Acta Pharmaceutica Turcica
47: 115-126 (2005)

Development and *In Vitro* Evaluation of Hydrophilic Matrix Tablets of Diltiazem Hydrochloride

B.Mishra*, A.Bansal and C.Sankar

Department of Pharmaceutics, IT, BHU, Varanasi - 221005, INDIA

Abstract

The present study aimed to formulate and evaluate hydrophilic matrix tablets of diltiazem hydrochloride to achieve a controlled and sustained drug release with reduced frequency of drug administration, reduced side effects and improved patient compliance. Matrix tablets of diltiazem hydrochloride were prepared using polymers like hyroxypropylmethylcellulose (HPMC K15, HPMC K4), sodium carboxymethylcellulose (SCMC) and Guar gum, and different diluents like lactose, starch, microcrystalline cellulose. All the batches were evaluated for thickness, weight variation, hardness, drug content uniformity and *in vitro* drug release characteristics as per USP XXIV monograph. The drug release rates from matrix tablets were compared with marketed SR formulations. Matrix erosion and swelling studies were also carried out. The release kinetics and mechanism of drug release by regression coefficient analysis and Peppas exponential release model equation were also investigated. SCMC matrix tablets showed more hydration and erosion than other matrix tablets. Tablets having HPMC K15 gave more sustained release than other hydrophilic polymers studied and it was comparable with marketed SR tablets. Amount of HPMC K15 and presence of different diluents significantly affected the drug release. It was observed that all the fabricated tablets delivered the drug following Higuchi diffusion mechanism.

Keywords: Dilitiazem, hydrochloride, hydroxypropylmethylcellulose, guar gum, sodium carboxymethyl cellulose, Higuchi diffusion.

Introduction

Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages. Sustained release dosage forms would be most applicable for drugs having low therapeutic indices and short elimination half-lives (George *et al.*, 1978). Sustained release can be achieved by formulating drugs as matrix devices using HPMC, Sodium CMC and other swellable polymer (Carstensen., 1987; Mockel and Lippold., 1993; Swarbrick., 1996). Combination of nonionic polymer HPMC and anionic polymer Sodium CMC as the polymer matrix resulted in near zero-order release (Rani and Mishra., 2001). Matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior (Mishra *et al.*, 2003). Diltiazem hydrochloride (DHL), a potent calcium channel blocker, is used in the management of angina pectoris, arrhythmia and

* Correspondence: E-mail: bmishra@banaras.ernet.in

hypertension. It has small plasma half-life ($t_{1/2}$ = 3.5 h) and usual dose is 30 mg thrice daily. As a result of its short half-life, the development of oral sustained release formulation of this drug is highly desirable, so as to improve therapeutic effects with minimum side effects and improved patient compliance (Chaffman and Brogden., 1985). So, the objective of the present study was to develop controlled and prolonged release formulation of DHL as matrix tablets. The drug release rates from matrix tablets were compared with marketed SR formulations. Matrix erosion and swelling studies were also carried out by gravimetric means (Munday and Cox., 2000). The release kinetics and mechanism of drug release by regression coefficient analysis and Peppas exponential release model equation i.e. $M_t/M_\infty = Kt^n$ (Agarwal and Mishra, 1999; Sankar *et al.*, 2001), were also investigated.

Materials and Methods

Materials: Diltiazem hydrochloride (DHL) was obtained as gift sample from Modimundi Pharma Ltd, Modipuram, India. HPMC K15, HPMC K4, SCMC and Guar gum were also obtained as gift samples from Recon Ltd, Bangalore, India. All other chemicals used were of analytical grade.

Fabrication of DHL matrix tablets: All the batches of matrix tablets were prepared using 90 mg of DHL, 60 mg of polymer and excipients and 1% w/w magnesium stearate in each tablet. The variables in batches were the type of polymers and the type of excipients (Table 1). Each batch size of tablets was 200. All the ingredients were passed through sieve No.85, blended uniformly and wet granulated using distilled water. Granules were dried at temperature 40° C until moisture content reached less than 0.5% w/w. Dried granules were lubricated with 1% w/w magnesium stearate and finally compressed on a single station tabletting machine Manesty E2 (England) using 6.5 mm standard flat surface punches at a pressure that gave Monsanto hardness of 7 kg/cm^2.

Table 1. Formula for preparing matrix tablets of Diltiazem hydrochloride

Batch code	Ingredients per tablet (in mg)							
	Drug	HPMC K15	HPMC K4	SCMC	Guar gum	Lactose	Starch	MCC
LH1	90	15	-	-	-	45	-	-
LH2	90	45	-	-	-	15	-	-
LH3	90	60	-	-	-	-	-	-
LK3	90	-	60	-	-	-	-	-
LC3	90	-	-	60	-	-	-	-
LG3	90	-	-	-	60	-	-	-
SH1	90	15	-	-	-	-	45	-
MH1	90	15	-	-	-	-	-	45

1% w/w of magnesium stearate was present in each tablet

- indicates not present

Evaluation: All the batches were evaluated for thickness, weight variation, hardness and drug content uniformity as per USP XXIV monograph.

Swelling and Erosion studies: The matrix tablets swelling and erosion studies were carried out by following slightly modified method (Munsday and Cox., 2000). The studies were done using the USP XXIV dissolution apparatus I fitted with six rotating baskets (Model Electrolab, India). All the batches of tablets were evaluated (3 runs for each batch) using 900 ml of sequential gastrointestinal release medium, i.e. 0.1N hydrocholric acid (pH 1.2) for first two h and then pH 7.4 phosphate buffer for next 6 h, maintained at 37 ± 0.1°C and stirred at 100 rpm. Each basket was thoroughly cleaned, accurately weighed before and after insertion of a matrix tablet, so that accurate weight of each matrix tablet (W_i) could be calculated. The baskets and tablets were then rotated in the dissolution medium, at regular time intervals a basket was detached, blotted with absorbent paper to remove any excess medium on the basket surface and accurately weighed on analytical balance. From this hydrated matrix tablet weight (W_h) was calculated. Then the hydrated matrices were dried in an oven at 40°C for 18 h, cooled in a dessicator (silica gel) and the dried residue weighed. The heating-cooling-weighing process was repeated until constant weight (W_d) was achieved. At the time of detachment of each basket, 5 ml samples of dissolution medium were withdrawn and an equivalent volume of medium at 37°C was added to maintain constant volume. Withdrawn samples were analysed spectrophotometrically at 237 nm using a Jasco UV/VIS Spectrophotometer (Model 7800, Japan). This gave the amount of drug released (Q_t) from tablets at time t. Percentage swelling and erosion of matrix tablet after dissolution at time t was calculated as follows:

$$\% \text{ Matrix Swelling} = \{(W_h + Q_t) - W_i\} / W_i \times 100$$

$$\% \text{ Matrix Erosion} = (W_i - W_d - Q_t) / W_i \times 100$$

where, W_i =Initial tablet matrix weight

W_h = Hydrated matrix tablet weight after time t

W_d = Dried matrix weight after time t

Q_t = Amount of drug released at time t

In vitro drug release studies: The studies were done using the USP XXIV dissolution apparatus II fitted with six rotating paddle type (Model Electrolab, India). All the batches of tablets were evaluated (3 runs for each batch) using 900 ml of sequential gastrointestinal release medium, i.e. 0.1N hydrocholric acid (pH 1.2) for first two h and then pH 7.4 phosphate buffer for next 6 h, maintained at 37 ± 0.1°C and stirred at 100 rpm. 5 ml of aliquots were withdrawn at different time intervals and an equivalent volume of medium prewarmed at 37°C was added to maintain constant volume. Withdrawn samples were analysed spectrophotometrically at 237 nm using a Jasco UV/VIS Spectrophotometer (Model 7800, Japan).

Marketed SR tablets; Dilcontin XL 90® of Modimundi Pharma Ltd, India (Code A) and Diliazem SR® of Torrent Pharma Ltd, India (Code B) were purchased from the market and were evaluated for thickness, weight variation, hardness, drug content uniformity and *in vitro* release characteristics following the above procedure.

Results and Discussion

The variation in the thickness, weight, hardness and drug content uniformity values of all the fabricated tablets and marketed tablets, in reference to average values for each parameter, were found within the official limits (Table 2).

Table 2. Physical characteristics (± S.D) of matrix tablets of Diltiazem hydrochloride

Batch code	Weight (mg)	Friability (%)	Hardness (Kg /cm^2)	Thickness (mm)	Drug content (%)
LH1	150.1 ± 0.8	0.06 ± 0.002	7.2 ± 0.2	6.3 ± 0.2	98.9 ± 0.22
LH2	149.7 ± 0.9	0.05 ± 0.002	6.9 ± 0.3	6.4 ± 0.2	97.9 ± 1.31
LH3	150.7 ± 1.3	0.52 ± 0.001	6.5 ± 0.4	6.7 ± 0.3	99.0 ± 0.21
LK3	150.2 ± 2.1	0.24 ± 0.002	6.8 ± 0.5	6.9 ± 0.4	99.5 ± 0.61
LC3	151.1 ± 2.5	0.19 ± 0.003	7.1 ± 0.3	6.6 ± 0.2	98.2 ± 0.91
LG3	152.0 ± 2.3	0.32 ± 0.002	7.0 ± 0.1	6.8 ± 0.3	98.7 ± 0.71
SH1	151.2 ± 1.2	0.45 ± 0.002	6.9 ± 0.2	6.6 ± 0.2	98.6 ± 1.01
MH1	149.2 ± 0.9	0.38 ± 0.002	7.1 ± 0.2	6.7 ± 0.2	96.2 ± 3.81
A	240.6 ± 3.2	0.39 ± 0.003	8.1 ± 0.4	7.6 ± 0.3	99.2 ± 0.81
B	189.2 ± 4.2	0.45 ± 0.002	7.8 ± 0.2	7.0 ± 0.2	98.6 ± 0.61

Swelling and erosion studies: The percent increase in weight of the hydrated matrices (i.e. water uptake) at various time intervals up to 8 hrs are shown in Fig.1. It was observed that swelling increased with increase in polymer concentrations. Initially at pH 1.2 swelling rate was higher for SCMC, HPMC K15, HPMC K4 but at pH 7.4 the swelling rate was comparatively slower. In case of guar gum, tablet swelled with higher rate at pH 7.4 than at pH 1.2. Erosion study (Fig.2) of HPMC K15 batches LH1, LH2, LH3 showed that matrix erosion decreased with increase in polymer concentration. Comparative erosion study showed that SCMC matrix tablet had a higher rate of erosion at both pH than the matrix having all other polymers. HPMC K15 and Guar gum based tablets eroded with a slower rate than the HPMC K4.

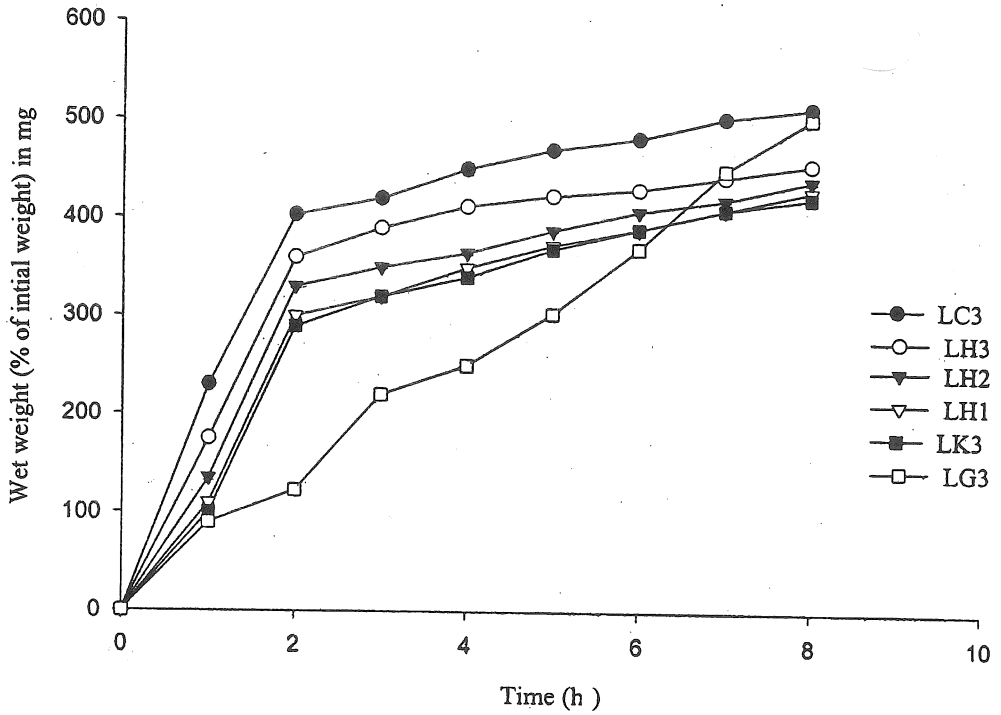

Fig. 1. Percentage increase in weight resulting sequenced gastrointestinal release medium uptake by matrix tablets. Bars represent ± S.D. (n = 3).

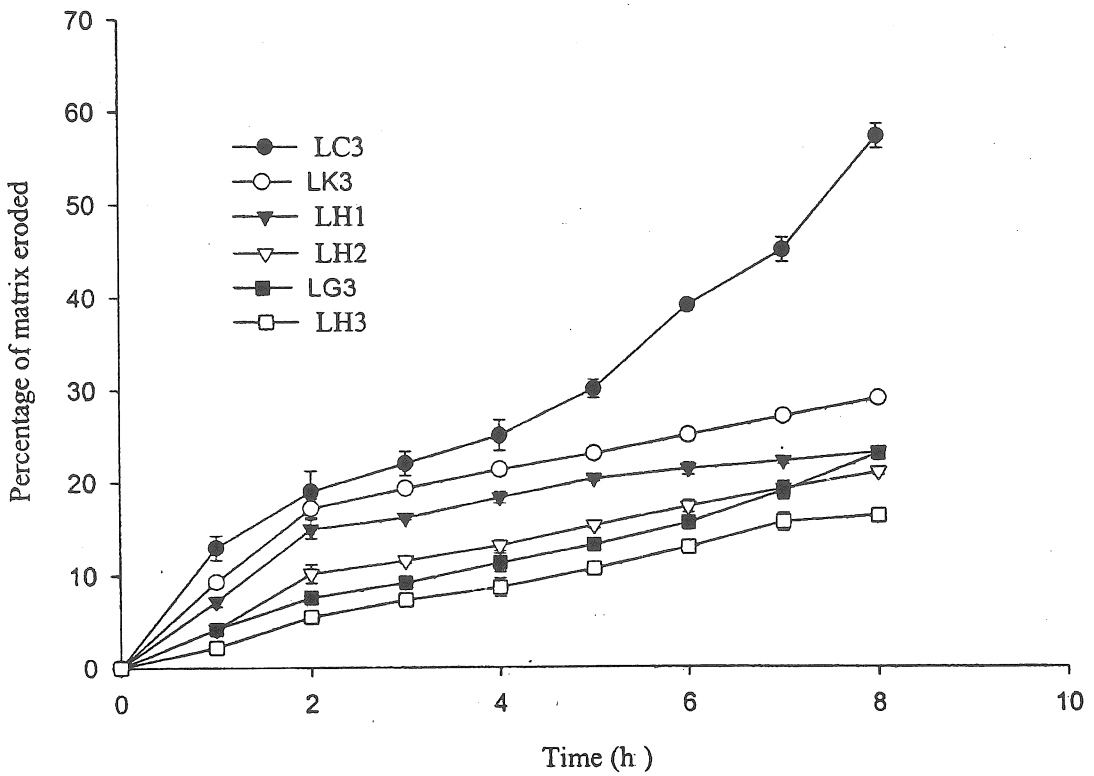

Fig. 2. Percentage of matrix eroded in sequenced gastrointestinal release medium at different time intervals. Bars represent ± S.D. (n = 3).

In vitro drug release studies: Three different polymer amounts were selected in order to study the effect of polymer HPMC K15 concentration on the *in vitro* drug release. Accordingly, three batches containing 15 mg/tab, 45 mg/tab, 60 mg/tab of HPMC K15 were prepared (batches LH1, LH2 & LH3 respectively). The results (Fig. 3) of *in vitro* studies indicated that the rate and extent of drug release were decreased significantly ($p < 0.05$) with an increase in polymer concentration, which may be attributed to increase in the density of polymer matrix followed by increasing diffusional path length for drug molecules (Sankar *et al.*, 2001).

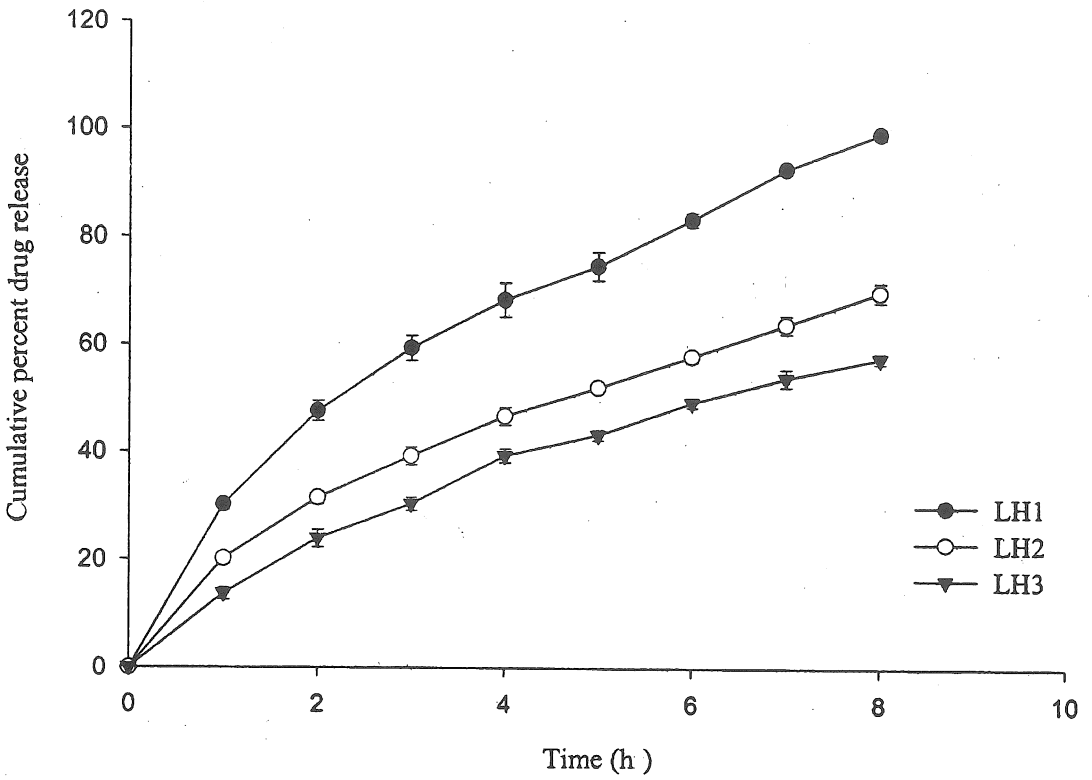

Fig. 3. *In vitro* DHL release profiles from HPMC K15 matrix tablets showing the effect of different amount of HPMC K15. Bars represent ± S.D. (n = 3).

In vitro drug release profiles of tablets using SCMC (LC3), guar gum (LG3), HPMC K4 (LK3) and HPMC K15 matrix tablet (LH3) are shown in Fig. 4. Faster drug release from SCMC tablets is attributed to faster erosion of anionic polymer SCMC (Fig. 2) in phosphate buffer pH 7.4. In comparison to HPMC K4 tablet (LK3), HPMC K15 tablets (LH3) exhibited significant sustaining effect on drug release. This might be due to more viscosity and high molecular weight of HPMC K15 (Lucy *et al.*, 1992) in addition to its slower rate of erosion (Fig. 2) and more swelling (Fig. 1) than HPMC K4. Guar gum, a natural gum, could be used in the preparation of sustained release matrix tablets and it showed swelling controlled release mechanisms (Khullar *et al.*, 1998). The higher *in vitro* drug release from LG3 than LH3 is attributed to little faster erosion of LG3 (as shown in Fig. 2) than LH3 and the drug release seems to follow diffusion and erosion controlled mechanism for both the tablets LG3 and LH3. Among all profiles HPMC K15 (LH3) showed more linear and prolonged drug release, indicated that HPMC K15 act as good sustaining agent.

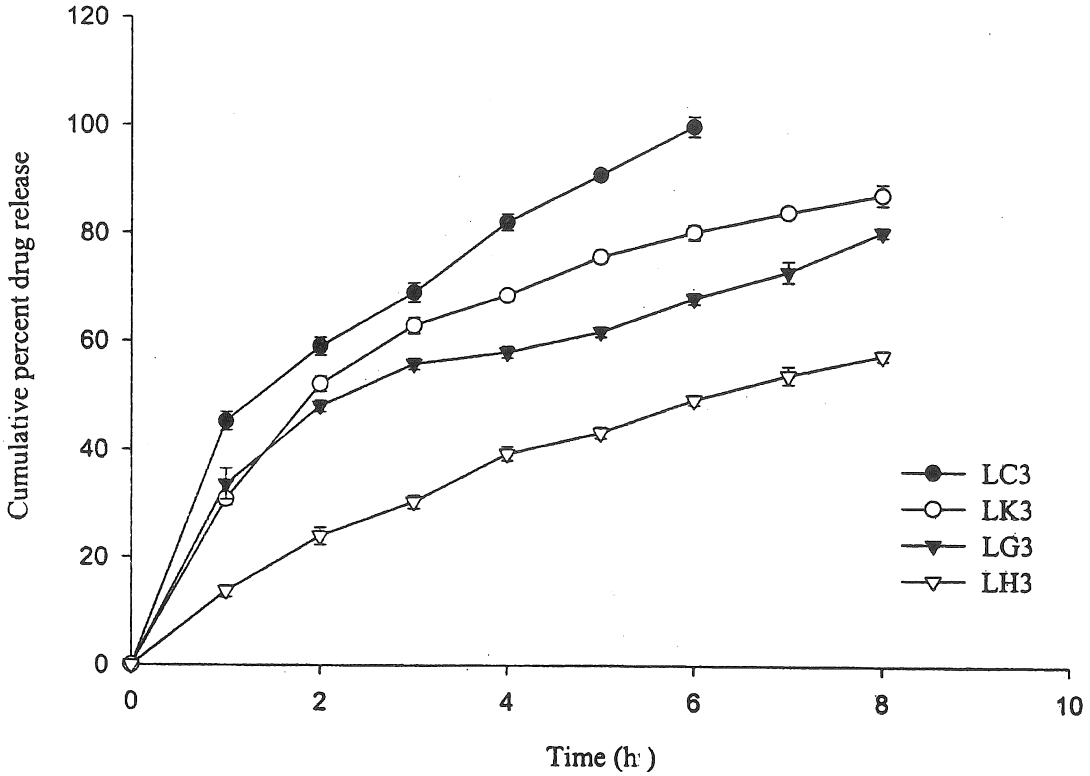

Fig. 4. *In vitro* DHL release from hydrophilic matrix tablets using same amount of different polymers. Bars represent ± S.D. (n = 3).

Lactose is the most useful filler used for tablet formulations. It is water-soluble and would modify the drug release for undergoing dissolution. Lactose in aqueous solution plays a major role as important physical barrier, affecting the release kinetics, by reducing the tortuosity of diffusion pattern of the drug (Gao *et al.*, 1995). Starch is of water swellable nature. The presence of starch in an HPMC matrix tablet could modify the drug release rate, due to its swelling phenomenon based on the fast water uptake, followed by HPMC swelling (Carstensen.,1977). Microcrystalline cellulose (MCC) plays an important role as a filler as well as release modifier (Lee *et al.*, 1999). To study the effect of diluents on drug release profiles, HPMC K15 batches with same amount of lactose (LH1), starch (SH1) and MCC (MH1) were prepared. The drug release profiles (Fig. 5) showed that the drug release rate and extent were in order of LH1 > SH1 >MH1. MCC based tablets provided sustained drug release. This is attributed to additive sustaining effect of MCC on sustaining effect of HPMC K15. This is in agreement with earlier reports (Colombo *et al.*, 1985; Lee *et al.*, 1999) indicating that MCC could retard the swelling and hydration of the HPMC matrix tablet due to its slow swelling and disintegration forces, resulting in a decreased release rate. In addition to above, Lactose being more water soluble, LH1 dissolved faster followed by SH1 which could contribute to more viscosity in hydrated matrix, thus giving slower drug release than LH1.

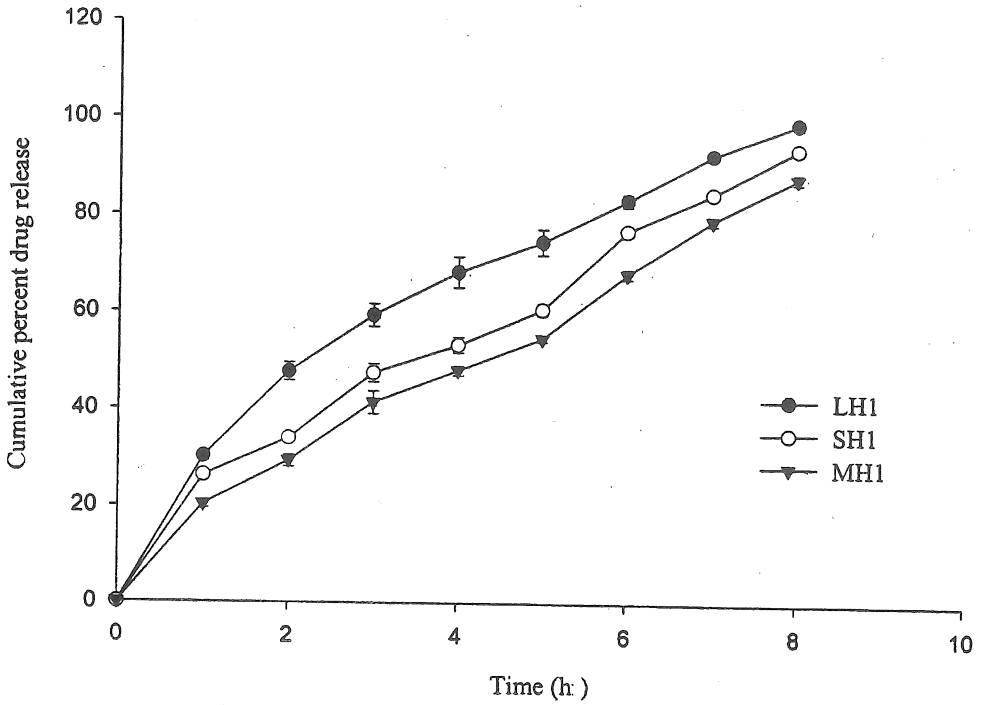

Fig. 5. *In vitro* DHL release profiles showing the effect of different diluents from HPMC K15 matrix tablets. Bars represent ± S.D. (n = 3).

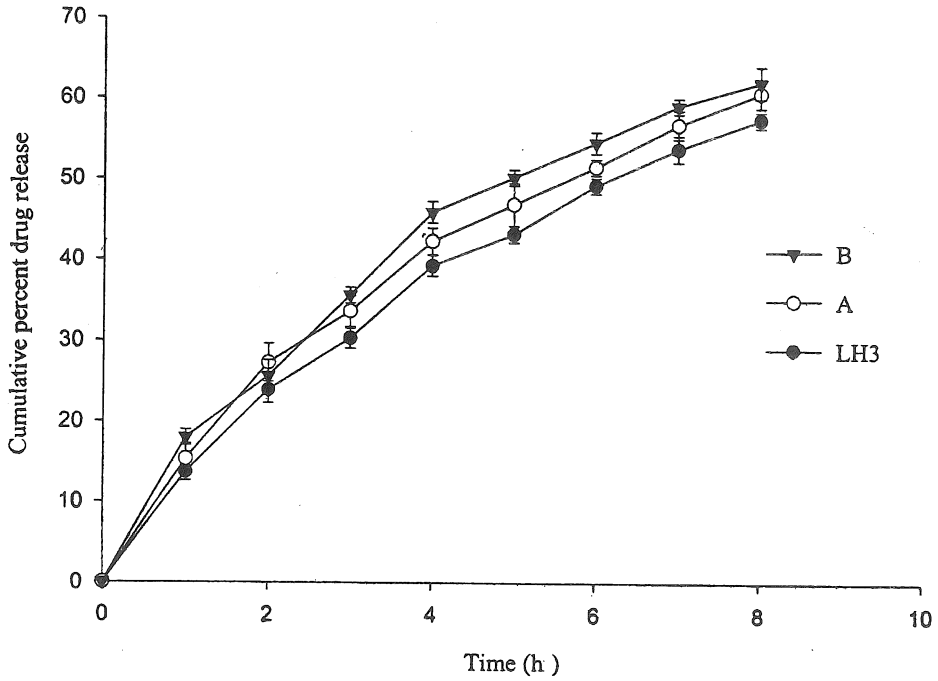

Fig. 6. Comparative *in vitro* DHL release profiles of fabricated HPMC K15 matrix and marketed SR tablets. Bars represent ± S.D. (n = 3).

The release profiles of LH3 (containing 40 % HPMC K15) was comparable with marketed SR tablets A & B as shown in Fig.6.

Drug release mechanisms: In order to investigate the release mechanism, the data were fitted to models (Sankar *et al., 2001*) representing zero-order, first-order and Higuchi's square root of time. The linear regression analysis shown as r values in Table 3, demonstrated that all the fabricated tablets followed Higuchi release kinetics (Table 3).

Table.3. Kinetics of *in vitro* drug release from different matrix tablets (using regression coefficient analysis)

S.No	Batches	r values		
		Zero order	First order	Higuchi
1.	LH1	0.9516	0.9227	0.9989
2.	LH2	0.9669	0.9678	0.9923
3.	LH3	0.8949	0.9904	0.9944
4.	LK3	0.9336	0.9546	0.9810
5.	LC3	0.9234	0.9653	0.9816
6.	LG3	0.9152	0.9523	0.9641
7.	SH1	0.9725	0.9687	0.9926
8.	MH1	0.9623	0.9568	0.9917

r = coefficient of correlation

Further, to understand the drug release mechanism, the data were fitted to Peppas exponential equation $M_t/M_\infty = Kt^n$, where M_t/M_∞ is the fractional drug release into the dissolution medium, K is a constant which incorporates the properties of the macromolecular polymeric system and drug and n is the diffusional exponent, which characterizes the drug transport mechanism (Agarwal and Mishra.,1999). When $n \leq 0.5$,indicates quasi-Fickian diffusion mechanism. For $n > 0.5$, an anomalous non-Fickian diffusion and the special case of $n = 1$ that has gained importance due to its potential application in the development of swelling controlled drug delivery systems with zero-order kinetics indicate pseudo-case-II transport mechanism (Lucy *et al.*, 1992). In the present study also it was observed (Table 4) that almost all the fabricated tablets followed non-Fickian diffusion mechanism, which indicates the drug release through diffusion and relaxation.

Table 4. Drug release kinetics from different matrix tablets (using Peppas exponential model equation)

S.No	Batches	K	n	r^2
1.	LH1	0.0935	0.8451	0.9804
2.	LH2	0.1230	0.8957	0.9862
3.	LH3	0.1686	0.9254	0.9650
4.	LK3	0.1232	0.6874	0.9883
5.	LC3	0.1095	0.8745	0.9767
6.	LG3	0.1197	0.7898	0.9768
7.	SH1	0.1589	0.6987	0.9732
8.	MH1	0.1565	0.9231	0.9498

Thus, it was concluded that the potential controlled and sustained release matrix tablets of DHL could be prepared using optimized amount of HPMC and other swellable polymers, like SCMC, guar gum.

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Received: 04.01.2005
Accepted: 01.02.2005