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Formulation and evaluation of Diltiazem hydrochloride matrix tablets using natural polymer

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ABSTRACT

The objective of present study was to formulate and evaluate hydrophilic matrix tablets of Diltiazem hydrochloride achieve a controlled and sustained drug release manner with reduced frequency of drug administration, reduced side effects and improved patient compliance. Matrix tablets of Diltiazem hydrochloride were prepared using natural polymers like Xanthan Gum, Guar gu, Sodium alginate and carrageenan. 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 release kinetics and mechanism of drug release by regression coefficient analysis and various exponential release model equations were also investigated. Tablets having xanthan gum gave more sustained release than other hydrophilic polymers studied. Amount of polymers 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: Diltiazem hydrochloride; Xanthan Gum; Guar gum; Sodium Carboxymethyl Cellulose, Higuchi diffusion.

INTRODUCTION

Diltiazem hydrochloride (DTZ) is a calcium channel blocker acting block Ca^{+2} entry by preventing L-type calcium channels. It is widely prescribed for the treatment of hypertension and angina. Bioavailability of DTZ is 30% to 40% owing to first pass metabolism. It has an elimination half-life of 3.5 hours. Therefore DTZ requires multiple drug therapy in order to

maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for sustained drug delivery. [1-2]

Sustained release oral delivery systems are designed to achieve therapeutically effective concentration of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction in both frequency of delivery of dosage form and the incidence of adverse side effects.[3] Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale –up points of view. It has been also use more suitable polymers as release retarding materials for appropriate modification of release characteristics of the drug from the dosage form. [4]

To formulate a successful hydrophilic matrix system, one must select a polymer substance that will enable to control the release of drug from dosage form. To achieve this, there are a number of synthetic, semi-synthetic and natural polymers used for the preparation of matrix tablets. Among these the natural polymer is preferred due to their non toxic, economic and easy availability.[5] In this study four natural polymers xanthan gum, guar gum, sodium alginate and carragennan for the preparation of DHL matrix tablets were selected to develop a controlled and prolonged release formulation of DHL as matrix tablets. Matrix erosion and swelling studies were also carried out.

MATERIALS AND METHODS

2.1 Materials

Diltiazem hydrochloride (DHL) was obtained as gift sample from Kauks Pharma Ltd, Faridabad, India. All other chemicals used were of analytical grade.

Table 1. Formula for preparing matrix tablets of Diltiazem hydrochloride

Batch Code	Ingredient per tablets (in mg)							
	Drug	Guar Gum	Xanthan Gum	Sodium Alginate	Carrageenan	Lactose	Starch	MCC
DG 01	90	45	-	-	-	208	-	-
DG 02	90	90	-	-	-	163	-	-
DG 03	90	135	-	-	-	118	-	-
DG 04	90	180	-	-	-	73	-	-
DX 01	90	-	45	-	-	208	-	-
DX 02	90	-	90	-	-	163	-	-
DX 03	90	-	135	-	-	118	-	-
DX 04	90	-	180	-	-	73	-	-
DS 04	90	-	-	180	-	73	-	-
DC 04	90	-	-	-	180	73	-	-
DGM 02	90	90	-	-	-	-	163	-
DGS 02	90	-	-	-	-	-		163

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

- indicates not present

2.2 Preparation of Matrix Tablets

All the batches of Matrix tablet of Diltiazem hydrochloride were prepared by wet granulation method using 90 mg of DHL, 253 mg of polymer and excipients and 1% w/w magnesium stearate as a lubricant and 1% talc as glident in each tablet. The variables in batches were the

type of polymers **Table 1**. Each batch size of tablets was 100 in numbers. All the ingredients were passed through sieve No. 60, blended uniformly and wet granulated using Milli-Q^{TM} Ultra pure water. Granules were dried at temperature 40°C until moisture content reaches less than 0.5% w/w.Dried granules were lubricated with 1% w/w magnesium stearate and finally compressed manually on a single punch tablet press, Hicon using 10 mm standard flat surface beveled edged punches at a pressure that gave Monsanto hardness of 7-8 kg/cm^2.

Evaluation

3.1 Drug Content and Physical Evaluation

All the batches were evaluated for thickness, weight variation, hardness, Friability and drug content uniformity as per reported procedure in IP monograph. Hardness was determined by using hardness tester. Friability was determined using Roche friability testing apparatus. Weight variation and uniformity of drug content were performed according to the IP procedures. Content uniformity in tablets was determined by extracting an accurately weighed amount of powdered tablet (50 mg) with simulated gastric fluid. The solution was filtered through 0.45- µm membrane and absorbance was measured at 237 nm after suitable dilution.

3.2 In Vitro Drug Release Studies

The studies were done using the USP XXIV dissolution apparatus II fitted with six rotating paddle type. All the batches of tablets were evaluated (3 runs for each batch) using 900 ml of pH 1.2 HCl buffer for first two hours and then pH 7.4 phosphate buffer for next 6 hours, 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 pre warmed at 37°C was added to maintain constant volume. Withdrawn samples were analyzed spectrophotometrically at 237 nm using a Shimadzu UV/VIS Spectrophotometer.

3.3 Polymer Swelling and Erosion studies

The matrix tablets swelling and erosion studies were carried out by following method. The studies were done using the USP XXIV dissolution apparatus I fitted with six rotating baskets. All the batches of tablets were evaluated (3 runs for each batch) using 900 ml of sequential gastrointestinal release medium, i.e. 0.1N hydrochloric acid (pH 1.2) for first two hours and then pH 7.4 phosphate buffer for next 6 hours, maintained at 37 ± 0.1°C and stirred at 100 rpm. At set time intervals, the previously weighed baskets containing the tablets were removed from dissolution medium, gently wiped with a tissue to remove surface water, reweighed. From this hydrated matrix tablet weight (W_h) was calculated. The wet samples (basket + sample) were then dried in an oven at 40°C for 24 h, cooled in a dessicator (silica gel) and finally weighed until constant weight was achieved (final dry weight). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. 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 analyzed spectrophotometrically at 237 nm using a UV/VIS Spectrophotometer (Shimadzu). This gave the amount of drug released (Q_t) from tablets at time t. Percentage swelling and erosion [6-7] of matrix tablet after dissolution at time t was calculated as follows:

% Matrix Swelling = $\{(W_h + Q_t) – W_i\} / W_i$ x 100

% Matrix Erosion = $(W_i – W_d – Q_t) / W_i$ x 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

RESULTS AND DISCUSSION

4.1 Evaluation of Physical Parameters

The variation in the thickness, weight, hardness and drug content uniformity values of all the fabricated 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 /cm2)	Thickness (mm)	Drug content (%)
DG 01	348.4±3.13	0.08 ± 0.002	7.5 ± 0.3	3.8 ± 0.2	97.9 ± 1.31
DG 02	350.3±2.31	0.06 ± 0.001	7.1± 0.4	3.8 ± 0.3	99.0 ± 0.21
DG 03	350.5±2.51	0.12 ± 0.002	7.1± 0.5	3.9± 0.4	99.5 ± 0.61
DG 04	350.2±4.2	0.15 ± 0.003	7.8 ± 0.3	4.2 ± 0.2	98.2 ± 0.91
DX 01	350.0±2.59	0.02 ± 0.002	7.8 ± 0.1	3.9± 0.3	98.7 ± 0.71
DX 02	349.6±2.59	0.05 ± 0.002	6.9 ± 0.2	4.1 ± 0.2	98.6 ± 1.01
DX 03	349.4±1.90	0.09 ± 0.002	7.1 ± 0.2	4.0 ± 0.2	99.2 ± 1.81
DX 04	351.4±2.30	0.09 ± 0.002	7.3 ± 0.2	3.8 ± 0.2	99.2 ± 1.78
DS 04	349.5±2.40	0.09 ± 0.002	7.7 ± 0.2	4.0 ± 0.2	99.2 ± 1.61
DC 04	349.2±2.40	0.11 ± 0.002	7.2 ± 0.2	4.1 ± 0.2	99.6 ± 1.31
DGM 02	349.4±1.90	0.09 ± 0.002	7.6 ± 0.3	4.1 ± 0.3	100.2 ± 1.56
DGS 02	349.4±1.90	0.09 ± 0.002	7.6 ± 0.2	3.8 ± 0.2	99.9± 1.45

4.2 In Vitro Drug Release Studies

Four different polymer amounts were selected in order to study the effect of polymer concentration on the in vitro drug release. Accordingly, four batches containing 45 mg/tab, 90 mg/tab, 135 mg/tab and 160 mg/tab of Xanthan gum were prepared. The results of in vitro studies indicated that the rate and extent of drug release were decreased significantly 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. [8] **Figure 1.**

In vitro drug release profiles of tablets using Xanthan Gum (DX4), guar gum (DG4),[9] Sodium alginate (DS4) and Carrageenan (DC 04) [10] are shown in **Figure 2**. In comparison to Guar Gum Matrix tablet (DG4), Xanthan Gum Matrix tablets (DX4) exhibited significant sustaining effect on drug release. Among all profiles Xanthan Gum Matrix tablets (DX4) showed more linear and prolonged drug release, indicated that Xanthan gum act as good sustaining agent in natural polymers. **Figure 2**

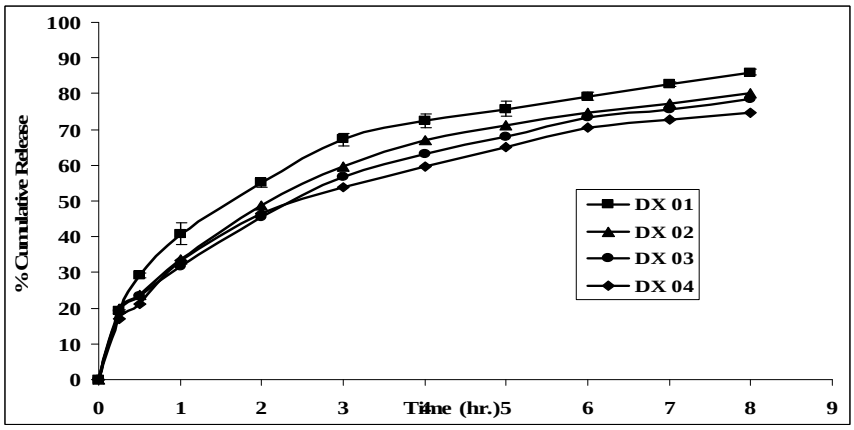

Figure 1 In-vitro Drug release profile of Xanthan Gum Matrix Tablets.

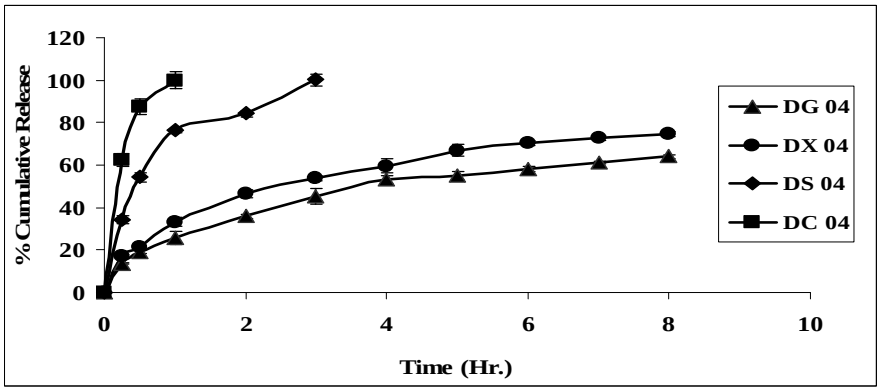

Figure 2 In-vitro DHL release from matrix tablets using same amount of different polymers.
Bars represent ± S.D. (n = 3).

4.3 Effect of Different Diluents on Drug Release

The effect of diluent or filler depends upon the nature of diluent. [11] Lactose is the most useful filler used for tablet formulations. It is water-soluble and would modify the drug release for undergoing dissolution [12]where as insoluble diluents like dicalcium phosphate reduce the release rate.[13] Microcrystalline cellulose (MCC) plays an important role as a filler as well as release modifier. For study the effect of diluents the comparative dissolution profile of different formulation containing 1:1 ratio polymer concentration is shown in Figure 4. Significant divergence in the release profile was observed using different diluents. The divergence between the dissolution profiles of different formulations may be attributed to their difference in solubility of diluents. Higher drug release was observed from batches DX 02 (1:1 polymer level and lactose) than batches DXM 02 and DXP 02, containing microcrystalline starch and dicalcium phosphate as diluent. This difference in release rate can be attributed to lactose, which diffuses outward through the hydrated gel layer, increasing the porosity and decreasing the tortuosity of the diffusional path of drug [14-15] while dicalcium phosphate, a water-insoluble material, decreases drug release owing to formation of a porous non-swellable and insoluble matrix [16]

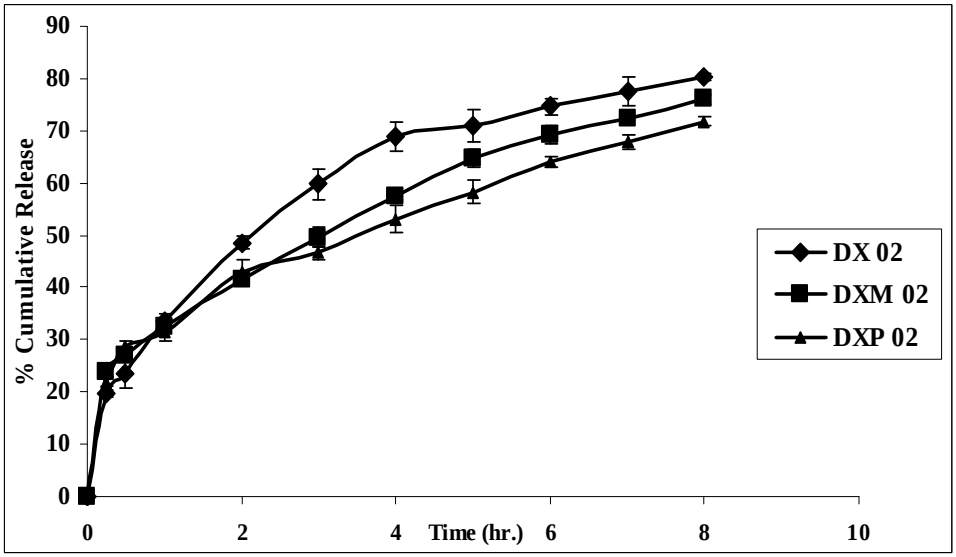

Fig.3 In-vitro DHL release profiles showing the effect of different diluents from Xanthan Gum matrix tablets.
Bars represent ± S.D. (n = 3).

4.4 Drug Release Mechanisms

In order to investigate the release mechanism, the data were fitted to models [17-20] 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.**

		r values		
S. No	Batches	Zero order	First order	Higuchi
1	DG 01	0.8243	0.9678	0.9701
2	DG 02	0.8856	0.9901	0.9904
3	DG 03	0.9238	0.9546	0.9962
4	DG 04	0.8676	0.9653	0.9884
5	DX 01	0.8308	0.9762	0.9703
6	DX 02	0.8671	0.9805	0.9841
7	DX 03	0.8848	0.9864	0.9895
8	DX 04	0.8676	0.971	0.9844
9	DS 04	0.7815	0.9119	0.9571
10	DC 04	0.7712	0.9101	0.9631
11	DGM 02	0.8919	0.9860	0.9979
12	DGP 02	0.9693	0.8389	0.9788

Table 3 In vitro dissolution kinetics of different matrix tablets

4.5 Water Uptake and Erosion Studies

The swelling behavior and erosion studies were carried out matrix tablets containing xanthan gum and guar gum. The results of swelling and erosion tests were shown in fig.4. & fig.5. The swelling behavior indicates the rate at which this formulation absorbs water from dissolution media and swells. The change in weight is characteristic of water uptake and swelling, started from the beginning and continued until 8 h of experiment (fig. 4). This matrix showed a high ability to swell. Visual observation denoted that the matrices appeared swollen almost from the

beginning, a viscous gel mass was created when they came into contact with the liquid. The matrix erosion measured the weight loss from matrix tablets immersed in dissolution media as a function of time. The weight loss of the tablets was in constant progression until the end of 8 h (fig. 5), It was observed that swelling was increased with increase in polymer concentrations**.** Initially at pH 1.2 swelling rate was higher for xanthan gum and guar gum but at pH 7.4 the swelling rate was comparatively slower.

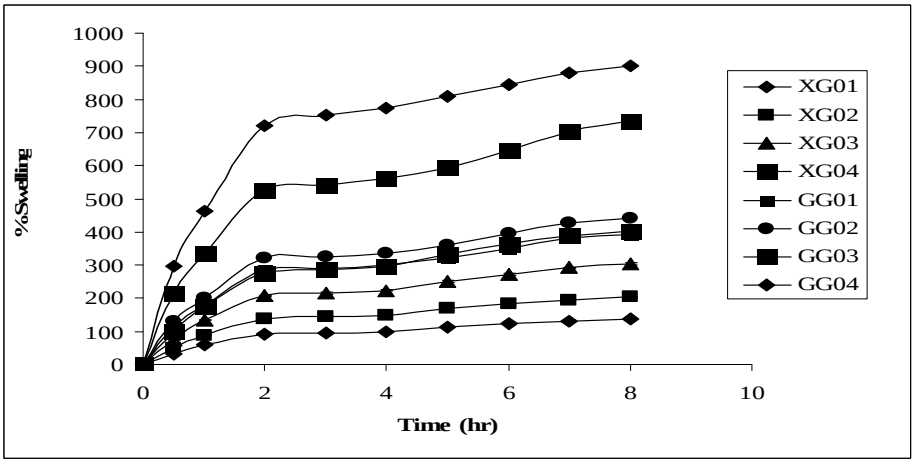

Fig. 4. Percentage increase in weight by matrix tablets.
Bars represent ± S.D. (n = 3).

Erosion study (Fig.5) of Xanthan Gum and Guar Gum batches XG 01, XG 02, XG 03, XG 04, GG 01, GG 02, GG 03, GG 04, showed that matrix erosion decreased with increase in polymer concentration. Comparative erosion study showed that Guar Gum matrix tablet had a higher rate of erosion at both pH than the matrix having all other polymers.

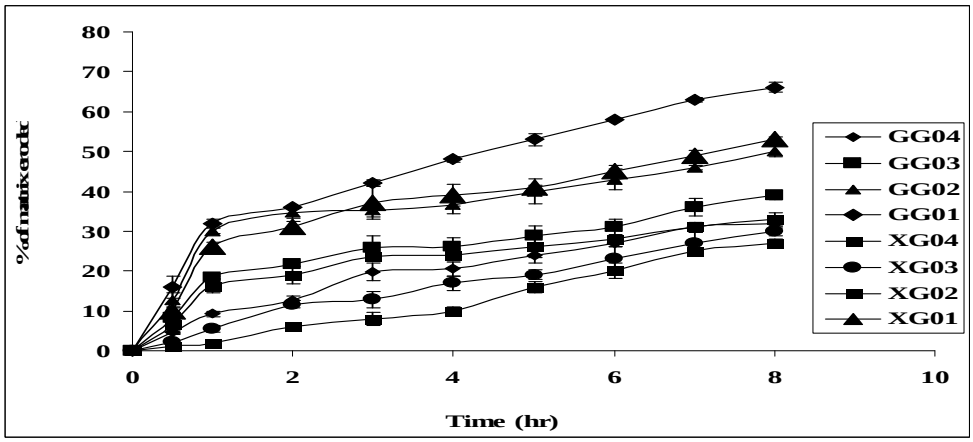

Fig. 5. Percentage of matrix eroded at different time intervals.
Bars represent ± S.D. (n = 3).

CONCLUSION

The result obtained indicates potential controlled and sustained release matrix tablets of DHL could be prepared using optimized amount of natural swellable polymers, like xanthan gum,

guar gum etc. single gum based formulations. It was also concluded that the drug release was greatly influenced by the nature of the diluent incorporated in the formulations.

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