Department of Pharmaceutical Technology[1], Faculty of Pharmacy, Gazi University, and Refik Saydam Central Institute of Hygiene[2], Ankara, Turkey

Formulation and evaluation of hydrophilic matrix tablets of diltiazem using factorial design based studies

N. Çelebi[1] and G. Ünlü[2]

Prolonged release diltazem tablets were prepared using three grades of hydroxypropylmethyl cellulose (HPMC) according to a 3^2 factorial design. The effects of two factors (polymer ratio and polymer type) on drug release $t_{50\%}$ from hydrophilic matrix tablets were studied at three levels. Tablets were compressed by a flat-faced punch having a diameter of 11 mm using a hydraulic press at 200 kg/cm^2. The *in vitro* release of diltiazem from tablets was determined according to the USP 23 paddle method in different media (pH 1.2, 4.0, 7.4) at 75 rpm and 37 °C. The effect of various excipients (lactose, mannitol and calcium dihydrogen phosphate) on the *in vitro* release of diltiazem has also been investigated. The releases of diltiazem from tablets which contained lactose and mannitol was greater than from formulations which contained calcium dihydrogen phosphate. Topographic release profiles show that the release of diltiazem decreased as pH increased. The best formulation (F14) contained lactose as a diluent. The F14 formulation showed compared with two commercial products a prolonged release profile whereas the commercial products released 92% and 98%, respectively, during 4 h. All the formulations except F13 which contains mannitol showed $Q \rightarrow \sqrt{t}$ kinetics. The most appropriate polymer HPMC K4M with a 1 : 0.5 ratio has been found by factorial design. The polymer ratio was effective on the release of diltiazem from hydrophilic tablets ($p < 0.05$).

1. Introduction

In the past few years, hydrophilic matrices became extremely popular in controlling the release of drugs. There are several advantages. Among these, the following stand out [1]:

- With proper control of the manufacturing process, reproducible release profiles are achievable. The variability associated with them is slightly less than that characterizing coated release forms.
- Though the structure makes the immediate release of a small amount of active principle unavoidable their is no risk of releasing of a large part of the dose.
- Their capacity to incorporate active principles is large, which is suitable for the delivery of large doses.
- The manufacturing processes are relatively straight forward. The usual route of formulating tablets is via direct compression or compression before granulation, either dry or wet.
- Compressed hydrophilic matrices, when properly formulated can be very suitable, cheap and readily manufactured dosage forms for the sustained release of drugs [2].

Hydroxypropylmethyl cellulose (HPMC) may be used for hydrophilic matrices for controlled release oral delivery [3]. Alderman et al. [4], described the prolonged release from HPMC matrices. They form a gelatinous layer when the polymer hydrates on contact with water, and control the release of drugs by two mechanisms. Water-soluble drugs were released by diffusion out of the gelatinous layer and by erosion of the gel, whereas poorly soluble drugs were released by erosion only.

The kinetics of drug release from hydrophilic matrices was examined for both freely soluble [5] and poorly soluble drugs [6] and matematical models have been developed to investigate the influences of hydration, swelling and glass transition temperatures on drug release [7–9]. It has been reported that several factors such as polymer hydration [10], polymer composition [11], polymer viscosity [12], drug solubility [13–15], polymer/drug ratio [9] polymer drug interaction [13] and tablet size and geometry [16] influence drug release from HPMC matrix tablets. The major factor for controlling drug release was the drug/HPMC ratio.

The active substance for this investigation, the calcium channel blocker diltiazem (DTZ), is widely used in the treatment of angina pectoris, arrhytmia and hypertension [17]. It has an important first-pass effect, which causes rather a low bioavailability.

In our previous study [18] we reported the effect of the polymer ratio on diltiazem release from HPMC hydrophilic matrix tablets. The objective of this study was to perform factorial design experiments to formulate and prepare hydrophilic matrix tablets and examine the modifications of *in vitro* release.

2. Investigations, results and discussion

2.1. Interaction of diltiazem with hydrophilic polymers

First, the interaction of DTZ with three grades of HPMC was investigated. The differential scanning calorimetry (DSC) thermograms are shown in Fig. 1. DTZ has a specific endothermic peak at 210 °C in all the mixtures, that were prepared with DTZ and were observed the specific peak of DTZ. The result indicated that an interaction of DTZ with three grades of HPMC was not observed.

2.2. Drug release mechanism

One of the proposed mechanisms for drug release from matrices of HPMC implies water penetration in the matrix (with drug dissolution on the surface, causing its immediate release), hydration and swelling of HPMC, diffusion of the dissolved drug, and the erosion of gelatinous polymer layer [19, 20]. The swelling of a matrix is divided into three stages: gel layer, swelling gelatinous layer, and dry core.

When the water reaches the center of the tablet, and the concentration of drug falls below the solubility value, or the release rate of drug begins to reduce, a time lag in the changing of release mechanism is recorded [19].

In the present study, when the HPMC matrix tablet is conducted in an aqueous environment, firstly DTZ is released from the surface of the tablet and then water penetrates into the matrix. The polymer swells to form a gel layer

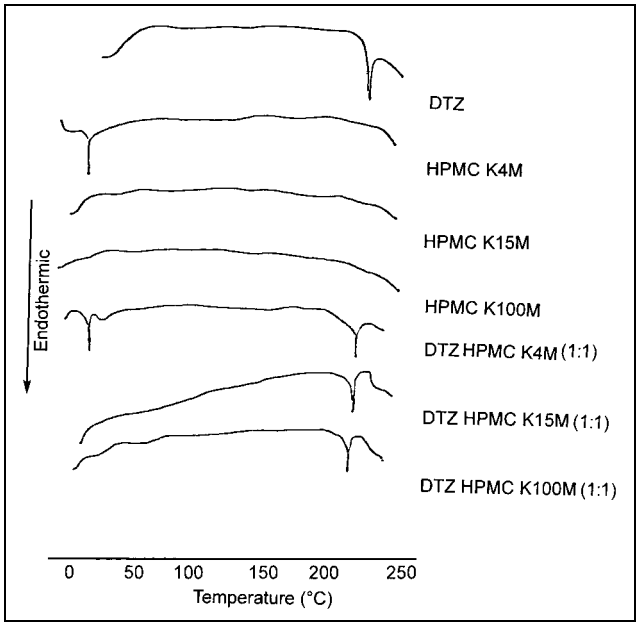

Fig. 1: Differential scanning calorimetry curves of diltiazem and three grades of HPMC

and the matrix increases. DTZ releases through the gel barrier and this process continues until the tablet is completely eroded.

2.3. *In vitro release studies*

In order to select an appropriate hydrophilic polymer ratio, HPMC K4M, HPMC K15M, HPMC K100M polymers, with low, medium and high viscosity degrees have been used for hydrophilic matrix tablets containing DTZ. Formulations of DTZ with three polymers having a ratio of 1 : 0.5, 1 : 1 and 1 : 2 have been prepared. According to the *in vitro* release results, the most appropriate polymer HPMC K4M with 1 : 0.5 ratio has been chosen [18].

A change in the drug/polymer ratios changed the release of DTZ (Fig. 2). When the with formulations F4 (1 : 0.5), F5 (1 : 1) and F6 (1 : 2), which were prepared with HPMC K4M the release of DTZ were found to be 87%, 56% and 46%, respectively at the end of the 8 h. The results indicated that drug/polymer ratio influenced the release of DTZ from hydrophilic tablets. The *in vitro* release of DTZ was decreased as the polymer ratio increased. This result was in accordance with Baveja et al. [21]. The drug/polymer ratio is generally used as a control variable in drug rate delivery.

The effect of polymer viscosity has also been investigated. The effect of viscosity is significant in formulations with low ratios of polymer. As the ratio of polymer increases, the effect of viscosity decreases. High viscosity polymers increase the resistance of the gel layer thereby opposing diffusion. High viscosity polymers were used in the study of Cheong et al. [12]. In this study it was reported that, as the amount of this polymer increased, the release rate decreased. This findings were supported by our results. Recently Vasquez [22] demonstrated that decreasing of matrix viscosity makes the drug diffusion easier.

2.4. *Evaluation of effect of excipients on in vitro release*

The effect of various excipients on *in vitro* release of DTZ has also been investigated. The effects of excipients, both soluble and insoluble, are well documented. If present in large enough quantities, they increase the release rate of water soluble drugs [23]. This effect has been attributed to an expansion of the gel layer, if the excipients swell and are insoluble, or the impossibility of a continuous gel barrier forming, if the matrix incorporates insoluble excipients which do not swell. In this study, the soluble diluents lactose and mannitol and the insoluble calcium dihydrogen phosphate were used in the tablet formulations. The release of DTZ from formulations F10, F11, F12, F14 were found to be 81%, 78%, 83% and 85%, respectively, within 8 h (Fig. 3). On the other hand, the release of DTZ from formulation F13 was 98% at the end of 3 h. The release of DTZ from F15 was 95% at the end of 6.5 h. This result can be explained by the differences in solubility of the diluents and their subsequent effects on the tortuosity factor. As the water soluble diluent dissolved it diffused outwords and decreased the tortuosity of the diffusion path of the drug. Similar results were found by Lapidus and Lordi [23]. DTZ was released very rapidly from formulations F13 and F14, because the polymer ratios (1 : 0.25 and 1 : 0.33) were decreased. On the other hand, F13 contains Avicel and the release of DTZ increased due to disintegration of the tablet.

Although formulations F10, F11, F12, F14 kept the shape of a tablet for 8 h, some tablets which are F13 and F15 formulations were disintegrated after 3 and 6.5 h, respectively. It was observed that the size of tablets (diameter and thickness) F10, F11, F12 and F14 increased two fold during the *in vitro* release experiments, because of the polymer swelling properties. When the *in vitro* release values of formulations F10–F15 were plotted according to

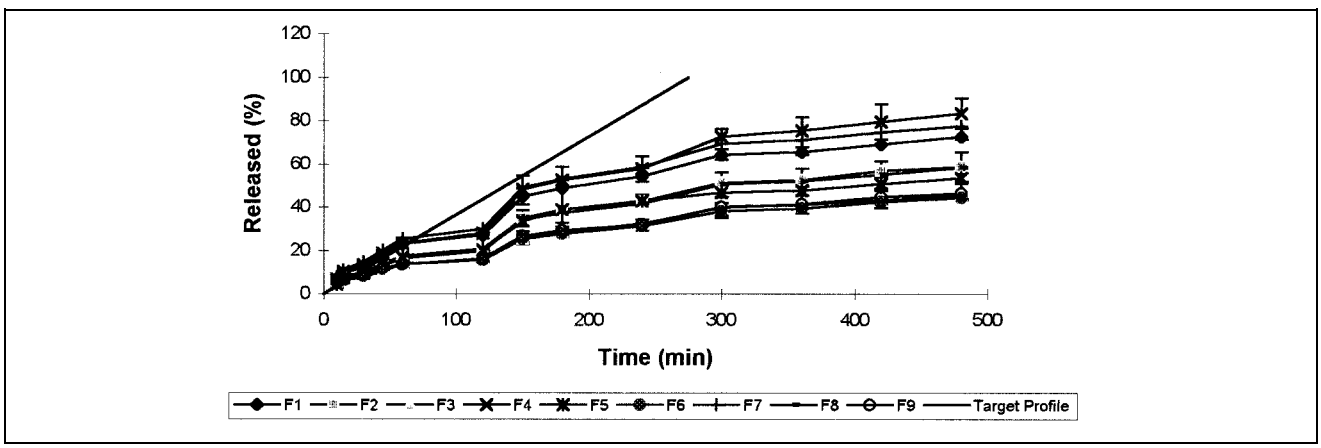

Fig. 2: Effect of polymer ratio on in vitro release of diltiazem from three grades of HPMC

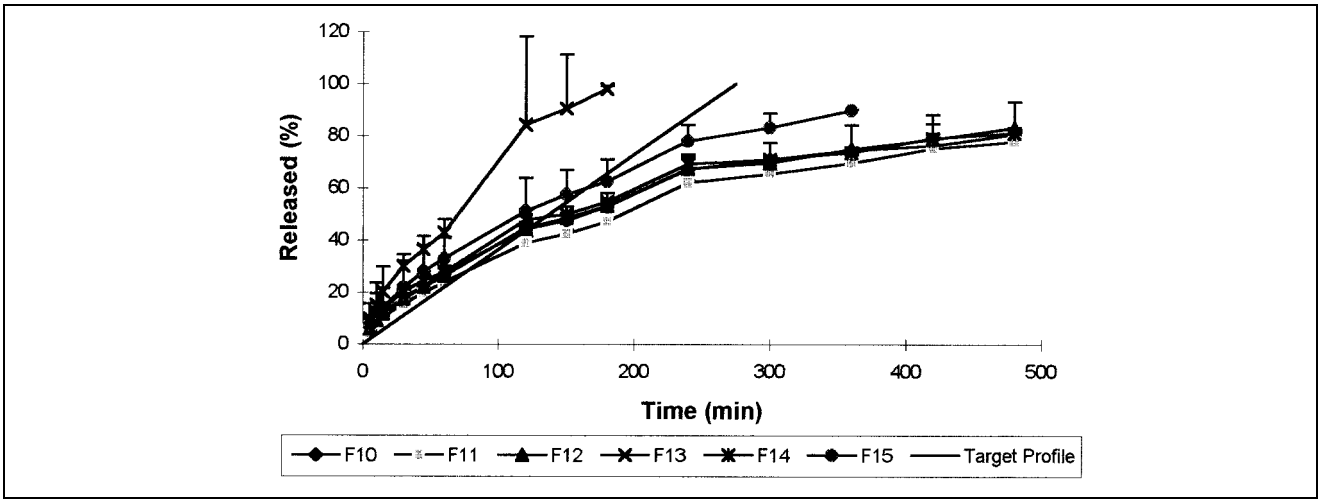

Fig. 3: Effect of various excipients on in vitro release of diltiazem from hydrophilic tablets

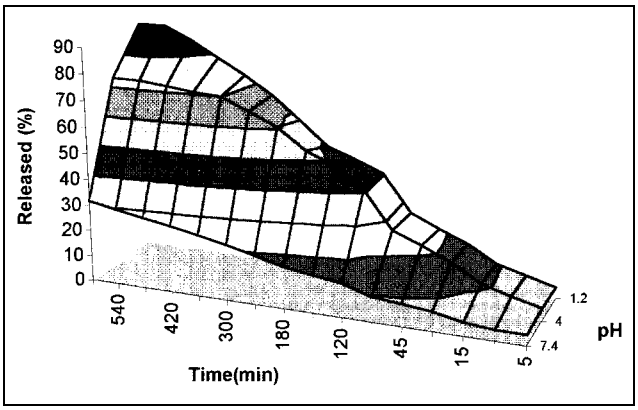

Fig. 4: Topographic release of profiles F14 formulation

time versus percent release of drug, F10, F11, F12 and F14 profiles were close to the target profile.

The *in vitro* release of DTZ from F14 (the best formulation) was also carried out in three different pH media (pH 1.2, 4.0, 7.2) for a period of 10 h.

Topographic release profiles of formulation F14 in three different pH media are shown in Fig. 4. The release of DTZ was found to be 89%, 75% and 31.5% at pH 1.2, pH 4.0 and 7.4, respectively. The *in vitro* release results indicated that the release of DTZ decreased as pH increased. This result depends on gelling of the polymer. When the pH increased the gelling capacity of polymer increased.

In addition, the best formulation was F14 compared to two commercial prolonged release products A and B. The

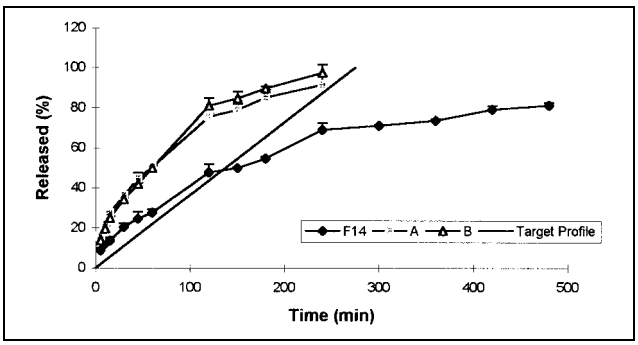

Fig. 5: *In vitro* release profiles of F14 formulation and two commercial diltiazem products

DTZ release rates of product A, B and formulation F14 were 92%, 98% and 85%, respectively at the end of 8 h. There was a better similarity between the profile of F14 and the target profile than with the others (Fig. 5).

Products A and B released 92% and 98% DTZ, respectively during 4 h whereas formulation F14 released 85% in 8 h. Thus, F14 formulation showed a prolonged release profile.

2.5. Evaluation of in vitro release kinetics

The *in vitro* release data were evaluated according to the DISSOL 92 kinetic program [24] which contains zero order, first order, $Q \rightarrow \sqrt{t}$, and Hixson-Crowell models. Upon checking the results, according to the determination coefficient, it was decided that except F13, all the formulations are in accordance with matrix kinetics ($Q \rightarrow \sqrt{t}$). The release rate has been found according to zero order kinetics from F14 as 7.21 mg/h. This is very close to the value of 7.84 mg/h which was calculated from dose design.

On the other hand, a semiempirical equation ($Mt/M\infty = kt^n$) was used to investigate the mechanism of release. The "n" values are given in Table 1. The result indicate that the release mechanisms of formulations F6, F7, F9, F14 were non-Fickian mechanisms. The non-Fickian re-

Table 1: Estimated values of k and n by regression of ln M_t/M_∞ on ln t

Code	n (mean) ± SD	k	r^2
F_1	0.555 ± 0.032	0.0279	0.992
F_2	0.559 ± 0.036	0.0214	0.990
F_3	0.550 ± 0.023	0.0174	0.996
F_4	0.582 ± 0.028	0.0267	0.994
F_5	0.564 ± 0.039	0.0199	0.988
F_6	0.525 ± 0.023	0.0193	0.996
F_7	0.538 ± 0.031	0.0330	0.992
F_8	0.565 ± 0.028	0.0207	0.994
F_9	0.510 ± 0.029	0.0219	0.992
F_{10}	0.588 ± 0.025	0.0242	0.996
F_{11}	0.638 ± 0.039	0.0168	0.990
F_{12}	0.598 ± 0.025	0.0229	0.996
F_{13}	0.650 ± 0.048	0.0335	0.994
F_{14}	0.501 ± 0.030	0.0377	0.992
F_{15}	0.594 ± 0.015	0.0286	0.998

lease mechanism is dependend on relaxation rate of the polymer, diffusion rate of the drug and penetration rate of the medium [25, 26]. It was observed that when the amount of polymer was increased the "k" value increased because of the tortuosity and porosity of the tablets.

Table 2: 3^2 Factorial design

Polymer type	Polymer ratio			Sum
	1 : 0.5	1 : 1	1 : 2	
K4M	3.49	4.29	4.75	12.53
K15M	3.68	4.16	4.66	12.50
K100M	3.53	4.13	4.62	12.28
Sum	10.70	12.58	14.03	37.31

Table 3: Drug release $t_{50\%}$ values

Formula code	$t_{50\%}$ (h)
F1	3.68
F2	4.16
F3	4.66
F4	3.49
F5	4.29
F6	4.75
F7	3.53
F8	4.13
F9	4.62

Table 4: Results of variance analysis

Source of variation	Response coefficient	Sum of square	Degree of freedom	Mean square	F
Polymer ratio					
A_L	3.33	1.8482	1	1.8482	412
A_Q	−0.34	0.0103	1	0.0103	99
					2.29
Polymer type					
B_L	−0.25	0.0104	1	0.0104	
B_Q	−0.19	0.0020	1	0.0020	2.38
Interactions					
A_LB_L	−0.17	0.0048	1	0.0048	
A_LB_Q	0.39	0.0127	1	0.0127	2.83
A_QB_L	0.23	0.0044	1	0.0044	
A_QB_Q	−0.49	0.0067	1	0.0067	
Exp. error			4	0.0045	

A and B have linear and quadratic terms. These are usually designated A_L and B_L and A_Q and B_Q respectively [26].

Table 6: Dose design parameters of diltiazem*

Pharmacokinetic parameters			Estimated parameters of DTZ design		
k_a	3.1 ± 1.7	h^{-1}	τ	8	h
k_d	0.169	h^{-1}	t_d	3.02	h
$t_{1/2}$	4.1 ± 0.3	h	h	4.65	h
C_{max}	125	mg/ml	kr_0	7.84	mg/h
F	0.44		D_s	36.4	mg
V_d	3.17	l			

k_a: Absorption rate constant, k_d: Disposition rate constant, V_d: Distribution volume, C_{max}: Peak plasma concentration, $t_{1/2}$: Half-life, τ: Dose interval, F: Bioavability constant, t_d: Blood level interval, h: Release interval, kr_0: zero order release rate constant, D_s: Sustaining dose.
* Dose 90 mg DTZ

2.6. Evaluation of factorial design

The importance of polymer type and their ratios have been investigated at low medium and high viscosity levels using 3^2 factorial design (Table 2). The differences of importance between $t_{50\%}$ (Table 3) values have also been examined by variance analysis (Table 4) Table F value is 7.71 ($p < 0.05$). For the factors polymer type and polymer ratio F values have been calculated. HPMC K4M with a 1 : 0.5 ratio has been found as the most appropriate polymer.

It was concluded that polymer ratio and polymer type influence DTZ release from hydrophilic tablets ($p < 0.05$). The polymer type factor was found to be less effective than the polymer ratio.

3. Experimental

3.1. Materials

Three grades of HPMC K4M (Visc. 3500–5600 cp), K15M (Visc. 12 000 to 21 000 cp) and K100M (Visc. 80 000–120 000 cp) (Methocel products, Dow Chemicals USA) were used as hydrophilic polymers. Diltiazem HCL was kindly supplied from Mustafa Nevzat Pharm. Comp. (Turkey), Lactose (Merck, Germany), calcium dihydrogen phosphate (Merck, Germany), mannitol (BDH-U.K), Avicel (F.M.C. Comp. USA) were used as diluents. Magnesium stearate (Riedel Mannouen, Germany) was used as lubricant.

3.2. Methods

3.2.1. Interaction of diltiazem with hydrophilic polymers

Differential scanning calorimetry (DSC) was used to investigate the interactions of diltiazem with hydrophilic polymers. Diltiazem was mixed with three types of polymers in the ratios of 1 : 0.5, 1 : 1, and 1 : 2. DSC scans were recorded on a DSC apparatus (Shimadzu DT-40) equipped with a cell and nitrogen as the purging gase. Each sample was subjected to DSC at a scanning speed of 100 °C/min from 0 to 250 °C.

3.2.2. Factorial design experiments

The primary experiments were designed by a 3^2 factorial design. The effects of polymer ratio (1 : 0.5, 1 : 1, 1 : 2) and polymer type (K4M, K15M, K100M-low, medium and high viscosity levels) on drug release ($t_{50\%}$) from a hydrophilic matrix tablet were studied at three levels.

Table 5: Composition of tablets

Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
DTZ (mg)	90	90	90	90	90	90	90	90	90	90	90	90	90	90	90
K15M (mg)	45	90	180	–	–	–	–	–	–	45	45	45	22.5	45	30
K4M (mg)	–	–	–	45	90	180	–	–	–	–	–	–	–	–	–
K100M (mg)	–	–	–	–	–	–	45	90	180	–	–	–	–	–	–
Avicel (mg)	–	–	–	–	–	–	–	–	–	15	15	–	20	15	–
Mannitol (mg)	–	–	–	–	–	–	–	–	–	48.5	–	–	65.5	–	78.5
Lactose (mg)	–	–	–	–	–	–	–	–	–	–	–	63.5	–	48.5	–
Ca-dihyd. phosphate (mg)	–	–	–	–	–	–	–	–	–	–	48.5	–	–	–	–
Mg-stearat* (mg)	1.01	1.35	2.03	1.01	1.35	2.03	1.01	1.35	2.03	1.5	1.5	1.5	2	1.5	1.5

* Magnesium stearate 0.75%

3.2.3. Preparation of hydrophilic tablets

Diltiazem (90 mg) was mixed manually with HPMC in proportions of 1 : 0.5, 1 : 1 and 1 : 2, as well as with different ratios of drug to total polymer. Lactose, calcium dihydrogen phosphate, mannitol and Avicel® were used as tablet excipients. Tablets were compressed by a flat-faced punch (diameter 11 mm pressure force 200 kg/cm^2). Tablet formulations are shown in Table 5. The physico-pharmaceutical parameters (average weight, thickness, hardness friability) were also determined. The data were found to be in requirement limits.

3.2.4. In vitro release studied

Drug release studies were performed with the USP 23 paddle method using three different pH media at 75 rpm and 37 °C. The dissolution media were pH 1.2, 4.0, and 7.4 for 1, 2, and 5 h, respectively. At appropriate intervals samples were withdrawn and assayed spectrophotometrically at 236 nm. The experiments were done in triplicate.

3.2.5. Assessment of release kinetics

The release kinetics and mechanism of all formulations have been evaluated, according to *in vitro* release data. A program (DISSOL) written for this purpose was employed [24]. The data were tested according to four different release kinetics (zero order, first order, $Q \rightarrow \sqrt{t}$, Hixson Crowell). The following semiempirical equation was also used to investigate the mechanism of release drug from the hydrophilic matrix [25]:

$$M_t/M_\infty = kt^n$$

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 tablet, and n is the release exponent, indicative of the mechanism of drug release.

3.2.6. Ploting of the target profile

On the basis of the pharmacokinetic parameters of DTZ (Table 6) [27–30] the required release rate of the drug was calculated as Ds = 36.4 mg and k_{r0} = 7.84 mg/h, respectively. Dose design parameters of diltiazem are shown in Table 6. But, the sustaining dose of diltiazem was selected as 90 mg in this study, because this dose provides a therapeutic blood level for 8 h. Therefore, k_{r0} value was calculated two and half time of 7.84 mg/h and the target profile was plotted.

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Prof. Dr. Nevin Çelebi
Gazi University
Faculty of Pharmacy
Department of Pharmaceutical Technology
Etiler-06330 Ankara
Turkey
nevin@tr.net.net.tr