

Formulation development and evaluation of Diltiazem HCl sustained release matrix tablets using HPMC K4M and K100M

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Abstract: The aim of this study was to develop a sustained release hydrophilic matrix tablet of Diltiazem HCl and evaluates the effect of formulation variables (e.g. lubricant, binder, polymer content and viscosity grades of HPMC) on drug release. Twelve different formulations (F1-F12) were prepared by direct compression. The results of the physical parameters and assay were found to be within the acceptable range. Rate of drug release was found to be slow as the fraction of the polymer was increased from 20-50%. The drug release rate from tablets containing K4M was effectively controlled by increasing the talc concentration, whereas the burst effect was reduced by increasing binder content. The drug release was higher with K4M as compare to K100M. Model-dependent and independent methods were used for data analysis and the best results were observed for K4M in Higuchi ($R^2=0.9903-0.9962$) and K100M in Baker and Lonsdale ($R^2=0.9779-0.9941$). The release mechanism of all formulations was non-Fickian. F7 (50% K4M, 2% talc, 10% Avicel PH101) and F11 (40% K100M) were very close to targeted release profile. F12 (50% K100M) exhibited highest degree of swelling and lowest erosion. The f_1 and f_2 test were performed taking F11 as a reference formulation.

Keywords: Diltiazem HCl, Hydroxypropyl methylcellulose (HPMC), Sustained release, Hydrophilic matrix tablets

INTRODUCTION

Sustained release (SR) oral drug delivery systems are effective for maintaining optimal concentration of drugs with narrow therapeutic range and short elimination half-life. In SR products plasma drug levels are achieved by immediate release of initial dose which is then sustained by maintenance dose for a predetermined time (Savaser *et al.*, 2005). For matrix tablets preparation, direct compression method still appears to be an efficient and cost effective technique and has many advantages over other methods, like less process validation steps, ease of fabrication and scaling up. However, in spite of the major advantages pre-formulation studies are necessary to achieve the appropriate targeted drug release profile (Ceballos *et al.*, 2005).

Hydroxypropyl methylcellulose (HPMC) is one of the widely used hydrophilic polymers for oral controlled drug delivery system because of its gel forming property, non-toxicity (Ebube and Jones, 2004), ease of compression, greater drug loading tendency (Fu *et al.*, 2004), pH independent solubility and flexibility to obtain desirable drug release profile (Alderman, 1984).

Diltiazem HCl is extensively used either alone or in combination therapy to treat hypertension, atrial fibrillation and flutter, paroxysmal supraventricular tachycardia and for the treatment of stable and unstable angina pectoris (Gal and Nussinovitch, 2007). It has short half-life of 2-3 h and bioavailability of 33-44% as only

40% of the oral dose reaches to systemic circulation in an unchanged form, mainly because of hepatic metabolism. The usual oral regimen is 30mg four times daily. Pharmacokinetic features of Diltiazem HCl make it a potential candidate for extended release once-a-day dosage form (Gal and Nussinovitch, 2007; Gondaliya and Pundarikakshudu, 2003).

The objective of the present study was to develop a sustained release formulation of Diltiazem HCl using two viscosity grades of HPMC i.e. K4M and K100M that presents significant challenges due to the hydrophilic nature of both drug and polymer. The influence of co-excipients, microcrystalline cellulose (MCC) and talc on in vitro release profiles was also studied to obtain an optimized formulation with acceptable physical and chemical characteristics. The release behavior was studied in relation to their swelling and erosion to investigate the relationship between their drug release profiles. Various kinetic models were also used to evaluate the release kinetics.

MATERIALS AND METHODS

Materials

Diltiazem HCl was kindly gifted by Novartis Pharma (Pak) Ltd. HPMC K4M (Methocel Premium) was purchased by Dow Chemical, USA whereas K100M was supplied by Colorcon, USA. Microcrystalline cellulose (Avicel PH-101) was obtained by FMC Corporation, USA, and talc was purchased from the BDH laboratory suppliers, England.

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Methods

Preparation of matrix tablets

The amount of Diltiazem HCl in each matrix tablet was kept constant at 90mg while the excipients and their quantities used for trial formulations are given in table 1. HPMC was used in concentrations ranging from 20-50%. Drug and selected pharmaceutical excipients were passed through ASTM (American Society of Testing and Materials) 100 mesh sieve, and their accurately weighed quantities were mixed thoroughly together by following geometric dilution method in a suitable size poly-bag through tumbling action. The powders blend was then compressed directly by single punch compression machine (KORSCII Erweka, Frankfurt Germany) at target weights given in table 1. Following are the pre-formulation tests performed to assess the physical characteristics of powder blends before compression.

Micromeritic of tablet blends

Bulk density (BD), tapped density (TD), compressibility index (CI), Hausner ratio (HR) and angle of repose (α) of all the powder samples from each formulation were determined with the help of following formulae (USP, 2006). The results are expressed in table 2.

$$BD = \frac{\text{Weight of the powder (M)}}{\text{Bulk Volume (V}_o\text{)}} \quad \text{Eq. 1}$$

$$TD = \frac{\text{Weight of the powder (M)}}{\text{Tapped Volume (Vf)}} \quad \text{Eq. 2}$$

$$CI = \left(\frac{V_o - Vf}{V_o} \right) \times 100 \quad \text{Eq. 3}$$

$$HR = \frac{V_o}{Vf} \quad \text{Eq. 4}$$

$$\tan(\alpha) = \frac{\text{height}}{0.5 \text{ base}} \quad \text{Eq. 5}$$

Physical evaluation of tablets

Twenty tablets from each formulation were tested for physical parameters including weight (Mettler Toledo B204-S), thickness (Seiko Brand, 0 to 150mm), diameter (Seiko Brand, 0 to 150mm), hardness variation (OSK Fujiwara, Ogawa Seiki Co. Ltd., Tokyo, Japan), and friability (Erweka GmbH D-63150, Husenstamm, Germany) according to the official pharmacopoeial methods (USP, 2006; BP, 2007).

Assay of Diltiazem HCl matrix tablets

Randomly twenty selected tablets of each batch were pulverized and quantity equivalent to mean weight was utilized to prepare sample solution of 24 μ g/ml strength in mobile phase having composition of Acetonitrile, Methanol, 0.04 M Ammonium Acetate in the ratio of 24: 40: 36 with 0.04 % Triethanolamine at pH 7.3 (adjusted with glacial acetic acid). Sonicated and filtered solution was then injected and signals were detected at 237nm. Assay was performed on HPLC (LC-10AT VP, No.C20973806986 LP, Shimadzu Corporation, Kyoto,

Japan) using column: 250cm x 4.6mm (5 μ m packing Ultrasphere-ODS C18). Each determination was carried out in triplicate (Lunn, 1997).

In vitro drug release studies

The release characteristics of Diltiazem HCl from matrix tablets were determined according to the official method using a six station USP Apparatus-II at 100rpm (Erweka DT600, Husenstamm, Germany) (USP, 2006). The test employed 900 ml of distilled water maintained at 37 \pm 0.5 $^{\circ}$ C as a dissolution medium. Dissolution samples of 10 ml were drawn at every 1-hour interval during a 24 hour time period and volumes were immediately replenished with fresh medium to maintain the sink condition or to keep the volume constant. Collected samples were filtered through 0.45 μ m millipore filters and then diluted to appropriate concentration. Samples were analyzed on spectrophotometer (UV-1800, Double beam Spectrophotometer, No.A11454500172CD, Shimadzu Corporation, Kyoto, Japan) at 237 nm. Cumulative percentage of drug released was calculated and plotted versus time (hours). The mean for six tablets was used for analysis. The adapted target profile design parameters of a SR product for Diltiazem HCl were as follow: (USP, 2006)

- After 1 h: % 5-20.
- After 4 h: % 30-50.
- After 10 h: % 70-90.
- After 15 h: % NLT 80.

Swelling and erosion kinetics

USP apparatus I (Erweka DT600, Husenstamm, Germany) with 900 ml of swelling medium (distilled water) at 100 rpm and 37 $^{\circ}$ C \pm 0.5 $^{\circ}$ C was used to determine swelling and erosion kinetics. Three different samples were subjected to the procedure for which initial, wet and dry weights of the tablets were determined at different time points 0, 4, 6 and 8 h. Degree of swelling (%) (Cao *et al.*, 2005), water uptake (%), weight loss or erosion % were studied (Efentakis *et al.*, 2000; Wada *et al.*, 1995).

Diltiazem HCl release kinetics

Model-Dependent methods

The release kinetics of the drug was described by fitting the data obtained from in-vitro drug release in various kinetic models such as Zero order, First order, Higuchi's model, Hixson and Crowell model, Baker and Lonsdale model and Jander's equation model.

Zero-order kinetic model

The zero-order kinetic describes the systems as a one in which the drug-release rate is independent of its concentration (Singh *et al.*, 1967).

$$Q_t = K_0 t \quad \text{Eq. 6}$$

Where, Q_t is the amount of drug released in time t , K_0 is the release rate constant for zero-order, t is the time in hours.

First-order kinetic model

According to first-order kinetic rate of release is concentration dependent (Desai *et al.*, 1965; Singh *et al.*, 1967).

$$\log Q_t = \log Q_o + K_1 t / 2.303 \quad \text{Eq. 7}$$

Where, Q_t is the amount of drug released in time t , Q_o is the initial amount of the drug in the tablet, K_1 is the first order release constant, t is the time in hours.

Higuchi kinetic model

Higuchi kinetic model explains release of drugs from an insoluble matrix as a square root of time dependent process based on Fickian diffusion (Higuchi, 1963).

$$Q_t = K_H t^{1/2} \quad \text{Eq. 8}$$

Where, Q_t is the amount of drug released in time t , K_H is the release rate constant for Higuchi model, $t^{1/2}$ is the square root of time.

Hixson-Crowell cube root model

The Hixson-Crowell cube root law describes the drug release from systems in which there is a change in the surface area and the diameter of the particles present in the tablet (Hixson and Crowell, 1931).

$$\sqrt[3]{Q_o} - \sqrt[3]{Q_t} = K_{HC} t \quad \text{Eq. 9}$$

Where, Q_o is the initial amount of the drug in the tablet, Q_t is the amount of the drug released in time t , K_{HC} is the release rate constant for Hixson-Crowell cube root model, t is the time in hours.

Baker-Lonsdale kinetic model

When a system consisting of a drug dispersed homogeneously or heterogeneously within a spherical diffusion rate-limiting matrix, the drug release can be satisfactorily modeled to the following equation: (Baker and Lonsdale, 1974)

$$3/2[1 - (1 - M_t / M_\infty)^{2/3}] - M_t / M_\infty = K_{BL} t \quad \text{Eq. 10}$$

Where, M_t is the amount of drug released in time t , M_∞ is the amount at infinite time, K_{BL} is the release rate constant for Baker and Lonsdale model, t is the time in hours.

Jander's equation model

This model considers the change in the interfacial area where the actual release of a solid drug from microspheres (which do not change in shape during drug release) occurs by diffusion within the micromatrix (Jander, 1927)

$$1 - (1 - M_t / M_\infty)^{1/3} = K_J t^{1/2} \quad \text{Eq. 11}$$

Where, M_t is the amount of drug released in time t , M_∞ is the amount at infinite time, K_J is the Jander's release rate constant, $t^{1/2}$ is the square root of time.

Mechanism of drug release

The mechanism of drug release from Diltiazem HCl SR formulations was evaluated by plotting the first 60% drug release data of each formulation in Korsmeyer-Peppas equation (Eq. 12) and exponent "n" was calculated through slope of the straight line.

$$M_t / M_\infty = K t^n \quad \text{Eq. 12}$$

Where, M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, n is an exponent which characterizes the different release mechanisms (Korsmeyer *et al.*, 1983).

Mean dissolution time

The drug release was characterized by calculating the mean dissolution time (MDT) for each formulation from dissolution data according to equation (Eq. 13) using n and K values derived from Eq. (12) (Mockel and Lippold, 1993).

$$MDT = (n / n + 1) k^{-1/n} \quad \text{Eq. 13}$$

Dissolution profile comparison**Model-Independent methods**

Difference in dissolution profiles was compared using similarity factor (f_2) and difference factor (f_1). The difference and similarity factor were calculated using the following equation (Eq. 14) and (Eq. 15) respectively:

$$f_1 = \left[\frac{\sum_{t=1}^n (R_t - T_t)}{\sum_{t=1}^n R_t} \right] \times 100 \quad \text{Eq. 14}$$

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad \text{Eq. 15}$$

Where, R_t is the amount of drug released from the reference formulation at each time point, T_t is the amount of drug released from the test formulation at each time point, n is the number of dissolution sample time, The release profiles are significantly different if $f_1 > 15$ and $f_2 < 50$ (Manikandan *et al.*, 2012).

RESULTS

Diltiazem Hydrochloride is a slow calcium channel blocker that blocks calcium ion influx during depolarization of cardiovascular smooth muscles. Its pharmacokinetic evidences presented it to be a good candidate for designing sustained release formulation. For this purpose different trial formulations were prepared by using HPMC K4M, K100M, and variable strengths of lubricant (talc) and binder (Avicel PH101). Bulk density, tapped density, compressibility index, hausner ratio and angle of repose of each trial formulation are presented in

table 2. Physical properties and percentage assay of Diltiazem HCl SR formulations are presented in table 3. Effect of the HPMC K4M and K100M concentration on the Diltiazem HCl release is shown in fig.1 and 4 respectively whereas, the effect of lubricant and binder concentration on Diltiazem HCl release is presented in fig 2 and 3 respectively. The different viscosity grades and their comparative release profiles are illustrated in fig. 5 (20%K4M & K100M), fig. 6 (30% K4M & K100M), fig.7 (40% K4M & K100M) and fig. 8 (50%K4M & K100M). Fig. 9 and 10 show the percent degree of swelling and water uptake of F-6 (8% binder), F-7 (10% binder) and F-8 (12% binder) containing equal proportions of HPMC K4M (50%) and lubricant (2%) but different binder (Avicel PH101) concentrations. Fig. 11 and 12 show percent degree of swelling and water uptake of F-10 (30% K100M), F-11 (40% K100M) and F-12 (50% K100M). Fig. 13 shows the percent erosion of F-6 (8% binder), F-7 (10% binder) and F-8 (12% binder). Fig. 14 shows percent erosion of F-10 (30% K100M), F-11 (40% K100M) and F-12 (50% K100M).

The in vitro release data obtained were fitted into various mathematical kinetic models (zero-order, first-order, Higuchi's equation, Hixson-Crowell, Baker and Lonsdale, and Jander's equation) in order to assess the kinetics of the drug release from Diltiazem HCl SR formulations. The most appropriate model was selected on the basis of the best goodness of fit. Correlations of individual formulation are given in table 4. The release rates were calculated from the slope of the plots and coefficient of correlation were determined. Release profiles of Diltiazem HCl from optimized formulation of HPMC K4M in comparison to K100M are illustrated in fig. 15. Similarity (f_2) and differential factor (f_1) values of HPMC matrix tablets compared with optimized tablet formulation F-11 is presented in table 5.

DISCUSSION

Micromeritics of tablet blends

Blends of each trial formulation were evaluated for bulk density, tapped density, compressibility index, hausner ratio and angle of repose (table 2) to obtain optimum flow and reproducible tablets with acceptable content uniformity. These parameters were found within the prescribed limits (USP, 2006) and no significant difference was observed between both the viscosity grades of HPMC (K4M & K100M). Similar results were also observed by Mandal and Pal (2008), who evaluated the flow properties of metformin sustained-release granules by using different viscosity grades of HPMC (K4M, K15M and K100M).

Physical evaluation of tablets

All the batches of HPMC K4M and K100M complied with the pharmacopoeial limits of weight, thickness and diameter (table 3). Crushing strength and % friability of

all the formulations were within acceptable limits indicating that the tablets had the capability to withstand shock and attrition during storage, transportation and consumption (BP, 2007).

Assay of Diltiazem HCl SR formulations

All the batches were analyzed and the percent content of Diltiazem HCl in the compressed tablets were found within 90-110% of the claim (90 mg / tablet) with relative standard deviation less than 2% (table 3).

Drug release characteristics

An ideal extended release formulation releases the required quantity of drug with predetermined kinetics to maintain effective drug plasma concentration. In present study the effect of various formulation factors like polymer concentration, polymer grades, and additives were observed to achieve the predetermined release profile. Similar trials were indicated by Saravanan *et al.* (2003).

Effect of HPMC K4M concentration

In present study HPMC K4M was used in the range of 20-50% in formulations F-1 to F-5 (table 1). Cumulative % release of Diltiazem HCl vs. time of F-1 to F-5 up to 15 h (fig. 1) shows inverse relationship. A similar trend was also studied by Coa *et al.* (2005), who reported that the viscous gel layer of HPMC not only increases the diffusion path length but also increases the resistance to diffusion. In the current study the maximum amount (50%) of HPMC K4M failed to control the drug release as per USP target profile (USP, 2006). F-1 and F-2 released 98% and 96% drug in 7h and 9h respectively. Although, 99% drug released was observed within 15 hours for F-3, F-4 and F-5. Tiwari *et al.* (2003) also observed faster dissolution of highly water soluble drug from hydrophilic matrix. Similar findings were also reported by Mehargan and Mortazavi (2005), who investigated the release pattern of Diltiazem HCl in the presence of 35%-45% HPMC K4M.

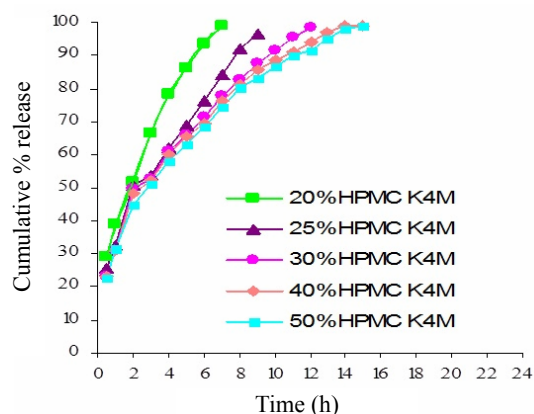


Fig. 1: *In vitro* release profiles showing effect of the polymer concentration on the diltiazem HCl release from HPMC K4M matrix tablets containing 20% (F-1), 25% (F-2), 30% (F-3), 40% (F-4) & 50% (F-5) HPMC K4M.

Effect of lubricant and binder concentration

Pharmaceutical excipients like lubricant and binder altered the rate of drug release so must be selected appropriately. When the amount of lubricant (talc) was increased up to 2% in F-6 containing HPMC K4M, an unusual reduction in the *in vitro* drug release was observed (fig. 2). Talc served as physical barrier hence, slowed down the release of drug from the matrix tablets (Gal and Nussinovich, 2007). However the burst effect was observed in the same formulation, which is then modified by increasing the amount of binder (Avicel PH 101) to form F-7 and F-8 containing 10% and 12% respectively. The release pattern of F-7 and F-8 is exhibited by fig. 3, which shows that the burst effect was not desirably controlled, however a slight reduction in overall drug release was observed, may be due to water insoluble nature of micro crystalline cellulose. Nerurker *et al.* (2005) also reported that the release of ibuprofen reduced when microcrystalline cellulose was incorporated in formulation.

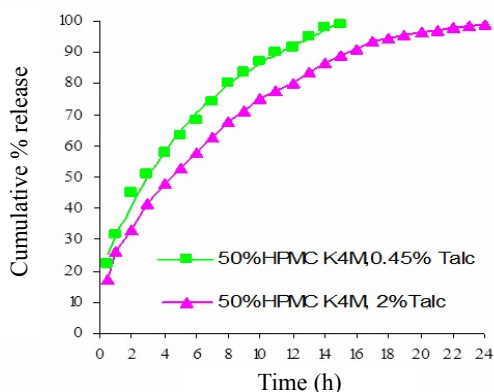


Fig. 2: *In vitro* release profiles showing effect of the lubricant (talc) concentration on diltiazem HCl release from HPMC K4M matrix tablets containing 0.45% (F-5) & 2% (F-6) talc.

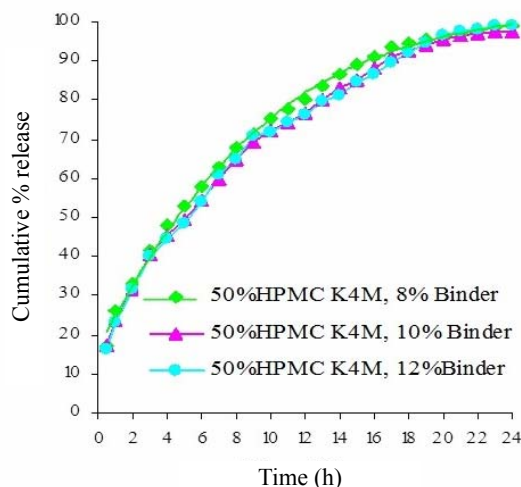


Fig. 3: *In vitro* release profiles showing effect of the binder concentration (MCC) on diltiazem HCl release from HPMC K4M matrix tablets containing 8% (F-6), 10% (F-7) & 12% (F-8) MCC.

Effect of HPMC K100M concentration

Formulations F-9 to F-12 was composed of HPMC K100M in the concentration range of 20-50%. F-9 (20%) and F-10 (30%) failed to control the drug release for 24 hours and showed 99% drug release within 15 h and 18 h respectively (fig. 4). The drug release was successfully sustained by F-11 up to 24 h containing 40% polymer. F-12 (50% HPMC K100M) showed only 76% drug release at 15h. However, Tiwari *et al.* (2003) reported that release of a highly water soluble drug Tramadol HCl was not significantly prolonged by increasing concentration of HPMC K100M.

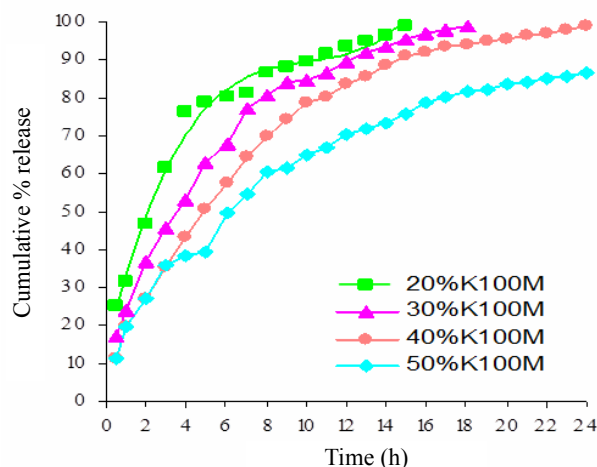


Fig. 4: *In vitro* release profiles showing effect of the polymer concentration on the diltiazem HCl release from HPMC K100M matrix tablets containing 20% (F-9), 30% (F-10), 40% (F-11) & 50% (F-12) HPMC K100M.

Comparison of HPMC K4M and K100M

In this study the influence of two different viscosity grades of HPMC on Diltiazem HCl release was compared. Fig. 5 shows 99% drug release at 7 h by F-1 (20%K4M) and at 15 h by F-9 (20% K100M). The comparison of drug release of F-3 and F-10 is shown in fig 6, indicating 99% drug release at 12 h for F-3 and at 18 h for F-10 containing 30% K4M and K100M respectively, whereas drug release comparison of F-4 (40% K4M) and F-11 (40% K100M) is presented in fig. 7, showing 99% drug release at 15 h by F-4, however, F-11 remarkably followed the targeted drug release profile and sustained 99% drug release for 24 h. Fig. 8 demonstrates that F-12 containing higher concentration of HPMC K100M (50%) released only 86% drug over a period of 24 h, however same concentration of K4M released 99% drug in 15 h. This type of dissimilarity in drug release profile was also reported by Gafourian *et al.* (2007), who studied the effect of HPMC K4M and E4M on release pattern of different drugs. However, Mandal and Pal (2008) reported no significant difference in the release profile of metformin from the matrix tablets composed of K4M, K15M and K100M.

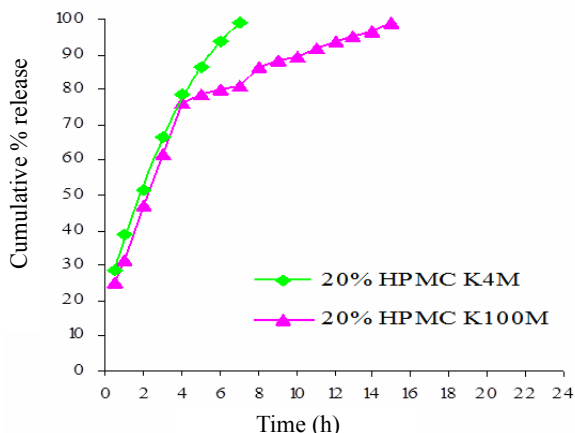


Fig. 5: Release profiles of diltiazem HCl from 20% HPMC K4M (F-1) matrix tablets in comparison to 20% HPMC K100M (F-9) matrix tablets.

Swelling

The swelling behavior of different polymer grades of HPMC was analyzed to compare their water uptake capacity. Swelling of the matrix, as indicated by the transition of the polymer from the glassy to the rubbery state, is an important parameter in the determination of the release characteristics of the matrix system (Ebube and Jones, 2004). Both the viscosity grades of HPMC created a highly viscous gel when contacted with the medium especially in case of HPMC K100M. Liquid uptake and swelling of HPMC K4M was achieved rapidly and then gradually increased with the passage of time. The percent degree of swelling was slightly greater for F-8 (12% binder) than F-7 (10% binder) and F-6 (8% binder) as shown in fig. 9. However, water uptake of F-6 (8% binder) was greater than F-7 (10% binder) and F-8 (12% binder) as shown in fig. 10.

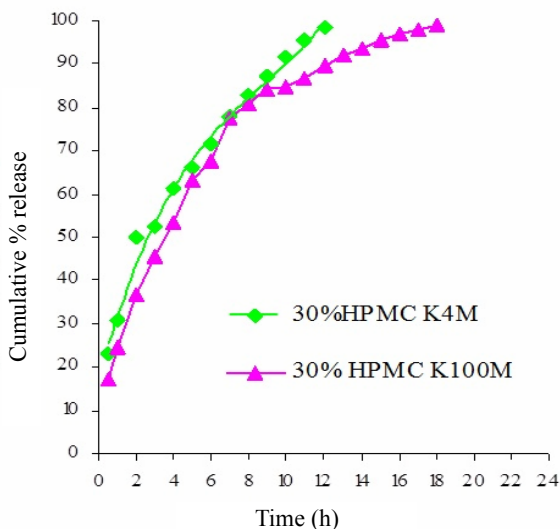


Fig. 6: Release profiles of diltiazem HCl from 30% HPMC K4M (F-3) matrix tablets in comparison to 30% HPMC K100M (F-10) matrix tablets.

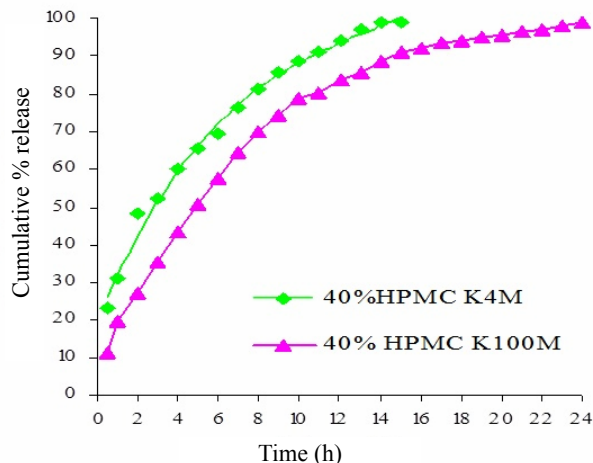


Fig. 7: Release profiles of diltiazem HCl from 40% HPMC K4M (F-4) matrix tablets in comparison to 40% HPMC K100M (F-11) matrix tablets.

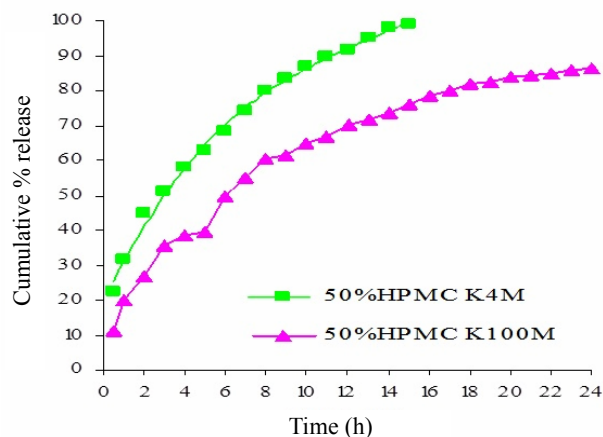


Fig. 8: Release profiles of diltiazem HCl from 50% HPMC K4M (F-5) matrix tablets in comparison to 50% HPMC K100M (F-12) matrix tablets.

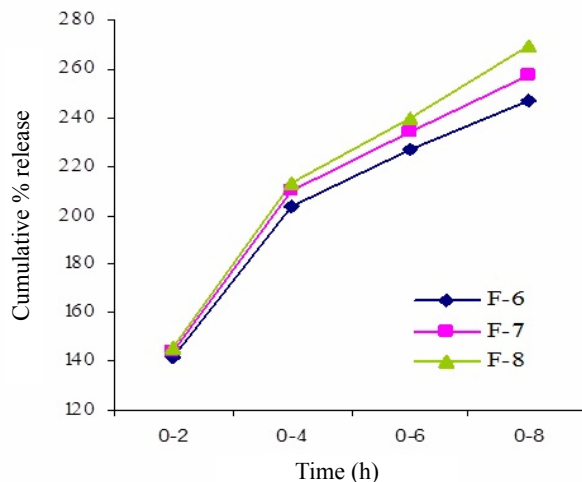


Fig. 9: Percentage degree of swelling of HPMC K4M matrix tablets containing 8% MCC (F-6), 10% MCC (F-7) & 12% MCC (F-8).

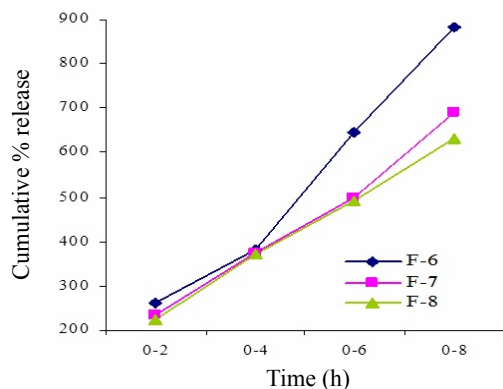


Fig. 10: Percentage water uptake of HPMC K4M matrix tablets containing 8% MCC (F-6), 10% MCC (F-7) & 12% MCC (F-8).

The formulations containing HPMC K100M exhibited a more distinctive swelling behavior than formulations containing HPMC K4M. The degree of swelling increased as the polymer concentration increased. The highest

degree of hydration and weight gained was achieved by F-12 (50% K100M) indicating the maximum ability to absorb and retain a larger amount of liquid (fig. 11). Fig. 12 shows water uptake decreases as the concentration of polymer increases.

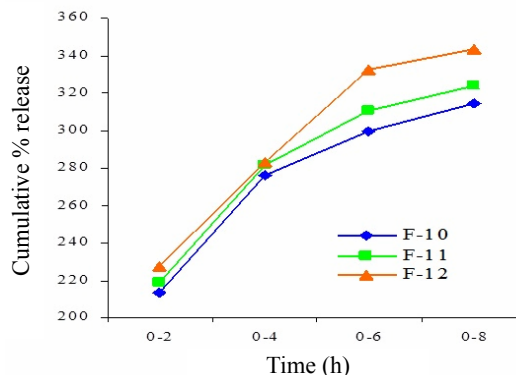


Fig. 11: Percentage degree of swelling of HPMC K100M matrix tablets containing 30% (F-10), 40% (F-11) & 50% (F-12) HPMC K100M.

Table 1: Composition of 90 mg Diltiazem HCl loaded matrix tablets

Formulation Code	HPMC K4M		HPMC K100M		AVICEL PH-101		TALC		Total Wt. of Tablets (mg)
	Qty./Tab	% Comp.	Qty./Tab	% Comp.	Qty./Tab	% Comp.	Qty./Tab	% Comp.	
	mg	%	mg	%	mg	%	mg	%	
F-1	30	21.28	-	-	20	14.18	1	0.71	141
F-2	40	26.50	-	-	20	13.24	1	0.66	151
F-3	50	31.06	-	-	20	12.42	1	0.62	161
F-4	75	40.32	-	-	20	10.75	1	0.54	186
F-5	112	50.22	-	-	20	8.97	1	0.45	223
F-6	115	50.00	-	-	20	8.70	5	2.17	230
F-7	120	50.00	-	-	25	10.42	5	2.08	240
F-8	125	50.00	-	-	30	12.00	5	2.00	250
F-9	-	-	30	20.69	24	16.55	1	0.69	145
F-10	-	-	50	30.30	24	14.55	1	0.61	165
F-11	-	-	77	40.10	24	12.50	1	0.52	192
F-12	-	-	115	50.00	24	10.44	1	0.43	230

Table 2: Micromeritics properties of formulation blends

Code	Bulk density g/ml	Tapped density g/ml	Compressibility index %	Hausner-ratio	Angle of repose degrees
F-1	0.32 ± 0.02	0.37 ± 0.04	14.29 ± 0.02	1.17 ± 0.03	31.00 ± 0.02
F-2	0.31 ± 0.03	0.37 ± 0.03	14.84 ± 0.03	1.17 ± 0.02	33.00 ± 0.02
F-3	0.31 ± 0.04	0.36 ± 0.02	15.38 ± 0.03	1.18 ± 0.03	32.00 ± 0.01
F-4	0.31 ± 0.03	0.36 ± 0.04	14.62 ± 0.02	1.17 ± 0.03	32.00 ± 0.02
F-5	0.30 ± 0.02	0.36 ± 0.06	15.15 ± 0.03	1.18 ± 0.04	31.00 ± 0.03
F-6	0.31 ± 0.02	0.35 ± 0.02	12.98 ± 0.04	1.15 ± 0.02	30.00 ± 0.01
F-7	0.30 ± 0.03	0.35 ± 0.03	13.64 ± 0.04	1.16 ± 0.04	32.00 ± 0.03
F-8	0.31 ± 0.02	0.36 ± 0.02	13.85 ± 0.03	1.16 ± 0.03	32.86 ± 0.02
F-9	0.32 ± 0.04	0.37 ± 0.04	14.29 ± 0.02	1.17 ± 0.02	31.00 ± 0.04
F-10	0.31 ± 0.02	0.37 ± 0.03	14.84 ± 0.03	1.17 ± 0.04	33.00 ± 0.02
F-11	0.31 ± 0.03	0.36 ± 0.04	14.73 ± 0.04	1.17 ± 0.02	32.00 ± 0.03
F-12	0.31 ± 0.02	0.36 ± 0.02	15.38 ± 0.03	1.18 ± 0.03	31.00 ± 0.02

Table 3: Physical properties and percentage assay of diltiazem HCl SR formulations

Code	Weight		Thickness		Diameter		Hardness		Friability	Assay	
	(mg)		(mm)		(mm)		(Kg)		(%)	(%)	
	n=20										
	Avg	SD	Avg	SD	Avg	SD	Avg	SD	Avg	Avg	RSD
F- 1	141.43	0.65	2.10	0.01	8.54	0.02	7.82	0.53	0.73	93.75	1.07
F- 2	151.42	0.76	2.16	0.02	8.52	0.03	8.59	0.94	0.34	92.77	0.14
F- 3	161.26	0.70	2.27	0.02	8.52	0.03	9.29	0.39	0.71	92.12	0.04
F- 4	186.36	0.56	2.59	0.03	8.41	0.02	10.20	0.49	0.54	96.90	0.01
F- 5	223.27	0.47	3.21	0.03	8.44	0.02	11.06	0.55	0.79	91.44	0.39
F- 6	230.09	0.59	3.26	0.03	8.51	0.04	12.10	0.61	0.48	91.08	0.59
F- 7	240.38	0.58	3.46	0.03	8.55	0.02	13.02	0.48	0.38	99.70	0.90
F- 8	250.27	0.48	3.56	0.03	8.55	0.01	14.09	0.61	0.34	93.17	0.40
F- 9	145.27	0.63	2.07	0.02	8.55	0.00	9.14	0.65	0.53	93.41	0.27
F- 10	165.21	0.58	2.33	0.02	8.55	0.01	12.40	0.50	0.32	91.79	1.13
F- 11	192.17	0.58	2.69	0.02	8.62	0.05	15.07	0.64	0.21	98.08	1.93
F- 12	230.13	0.84	3.11	0.03	8.41	0.02	18.03	2.29	0.25	96.33	0.59

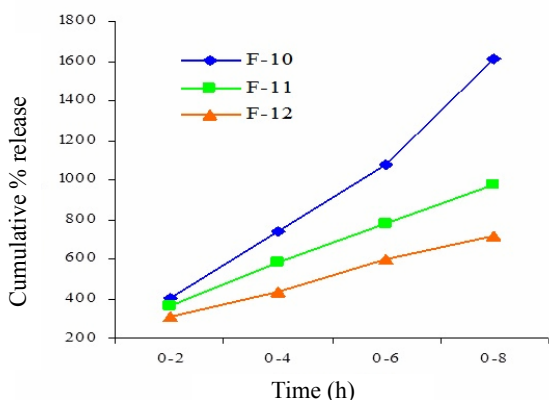


Fig. 12: Percentage water uptake of HPMC K100M matrix tablets containing 30% (F-10), 40% (F-11) & 50% (F-12) HPMC K100M.

Erosion

The percent degree of erosion was greater for F-6 (8% binder) than F-7 (10% binder) and F-8 (12% binder) indicating that the percent erosion decreased with increase in binder concentration as shown in fig. 13.

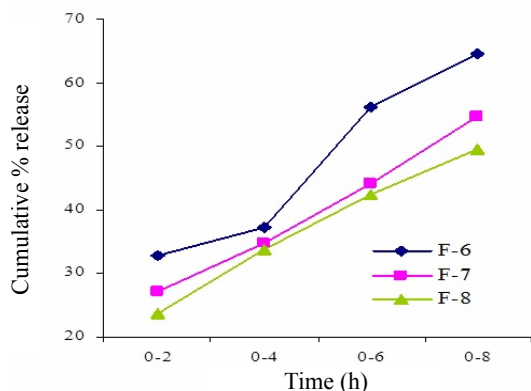


Fig. 13: Erosion kinetics of HPMC K4M matrix tablets containing 8% MCC (F-6), 10% MCC (F-7) & 12% MCC (F-8).

The formulations containing HPMC K100M showed limited erosion than formulations containing HPMC K4M. The percent erosion decreased as the polymer concentration increased. Therefore the lowest percent erosion was achieved by F-12 (50% K100M) (fig. 14).

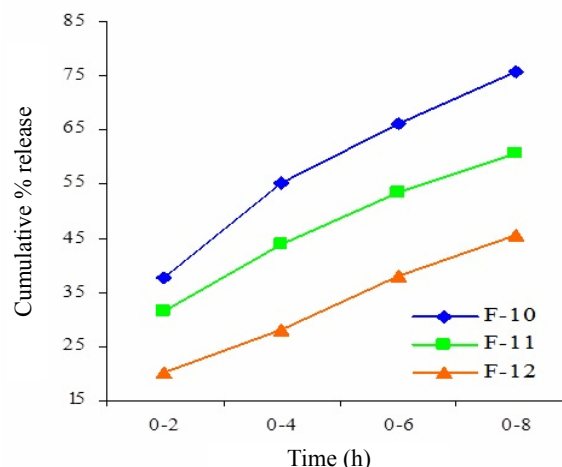


Fig. 14: Erosion kinetics of HPMC K100M matrix tablets containing 30% (F-10), 40% (F-11) & 50% (F-12) HPMC K100M.

Diltiazem HCl release kinetics

The curvilinear nature of the cumulative % drug released versus time plots suggested that none of the formulations follow zero order kinetics which was confirmed by poor correlation coefficients in all the cases. Similarly poor correlations of the data for all the formulations except F-12 ($R^2=0.9901$), suggested non-applicability of First-order kinetic model (table 4).

A linear relationship was obtained for formulations F-1 to F-8 (HPMC K4M) when applied to the Higuchi's kinetic equation (Eq. 8) (R^2 ranged from 0.9903-0.9962). The value of R^2 obtained from Hixson Crowell's equation (Eq.

9) of all formulations ranges from 0.9557 to 0.9981 indicating change of surface area and diameter with the progressive dissolution of the matrix as a function of time. The in vitro release of formulations F-9 to F-12 (HPMC K100M) was best explained by Baker and Lonsdale model (Eq. 10) with highest linearity ($R^2=0.9779-0.9941$). The dissolution data was also plotted in accordance with Jander's equation model (Eq. 11) and linear relationship was obtained for formulations F-9 to F-12 (R^2 ranged from 0.9746-0.9927) indicating no change in the shape of the tablets during the process of dissolution.

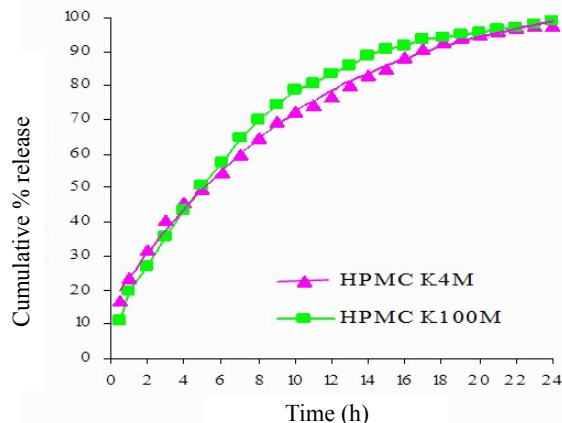


Fig. 15: Release profiles of diltiazem HCl from optimized formulation of HPMC K4M containing 50% HPMC K4M, 2% talc and 10% MCC (F-7) in comparison to HPMC K100M containing 40% HPMC K100M (F-11).

The release constants (table 4) are higher for the higher drug mass fraction and lower for the higher weight ratio of cellulosic-hydrophilic component. Therefore, continuous barrier with increased thickness of cellulosic polymer, surrounding the drug particles upon matrix hydration and/or erosion was developed, resulted in decreased diffusion rate of the dissolved drug and consequently in reduced release rate (Kiortsis *et al.*, 2005).

Concerning the effect of cellulosic polymer grades, lower release constants (table 4) were observed in HPMC K100M as compare to HPMC K4M. This greater reduction was due to the retarded hydration, greater swelling and slower erosion of the K100M matrix.

Drug release mechanism

First 60% of the in-vitro release data were applied in Korsmeyer-Peppas equation (Eq. 12) to find out the mechanism of drug release (Savaser *et al.*, 2005). As observed from table 4 the correlation co-efficient for all the formulations were high (R^2 ranged from 0.9549-0.9973) enough to evaluate the drug dissolution behavior by Eq. 12. The release exponent (n), kinetic rate constant (k) and mean dissolution time (MDT) as calculated from Eq. 12 and Eq. 13 are presented in table 4.

Table 4: Kinetic parameters for dissolution data of different diltiazem HCl SR formulations according to various kinetic models

Code	Zero order		First order		Higuchi model		Hixson-Crowell model		Baker and Lonsdale model		Jander's equation model		Korsmeyer-Peppas model			MDT
	R^2	$K_0(h^{-1})$	R^2	$K_1(h^{-1})$	R^2	$K_H(h^{-1/2})$	R^2	$K_{HC}(h^{-1})$	R^2	$K_{BL}(h^{-1})$	R^2	$K_J(h^{-1/2})$	R^2	$K_{KP}(h^{-n})$	n	
F-1	0.9702	10.8620	0.9697	0.4924	0.9962	37.4240	0.9789	0.4547	0.9615	0.0401	0.9195	0.3321	0.9961	0.303	0.6081	2.694
F-2	0.9777	8.0397	0.9069	0.2901	0.9907	30.6680	0.9638	0.2831	0.9316	0.0325	0.9051	0.2337	0.9902	0.2788	0.5764	3.353
F-3	0.9501	6.1039	0.9036	0.2893	0.9937	26.9260	0.9797	0.2411	0.9604	0.0306	0.9255	0.2149	0.9927	0.2829	0.5015	4.142
F-4	0.9247	4.9605	0.9300	0.2674	0.9903	24.5640	0.9923	0.2176	0.9837	0.0321	0.9473	0.2164	0.9965	0.2354	0.5303	5.299
F-5	0.9344	4.9109	0.9200	0.2471	0.9935	24.2300	0.9895	0.2058	0.9791	0.0309	0.9421	0.2065	0.9973	0.2467	0.5124	5.204
F-6	0.9008	3.2021	0.9722	0.2406	0.9820	20.0430	0.9981	0.1395	0.9925	0.0266	0.9676	0.1993	0.9933	0.1957	0.5101	8.27
F-7	0.9214	3.2791	0.9469	0.2407	0.9900	20.3760	0.9963	0.1410	0.9846	0.0228	0.9502	0.1902	0.9966	0.152	0.5896	9.055
F-8	0.9264	3.2871	0.9292	0.2058	0.9916	20.3870	0.9904	0.1390	0.9760	0.0215	0.9392	0.1850	0.9964	0.1198	0.6645	9.727
F-9	0.7979	4.3677	0.9356	0.4174	0.9181	22.4190	0.9557	0.1901	0.9779	0.0218	0.9746	0.2561	0.9549	0.1806	0.6281	5.883
F-10	0.8687	4.3170	0.9645	0.3952	0.9645	23.7340	0.9906	0.1816	0.9941	0.0214	0.9783	0.2217	0.9823	0.1541	0.6435	7.161
F-11	0.8564	3.4105	0.9834	0.3453	0.9591	21.6370	0.9887	0.1412	0.9939	0.0217	0.9851	0.2052	0.9755	0.1234	0.6552	9.648
F-12	0.8957	2.9080	0.9901	0.1390	0.9784	18.2210	0.9699	0.0869	0.9927	0.0160	0.9927	0.1361	0.9838	0.1161	0.6319	11.687

" R^2 " is the regression coefficient; " K " is the release rate constant for respective models; " n " is the diffusion exponent; " MDT " is the mean dissolution time.

The release exponent (n) was found to be a function of polymer used and the physico-chemical property of the drug molecule itself. The release exponent *n* (0.5015-0.6645) indicated non-Fickian diffusion mechanism also called anomalous transport. Non-Fickian release is described by two mechanisms, the coupling of drug diffusion and polymer relaxation (Ritger and Peppas, 1987). Thus, diffusion was the dominant mechanism of drug release. This was found in accordance with the studies of Mandal and Pal (2008), who reported that the formulations of Metformin HCl SR formulated using different grades of hydroxy propyl methyl cellulose (HPMC K4M, K15M, K100M) showed good linearity (R^2 : 0.989 to 0.996), with slope (n) ranging from 0.535 to 0.587 indicating that the diffusion was the dominant mechanism of drug release. This finding was also in agreement with those obtained by Mehragan and Mortazavi (2005) for Diltiazem HCl SR using HPMC.

MDT was used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. Thus, MDT was directly related to the polymer loading, polymer nature and physico-chemical property of the drug molecule (Reza *et al.*, 2003). In this study MDT increased as the concentration of polymer increased specially in case of HPMC K100M.

Formulation optimization

For the purpose of optimization, twelve different formulations were prepared using two different viscosity grades of HPMC (K4M & K100M) with different quantities of the same excipient. In vitro dissolution test was considered essential for the quality of the developed dosage forms (Savaser *et al.*, 2005). In comparison of all formulations, on the basis of in vitro dissolution and kinetic studies, F-7 (HPMC K4M) and F-11 (HPMC K100M) were selected as the most optimized formulation. F-7 showed 23%, 45%, 72% and 85% release of Diltiazem HCl in 1 h, 4 h, 10 h and 15 h, respectively. F-11 showed 19%, 43%, 78% and 90% release of Diltiazem HCl in 1 h, 4 h, 10 h and 15 h, respectively, i.e. to the targeted profile (fig. 15). F-7 best fitted into Higuchi's kinetics while F-11 into the Baker and Lonsdale kinetics. Mechanism of drug release for both HPMC K4M and K100M tablets was indicative of anomalous diffusion mechanism or non-fickian diffusion. However, F-11 (HPMC K100M) was chosen as an optimal formulation due to its closest profile to the target in terms of release.

Dissolution profile comparison

Formulation F-11 (HPMC K100M) was taken as reference formulation and dissolution profile was compared with other formulations using the f_1 differential and f_2 similarity test. The profile of F-11 was observed to be similar with F-6, F-7, F-8, F-10 and F-12 (table 5).

Table 5: Similarity (f_2) and Differential factor (f_1) values of HPMC matrix tablets compared with F-11

Comparison	f_2 Values	f_1 Values	Dissolution Profile
HPMC K4M			
F-11 and F-1	26.081	75.48	Dissimilar
F-11 and F-2	35.946	41.42	Dissimilar
F-11 and F-3	41.009	27.61	Dissimilar
F-11 and F-4	44.547	20.62	Dissimilar
F-11 and F-5	47.245	18.20	Dissimilar
F-11 and F-6	74.031	0.64	Similar
F-11 and F-7	68.196	2.47	Similar
F-11 and F-8	67.3904	2.69	Similar
HPMC K100M			
F-11 and F-9	37.44	26.92	Dissimilar
F-11 and F-10	54.21	11.72	Similar
F-11 and F-12	78.54	13.92	Similar

CONCLUSION

The results obtained from the present study showed that the hydrophilic matrix of HPMC K4M failed to control the Diltiazem HCl release effectively for 24 hours even at a higher concentration of 50%. This study suggests that matrix tablets prepared with HPMC K4M (50%) and talc in concentration of 2% is better system for once-daily sustained release of a highly water soluble drug Diltiazem HCl. Burst effect can be minimized by incorporation of Avicel PH 101 at a concentration of 10% or more with 2% talc. Higher concentration of HPMC K100M (40%) successfully sustained the drug release up to 24h. HPMC K100M matrices have a higher tendency to swell and lower tendency to erode resulting in overall decreased Diltiazem HCl release in comparison with HPMC K4M. The increase concentration of polymer and binder increases the percent degree of swelling and decreases the percent erosion. The drug release data for all HPMC K4M formulations fitted well to the Higuchi model while Baker and Lonsdale's model was well fitted with the drug release profiles for HPMC K100M tablets. However, K4M and K100M formulations had identical drug release mechanism i.e. non-fickian diffusion. F7 (50% K4M, 2% talc, 10% Avicel PH101) and F11 (40% K100M) were very close to targeted release profile and F-11 was selected as an optimized and reference formulation for dissolution profile comparison. Thus the results showed that the two co-excipients successfully enhanced the drug release profiles with talc being the more efficient co-excipient. The different grades of HPMC could be successfully used to prepare sustained release matrix tablets of Diltiazem HCl.

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