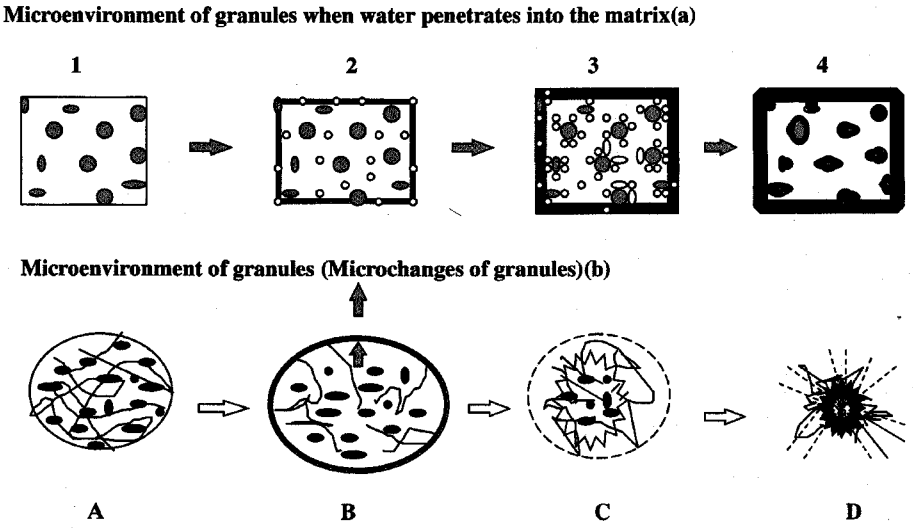


Figure 2–(a) Schematic representation of microenvironment around granules when water penetrates into the matrix. 1.granules with Diltiazem hydrochloride in the designed matrix, 2.water is penetrated into the matrix, 3.water is absorbed onto the granulated particles, and 4.swelling gel layer boundary is created around granules. (b) Schematic representing microenvironmental changes of granulated particles during dissolution study (among drug particles and granulation materials). A. Diltiazem HCl is granulated with gelatin (black point is drug), B. diffusion process in the begining of gelation, C. granule and drug dissolution and disruption within the matrix system during water permeation, and D. possible formulation of micropores and accelerate ion of drug release.

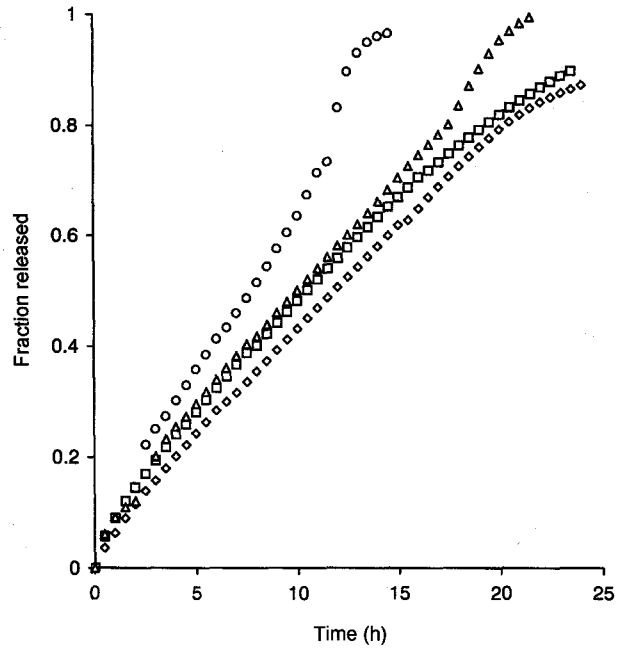


Figure 3–Dissolution profiles of diltiazem hydrochloride from formulation B in 900 ml of dissolution media and different pH conditions at 37°C using USP 23 apparatus II at 50 rpm (n=3). Key : (○) pH 1.7; (□) pH 4.5; (△) pH 6.5; (◇) deionized water.

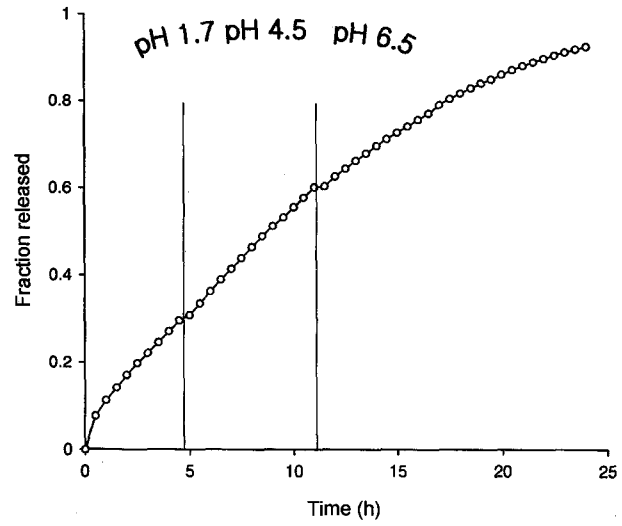


Figure 4–Dissolution profiles of diltiazem hydrochloride in different dissolution media (in pH 1.7 for 4 hours, pH 4.5 for 6 hours, and pH 6.5 for 14 hours) at 37°C using USP 23 apparatus II at 50 rpm (n=3).

The sampling was done after 24 hrs and the data were analyzed according to a usual Scatchard plot. The Scatchard plots of diltiazem hydrochloride interaction with gelatin in deionized water is shown in Figure 5. There are reports indicating that cationic soluble drugs may bind to two pectin sites. Figure 5 may indicate that there are two binding site on

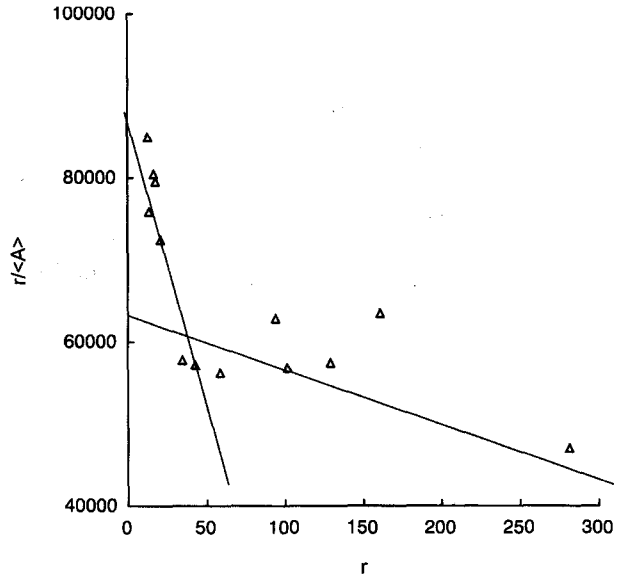


Figure 5–Scatchard plot for diltiazem hydrochloride showing interaction with gelatin in deionized water at 37°C.

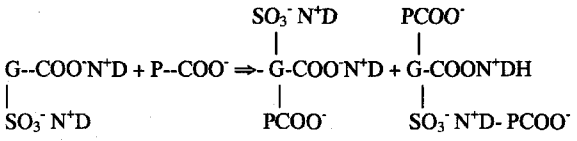
gelatin that will interact with diltiazem hydrochloride. For example, in this study, gelatin is the natural polymer of choice. Gelatin (G) is a heterogeneous product obtained by collagen hydrolysis and is a polyelectrolytic polymer[6-8]. Through an ion-exchange reaction the sodium carboxylate or sulfonate groups of gelatin with diltiazem (D) hydrochloride can produce carboxylates or sulfonates of diltiazem as shown.

$$\begin{array}{l} G\text{--}COO^{-}Na^{+} + D\text{-}N^{+}HCl \rightarrow G\text{--}COO^{-}N^{+}D + NaCl \\ \quad\quad | \qquad\qquad\qquad\quad | \\ \quad SO_3^{-}Na^{+} \qquad\qquad SO_3^{-}N^{+}D \end{array} \quad (I)$$

The organic cations such as diltiazem are probably dispersed molecularly throughout the gelatin and bound to it. Pectin (P), an anionic long chain polygalacturonic acid and a substance which is partially methoxylated[9,10], is reported to complex with cationic drugs, suggesting its usefulness as a possible matrix for sustained-release preparations[11-13]. Therefore, the fundamental complex ionic relations between the amphoteric protein, type B gelatin, and the low equivalent weight anionic polysaccharide, pectin has been shown to yield controlled release property for possible application as a pharmaceutical drug delivery[14].

Through polyionic interaction the obtained carboxylates of diltiazem-gelatin can also react with pectin and produce an associated complex system of the drug-gelatin-pectin as shown.

The importance of the determination of small molecule-macromolecule interaction(binding) parameters is therefore of



(II)

interest to investigate the behavior of the compounds in pharmaceutical formulations which can affect drug liberation. Binding of drug molecules to the charged site of the gelatin and pectin can be determined by standard Scatchard approach[15,16] as follow:

$$n = \frac{nk\langle A\rangle}{1+k\langle A\rangle} \quad (3)$$

$$\frac{r}{\langle A\rangle} = Kn - Kr \quad (4)$$

where r represents the mole ratio of drug bound per mole of macromolecule, n is the number of similar binding sites available on the macromolecule, K is the association (binding) constant, and <A> is the concentration of unbound (free) drug.

The comparison of the designed system with Dilacor 240 mg

Dilacor XR capsules contain 3 or 4 units of 60 mg tablets in a capsule cell, resulting in 180 mg or 240 mg dosage strengths designed to release diltiazem over a 24-hour period. This commercial product, a Dilacor XR unit is triple layered tablet which contains two outer layers and one middle layer, therefore, polymeric outer layers control the drug release in middle layer to give zero-order release kinetics. The dissolu - tion profile for the designed ternary system (formulation B) and commercial product (dilacor 240 mg) are shown in Figure 6. For comparison purposes f_1 and f_2 factors recommended in SUPAC guidelines were used:

$$f_1 = \left\{\left[\sum_{i=1}^{P}|\mu_{ti}-\mu_{ri}|\right] \Big/ \left[\sum_{i=1}^{P}\mu_{ri}\right]\right\} \cdot 100 \quad (5)$$

$$f_2 = 50 \log\left\{[1+(1/P)\sum_{i=1}^{P}(\mu_{ri}-\mu_{ri})^2]^{-1/2} \cdot 100\right\} \quad (6)$$

where f_1 and f_2 are dissimilarity factor and similarity factor considering the dissolution profiles of the two batches generated by using P number of sample points, μ_{ti} and μ_{ri} are the dissolution measurements at certain time points on the test profile and on the reference profile, and log is the logarithm based on 10. The values of f_1 factor calculated in accordance with equation 5 were 6.33 up to 16 hours and 7.81 up to 24 hours on two dissolution profiles. With an average difference of no more than 10% it may be accepted that the products are similar. The calculated f_2-factor values were 99.99 up to 16 hours and 99.97 up to 24 hours of dissolution profiles, respectively. In dissolution analysis with f_1 factor and f_2 factor it is obvious that the designed ternary monolithic polymeric matrix system is capable of releasing its content in a similar manner to the multi-unit, commercial product Dilacor 240 mg.

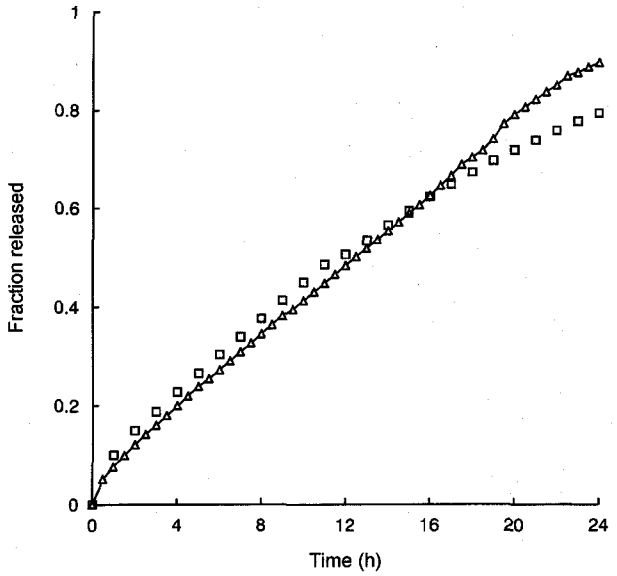


Figure 6–Comparison of dissolution profiles of diltiazem hydrochloride in phosphate buffer soln (pH 4.5) at 37°C using USP 23 apparatus II at 50 rpm (n=3). Key : (□) Dilacor 240 mg; (△) designed matrix 240 mg.

Conclusion

The controlled release delivery system for high drug loading of a highly soluble drug, diltiazem HCl was investigated. This simple monolithic system was successfully manufactured and provided almost zero-order release kinetics. The designed system was not sensitive to pH changes. Binding properties of diltiazem HCl to pectin and gelatin indicate that there are two binding sites in both polymers.

Comparable release profiles between commercial product and the designed ternary polymeric system showed a similar pattern.

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