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Original Article

The Release Behavior and Kinetic Evaluation of Diltiazem HCl from Various Hydrophilic and Plastic Based Matrices

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Abstract

In this study, the effects of various hydrophilic (HPMC and Carbopol 971) and plastic (Ethylcellulose and Eudragit RL100) polymers on the release profile of diltiazem HCl from matrix tablets were evaluated in-vitro. For this purpose, tablets containing 60 mg of diltiazem HCl along with various amounts of the aforementioned polymers were prepared using the wet granulation technique. Tablets prepared were placed in a USP apparatus I dissolution tester containing a pH-1.5 HCl solution for the first 2 h and a pH-6.8 phosphate buffer for the next 10 h of the study. The amount of drug released was determined at 237 nm by a UV-visible spectrophotometer. The results showed that all the polymers used in this study could slow down the release of diltiazem HCl from the matrices prepared. This effect, except for HPMC, generally increased proportionately with the amount of polymer. HPMC imparted the best control over drug release and could sustain it for approximately 6 h. All the matrices prepared had a burst release initially; however, it was minimum with HPMC-containing formulations. Fitting of release data to different kinetic models showed that HPMC-matrices conformed best to Hixson-Crowell model, ethylcellulose-matrices to Higuchi and both Eudragit RL100 and Carbopol 971-formulations to either of Hixson-Crowell, Higuchi and first-order kinetics. Release exponent (n) derived from Korsmeyer-Peppas equation for the studied formulations implied that the release of diltiazem HCl from HPMC-matrices was non-Fickian (0.62-0.66) and that of ethylcellulose-formulations was Fickian (n~0.4). The values of n for Eudragit RL100 and Carbopol 971-matrices ranged from 0.46-0.59, indicating that the drug release was mainly governed by diffusion. Briefly, HPMC was found to be suitable for sustaining the release of diltiazem HCl from matrix-type tablets. Nevertheless, to achieve better results with this polymer, further investigations seem to be necessary.

Keywords: Diltiazem hydrochloride; Sustained release; HPMC; Ethylcellulose; Carbopol 971; Eudragit RL100; Matrix tablets.

Introduction

Diltiazem is a calcium channel blocker widely used for the treatment of angina pectoris, arrhythmia and hypertension. Its short biological half-life (3-5 h) and thus, frequent administration (usually three to four times a day) makes it a good candidate for controlled release preparations (1).

Extended release dosage forms are prepared in order to achieve a desirable and predictable

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pharmacodynamic response, appropriate pharmacokinetics parameters, an improved patient compliance, minimization of side effects, and a maximized drug efficacy (2). One of the most commonly used methods of modulating drug release is its inclusion within a matrix system. Matrix systems have achieved extensive importance in controlled drug delivery, thanks to a simple and fast producing technology, low cost and low influence of physiological variables on their release behavior (3). Based on the features of retarding polymer, matrix systems are usually classified into three main groups: hydrophilic, hydrophobic and plastic (inert).

Hydrophilic polymers, based on their solubility in water, could be divided into two types: i) water insoluble polymers including some carbomers and ii) water soluble polymers such as HPMC (4). HPMC is the most important hydrophilic polymer used at levels of 10-80% *w/w* to retard the release of drugs from the oral delivery systems (5-10). This extensive use originates from the non-toxicity, high-drug loading capacity and non-pH dependence of the polymer (11). Carbomers (Carbopols®) are high molecular weight, cross-linked polymers of acrylic acid, forming a hydrogel in basic solutions. There is a growing interest in the application of these polymers in controlled drug delivery (11-13). When a hydrophilic matrix comes into contact with an aqueous medium, it absorbs water, hydrates and swells to form a gel through which the dissolved drug diffuses out. In terms of water soluble polymers, dissolution of the polymer results in a gradual erosion of this gel layer. However, at higher concentrations, the polymer chains entangle to a greater degree culminating in "virtual cross-linking" and therefore formation of a stronger gel layer. In the case of carbomers, they form a cross-linked network, which could entrap various drugs. These hydrogels do not erode in the same manner to HPMC and therefore remain intact in the release medium, and the drug continues to diffuse through the gel layer at a uniform rate (12).

Plastic polymers, which are capable of forming insoluble or skeleton matrices, have been widely used for controlling the release of drugs due to their inertness and drug embedding ability. Liquid penetration into the matrix is the rate-controlling step in such systems, unless channeling agents are used (9). Ethylcellulose (EC) and Eudragit RL or RS are among the well-known polymers in this category. EC is mainly used in oral formulations as a hydrophobic coating agent for the preparation of tablets and granules (14, 15). Modified release matrix tablets could also be prepared using EC (3, 8). On the other hand, Eudragits (poly methyl methacrylates) are extensively used as release controlling film coats. They are also employed to develop matrix systems at quantities of 5%-20%. Solid polymers may also be used in direct-compression processes at higher amounts, i.e. 10-50% (3, 13, 16, 17).

Some attempts have been made to develop sustained release dosage forms of diltiazem. In this respect, different devices have been prepared such as osmotic pumps (18), buccal tablets (19), microspheres (20), coated tablets (21) and transdermal patches (22). Matrix devices have also been formulated using diverse polymeric excipients including a mixture of HPMC and xanthan (23), a combination of HPMC and pectin (24), guar gum grafted with acrylamide (25), polyethylene oxide plus carbopol (26) as well as carnuba wax, cross-linked povidone (Kollidon SR) or HPMC (9). Once-a-day dosage forms of diltiazem such as Cardizem CD and Dilacor XL are currently available, but the production process of both formulations is complicated and cumbersome. Therefore, an extended-release diltiazem formulation consisting of a simple matrix, which could be manufactured with a high-speed tableting machine, will represent a significant advance. The objective of this study was to evaluate the effect of two groups of polymers, i.e. hydrophilic polymers such as Methocel K4M (HPMC) and Carbopol 971 (C971) as well as plastic polymers including Ethocel 100 (EC) and Eudragit RL100 on release behavior and kinetics of the highly soluble diltiazem HCl from matrix systems.

Experimental

Materials

Diltiazem HCl (Fabbrica Italiana Sintetici SPA, Italy), HPMC (Methocel K4M, Colorcon,

England), ethylcellulose 100cP (Ethocel, Dow, USA), Carbopol 971 (B.F. Goodrich, UK), Eudragit RL100 (Röhm-Pharma, Germany), Polyvinylpyrrolidone K-25 (PVP) (Plasdone K-25, ISP Technologies Inc., USA), Microcrystalline cellulose PH 101 (Avicel PH 101, ISP Technologies Inc., USA), anhydrous dibasic calcium phosphate (DCP) (gifted by Iran Daru Pharmaceutical Co.) and magnesium stearate (MgSt) (Nordland Chemie, Germany) were used as received.

Methods

Preparation and characterization of matrix tablets

Tablets containing 60 mg diltiazem HCl were prepared by the wet granulation technique. The complete list of tablet formulations prepared is shown in Table 1. In the case of hydrophilic polymers, i.e. series A and D formulations, diltiazem HCl, retarding polymer and filler were passed through an 80-mesh sieve to obtain uniform particles. Thereafter, they were thoroughly blended and then kneaded with an ethanolic PVP solution (10%, *w/v*) as the granulating agent using a laboratory granulator (Erweka, Germany) equipped with a 1.25-mm sieve. Granules obtained were dried in an oven at 50°C for 30 min. In terms of series D formulations, to avoid any possible interference/interaction of the retarding polymer and filler, Avicel was used instead of DCP. In order to prepare formulations containing the plastic polymer EC (series B), diltiazem HCl and DCP were passed through the 80-mesh sieve. They were then completely mixed and granulated with a solution of EC in acetone (15%, *w/v*) by means of the granulator. The resultant granules were dried at 40°C for 15 min. In case of formulations prepared with Eudragit RL, diltiazem HCl and DCP were screened through the 80-mesh sieve. Afterwards, the required ingredients were combined and the mixture wetted with a solution of Eudragit RL in ethanol (30%, *w/v*) and then granulated using the granulator. Granules obtained were dried at 50°C for 30 min. In all cases, the dried granules were comminuted using an Erweka FGS oscillating granulator (Erweka, Germany) equipped with a 0.80-mm screen. Final granules were mixed with 1% MgSt by means of a cubic mixer (Erweka, Germany) and then compressed into 7-mm convex tablets using a single-punch tablet machine (Erweka, Germany). The compression force was adjusted so that the corresponding hardness of tablets was at maximum.

The physical properties of tablets prepared were investigated. Friability was determined using 10 tablets from each formulation, by means of an Erweka TA Roche-type friabilitor at a speed of 25 rpm for 4 min. For each formulation, the hardness of 10 tablets was also tested using an Erweka TBH 28 apparatus (Erweka, Germany).

Dissolution studies

In vitro drug release studies from the prepared matrix tablets were conducted for a period of 12 h using an Erweka DT6R model dissolution tester (Erweka, Germany) USP 23 type I apparatus (rotating basket) set at 100 rpm and a temperature of 37 ± 0.5°C. Initially, tablets were placed in 900 ml of a hydrochloric acid solution at pH 1.5 for 2 h. Afterwards, the dissolution medium was completely removed and replaced with 900 ml of a pH 6.8-phosphate buffer solution. The study continued for a further 10 h. At specified intervals 5 ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. After appropriate dilution, the sample solution was analyzed at 237 nm for the presence of diltiazem HCl, using a UV-visible spectrophotometer (Shimadzu 1201, Japan). It was justified that none of the ingredients used in the formulations interfered with the assay method. The amount of drug released were calculated using the calibration curves constructed in the two dissolution media and the means of three determinations were used for data analysis.

Assay of diltiazem HCl in matrix tablets

Twenty randomly chosen tablets from each formulation were thinly powdered in a mortar and a portion of the resulting powder equal to the weight of the respective tablet was solubilized in 0.1 N HCl to make a solution of 9 mg of diltiazem HCl per ml. Several aliquots were then filtered using a sintered glass filter and assayed spectrophotometrically at 237 nm. Each

measurement was carried out in triplicate and the results averaged. A blank solution containing all the components, except for the drug, was also prepared. Corresponding concentrations were calculated from the standard curve. No other assay method was considered necessary, since no interference was observed at 237 nm.

Release kinetics

To study the release kinetics of diltiazem HCl from the matrix tablets, the release data were fitted to the following equations:

Zero order equation (27):

$$Q_t = k_0.t \qquad [1]$$

where Q_t is the percentage of drug released at time t and k_0 is the release rate constant;

First order equation (28):

$$\ln (100\text{-}Q_t) = \ln 100 - k_1.t \qquad [2]$$

where k_1 is the release rate constant;

Higuchi's equation (29):

$$Q_t = k_H.t^{1/2} \qquad [3]$$

where k_H is the Higuchi release rate constant;

Hixson-Crowell (30):

$$(100\text{-}Q_t)^{1/3} = 100^{1/3} - k_{HC}.t \qquad [4]$$

where k_{HC} is the Hixson-Crowell rate constant.

Furthermore, in order to better characterize the drug release mechanisms for the polymeric systems studied, the Korsmeyer-Peppas (31) semi-empirical model was applied:

$$Q_t/Q_\infty = k_{KP} . t^n \qquad [5]$$

where Q_t/Q_∞ is the fraction of drug released at time t, k_{KP} a constant compromising the structural and geometric characteristics of the device, and n, the release exponent, which is indicative of the mechanism of drug release. For the case of cylindrical geometries such as tablets, n=0.45 corresponds to a Fickian diffusion release (Case I), $0.45<n<0.89$ to a non-Fickian (Anomalous) transport, $n = 0.89$ to a zero order (Case II) release kinetics (32) and $n>0.89$ to a super Case II transport (10). For fitting the release data to the equations, only the points within the interval 10%-70% were used. In the case of Higuchi model, the range was 10%-60%.

Statistics

All the results were expressed as mean values ± standard deviation (SD), unless otherwise specified elsewhere. The release rate constants (k), calculated based on the best model, were compared using a single-factor analysis of variance (ANOVA) with a Tukey post hoc test, at a 5% significance level. A direct non-linear fitting of the release data was carried out for the Korsmeyer-Peppas model. All data analyses were performed using the SPSS® 10.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results and discussion

In this study, the effect of various polymers including hydrophilic (HPMC K4M and Carbopol 971) and plastic types (ethylcellulose and Eudragit RL100) on the release behavior as well as kinetics of diltiazem HCl from matrix type tablets were evaluated. Based on the results of preliminary studies, it was evident that due to the improvement of flowability and compressibility of diltiazem HCl granules, tablets with desirable physical characteristics could be prepared using the wet granulation technique. Table 1 shows the composition of various formulations containing diltiazem HCl and different polymers and inactive ingredients, prepared in this study.

Table 2, indicates the results of physicochemical quality control tests (including hardness, friability and assay) performed on the formulations. As summarized in Table 2, the evaluation of the prepared matrix tablets showed that the drug content of all formulations ranged from 95.57% to 99.75%, indicating the

Table 1. Composition (%) of 60-mg diltiazem HCl loaded matrix tablets.

Series	HPMC (Retarding polymer)	DCP (Filler)	PVP (Binder)	MgSt (Lubricant)
A1	35	10	5	1
A2	40	10	5	1
A3	45	10	5	1
	EC			
B1	15	30	-	1
B2	20	30	-	1
B3	25	30	-	1
B4	30	30	-	1
	Eudragit RL			
C1	35	30	-	1
C2	40	30	-	1
C3	45	30	-	1
	C971	Avicel PH 101		
D1	7	30	5	1
D2	10	30	5	1
D3	13	30	5	1

presence of an acceptable amount of drug in the formulations. Different polymers yielded matrix tablets with various hardness values, ranging from 7.5 KP (for formulations containing Eudragit RL100) to 21.17 KP (for those prepared using HPMC). The tablets also passed the friability test (F<1%), showing that all formulations are within the USP 23 limits (33).

The effect of HPMC at different concentrations ranging from 35%-45% on the release of diltiazem HCl from tablet matrices was examined. Figure 1 shows the release profiles of the drug from HPMC matrix tablets. Formulations A1, A2 and A3 released 80% of their diltiazem HCl in 5-6 h, indicating that the polymer could retard the drug release. Different authors reported identical data for other drugs (6-8, 10, 34). Increasing the concentration of HPMC within the matrix did not alter the drug release profile significantly ($p>0.05$). This finding was in agreement with those obtained by other researchers (7, 8, 34).

When considering the effect of EC on the release profile of diltiazem HCl, polymer concentrations varying from 15%-30% were employed. Figure 2 depicts the release profiles of the drug from EC matrix tablets. Raising the amount of polymer reduced the release rate, so that with the exception of formulations B2 and

Table 2. Physical characterization of diltiazem HCl matrix-type sustained release tablets.

Formulation	Hardness (KP) (n=10) [a]	Friability (%) (n=1)	Drug content (%) (n=3)
A1	16.74 ± 0.59 [b]	0.16	96.77 ± 0.09 [b]
A2	21.17 ± 0.88	0.00	96.51 ± 0.13
A3	14.27 ± 0.73	0.14	97.67 ± 0.15
B1	10.84 ± 0.30	0.53	95.57 ± 0.16
B2	11.57 ± 0.37	0.33	97.84 ± 0.08
B3	11.49 ± 0.68	0.00	95.61 ± 0.21
B4	13.20 ± 0.26	0.13	96.24 ± 0.19
C1	7.54 ± 0.53	0.23	95.75 ± 0.21
C2	7.75 ± 0.52	0.29	96.54 ± 0.19
C3	7.71 ± 0.42	0.39	97.03 ± 0.13
D1	17.38 ± 0.81	0.19	97.79 ± 0.15
D2	18.56 ± 0.90	0.36	99.75 ± 0.12
D3	16.80 ± 0.59	0.34	97.53 ± 0.06

[a] n is the number of measurements. [b] Values represent mean ± SD.

Table 3. Kinetic parameters of diltiazem HCl release from the matrix tablets [a].

Formulation	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	k_0 (%h^{-1})	R^2	k_1 (h^{-1})	R^2	k_H (%h$^{-1/2}$)	R^2	k_{HC} (%h^{-1})	R^2	K_{KP} (%h^{-n})	n	R^2
A1	16.153	0.9852	0.127	0.9978	38.226	0.9932	0.368	0.9995	28.759	0.657	0.9994
A2	15.021	0.9878	0.111	0.9987	35.285	0.9907	0.328	0.9995	26.451	0.664	0.9989
A3	15.100	0.9821	0.115	0.9993	35.976	0.9959	0.338	0.9985	29.098	0.616	0.9996
B1	44.765	0.9774	0.440	0.9986	66.905	0.9998	1.186	0.9944	71.922	0.419	0.9996
B2	29.143	0.9650	0.251	0.9944	50.432	0.9982	0.708	0.9874	56.265	0.414	0.9995
B3	23.459	0.9612	0.215	0.9951	46.755	0.9981	0.593	0.9876	53.956	0.395	0.9995
B4	18.405	0.9607	0.159	0.9925	38.092	0.9922	0.447	0.9856	47.260	0.394	0.9982
C1	32.243	0.9755	0.285	0.9979	54.596	0.9972	0.797	0.9938	57.565	0.456	0.9983
C2	25.504	0.9843	0.216	0.9986	46.116	0.9992	0.612	0.9979	48.545	0.489	0.9984
C3	23.374	0.9962	0.197	0.9846	43.793	0.9898	0.558	0.9941	40.899	0.591	0.9918
D1	40.669	0.9846	0.322	0.9984	58.122	0.9999	0.936	0.9954	60.230	0.472	1.0000
D2	32.444	0.9772	0.249	0.9959	53.887	0.9977	0.730	0.9927	49.881	0.552	0.9975
D3	27.179	0.9786	0.218	0.9962	49.324	0.9983	0.628	0.9947	45.292	0.567	0.9985

[a] Values are mean of three determinations.

B3, statistical analysis revealed a significant difference between the EC matrices ($p<0.0001$). Formulation B1 liberated 80% of its drug content within 1.5 h and formulation B4 in 4 h. The effect of polymer content on the drug release rate could be explained in two ways, i) a decrease in the total porosity of the matrices (initial porosity plus porosity due to drug dissolution) (3) and ii) an increase in the hydrophobicity of the matrix leading to a decreased penetration of the solvent molecules into the system, which in turn lessens diffusion of the drug from the matrix (8). EC matrices were not capable of retarding diltiazem HCl release rate desirably. Other researchers have stated the same problem with EC in the production of sustained release formulations for hydrophilic drugs (3). However, in a study with the water soluble drug pseudoephedrine HCl, EC could make a sustained release system (35). This success, as explained in the related article, was because of the lower viscosity of the polymer used (10 cP) and its higher compressibility compared to the 100-cP EC used in our study. Some investigators have illustrated that release rate from matrices prepared from physical mixtures of drug and EC was considerably faster than those produced by the solid dispersion technique (36). This phenomenon was attributed to the encapsulation of drug particles by polymer in matrices prepared from solid dispersion system, which caused a great delay in diffusion of the drug through polymer and made diffusion as a rate retarding process in drug release mechanism. Since methods of application of EC as a retarding agent would influence its effectiveness, it is speculated that the use of proper methods such as microencapsulation, particle coating or solid dispersion may provide suitable results.

Next, the effect of Eudragit RL100 at different concentrations (35%-45%) on the release of diltiazem HCl was explored. Although increasing the amount of the polymer significantly ($p<0.02$) diminished the drug release rate from the tablets prepared, none of the formulations prepared were found to release their drug content with a sustained and desirable rate. Formulations C1-C3 released 80% of their diltiazem HCl within 2-3 h (Figure 3). The unsuccessful use of Eudragit RL could be due to a high water solubility of diltiazem HCl on one hand, and the high polymer permeability to water (16) on the other hand. Other researchers, however, succeeded to prepare sustained release matrices using Eudragit (3, 13). In one of these studies (3), the hydrophilic drug lobenzarit was formulated by means of Eudragit RS, which is slightly permeable to water because of its low content of quaternary ammonium groups (16). In another study (13), dimenhydrinate, a sparingly soluble drug, was used together with Eudragit RL.

Eventually, the effect of C971 at different levels ranging from 7%-13% on the release profile of diltiazem HCl was investigated. As shown in Figure 4, during the initial 2 h, a fast release of diltiazem occurred. This was then followed by a remarkable decrease in the release rate. Carbopols form a gel at basic pHs, therefore, the initial fast release is related to an acidic pH

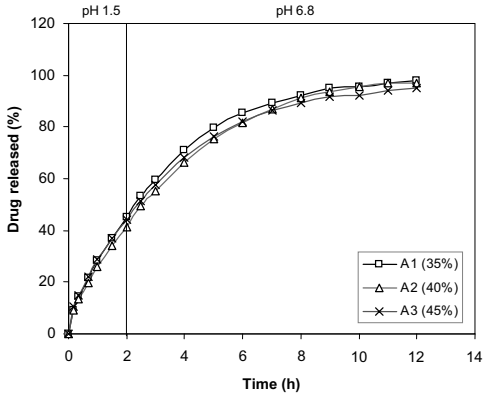

Figure 1. Effect of various HPMC concentrations on diltiazem HCl release from matrix tablets (n=3, SDs: 0.007-0.509).

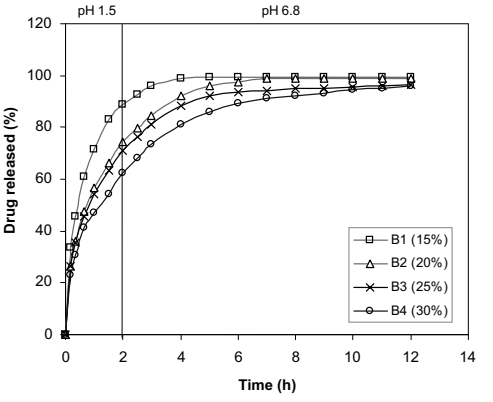

Figure 2. Effect of various EC concentrations on diltiazem HCl release from matrix tablets (n=3, SDs: 0.017-0.480).

of the dissolution medium (i.e. pH 1.2) in which the polymer forms a weak gel not capable of controlling the drug release. However, in the second dissolution medium (phosphate buffer pH 6.8), C971 forms a stronger gel through which the drug could slowly diffuse out (11). The amount of polymer used within the formulations imparted a significant ($p<0.01$) control over the drug release. This could be owing to a stronger gel formation at higher polymer levels. Formulations D1-D3 liberated 80% of their drug content over 2-4 h. This rapid release, in addition to the influence of acidic pH on the polymer, could be attributable to the presence of Avicel, having inherent disintegrant properties. This result is in agreement with that observed by other researchers (12). Some investigators, however, used carbopols successfully for controlling the release of slightly water soluble drugs of diclofenac and ibuprofen (11, 12). Addition of suitable basic salts such as sodium bicarbonate to formulations containing carbopols may improve their retarding effect in acidic media by making the matrices form a stronger polymer network. Alternatively, some researchers added HPMC to formulations containing carbopols to correct the release pattern (11, 34). Their data have shown that a combination of anionic polymer (carbopols) with nonionic HPMC produces a synergistic increase in viscosity. This is probably due to the stronger hydrogen bonding between the carboxyl groups of carbopols and hydroxyl groups of HPMC, leading to stronger cross-linking between the two polymers, which could also diminish the release fluctuations (34). Besides, HPMC is not affected by pH variation and forms a gel upon contact with different dissolution media to control drug release (11).

With all formulations, a burst release was observed that could be attributed to dissolution

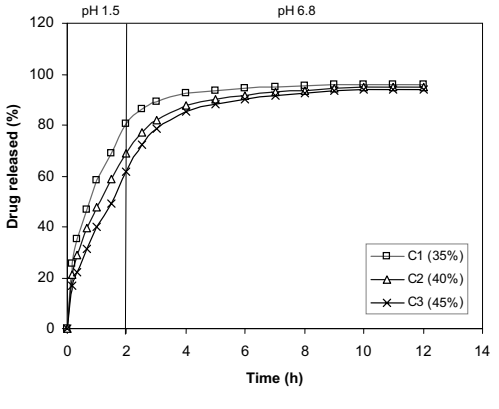

Figure 3. Effect of various Eudragit RL 100 concentrations on diltiazem HCl release from matrix tablets (n=3, SDs: 0.021-0.604).

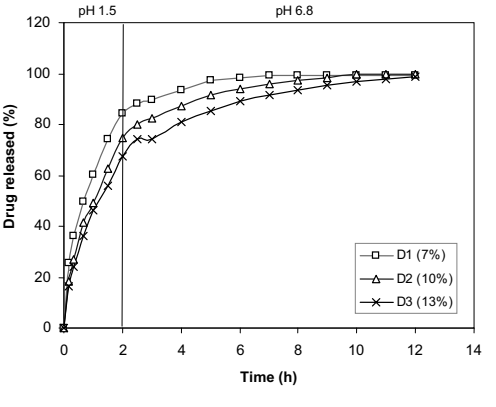

Figure 4. Effect of various C971 concentrations on diltiazem HCl release from matrix tablets (n=3, SDs: 0.006-0.819).

of water soluble diltiazem HCl from the surface of the tablets (8, 9). Yet, this effect was least with HPMC-containing formulations. This finding could be explained by the hydrophilic nature of HPMC. When exposed to the dissolution medium, the solvent penetrates into the free spaces between macromolecular chains of the polymer. After solvation of the polymer chains, the dimensions of the polymer molecule increase due to the polymer relaxation by the stress of the penetrated solvent. This phenomenon is defined as swelling and is characterized by the formation of a gel-like network surrounding the tablet. This swelling and hydration property of HPMC causes an immediate formation of a surface barrier around the matrix tablet, which reduces the burst release (32).

In order to describe the kinetics of drug release from controlled release preparations, various mathematical equations have been proposed. The zero order model Eq. [1] describes the systems, where the drug release is independent of its concentration (27). The first order equation Eq. [2] describes the release from systems, where release rate is concentration dependent (28). According to Higuchi model Eq. [3], the drug release from matrix is directly proportional to a square root of time and is based on the Fickian diffusion (29). The Hixson-Crowell cube root law Eq. [4] describes the release from the systems, where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in case of systems, which dissolute or erode over time (30). A more comprehensive, but still very simple, semi-empirical equation to describe drug release mechanism from polymeric systems more precisely is the so-called Korsmeyer-Peppas power law, i.e. Eq. [5]. Thus, drug release data were fitted to these kinetic models to explain the drug release kinetics and mechanism from the matrices prepared. Criterion of selecting the most appropriate model was based on the best goodness of fit. The values of the release exponent (n), kinetic rate constant (k) and correlation coefficient (R^2) as calculated from Eqs. 1-5 are presented in Table 3. Generally speaking, the majority of formulations did not seem to follow a zero order profile of drug release based on the lower R^2 values obtained compared to the other three kinetic models examined. On the other hand, the R^2 values obtained from examining the first order, Higuchi and the Hixson-Crowell models were found to be very close to each other throughout the whole series of formulations investigated. Nevertheless, with the HPMC-matrices (A1-A3), the R^2 values for Hixson-Crowell model were slightly higher than the other models, showing a better conformance to this model. Applicability of the release curves to Hixson-Crowell model indicated a change in surface area and diameter of the tablets, with a progressive dissolution of the matrix as a function of time. This result was similar to that obtained elsewhere (23) for the release of diltiazem HCl from matrix tablets containing HPMC and xanthan. The values of n determined for HPMC matrices studied ranged from 0.62-0.66 and confirmed that the formulations followed non-Fickian diffusion kinetics (anomalous transport), i.e. the release is ruled by both diffusion of the drug and dissolution of the polymer. In case of formulations containing EC (B1-B4), the R^2 values obtained from the Higuchi model appeared to be slightly higher than the other two models, indicating that the release is principally controlled by diffusion. In fact, matrices prepared using EC were the only tablets in this study that remained intact during the dissolution study. As a result, dissolution or erosion of the matrix was not the parameter influencing the release. Values of n~0.4 for these formulations disclose a Fickian diffusion mechanism of release. In terms of matrices prepared using Eudragit RL100 and C971, both fitted the first order, Higuchi and Hixson-Crowell's models. In both cases, increasing the proportions of polymer within the tablet matrix increased the value of the exponent n, indicating that the release mechanism shifted from diffusion-controlled to an anomalous transport in which both diffusion and erosion are governing the release. Analogous results have also been observed with C971 in another study (37). They explained that increasing the polymer content decreases the release rate. This reduction of the release constant increases the time needed to release a given quantity of drug, allowing a greater hydration and relaxation of the polymer matrix before release, which in turn shift the release mechanism toward relaxation-

erosion.

In conclusion, although all the polymers studied could slow down the release of diltiazem HCl from the matrices, HPMC showed the best results. The matrices prepared using HPMC, yet, need some further modifications. Diltiazem HCl has a bitter taste and application of film coating is the simplest approach to mask the taste. Coating the tablets using appropriate polymers would have a dual action of taste masking and controlling the initial fast release. Preparation of matrices by means of HPMC polymers with higher viscosities may also be another solution.

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