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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

Controlled release and sustained release drug delivery has become the standards in the modern pharmaceutical design and intensive research for achieving better drug product effectiveness, reliability and safety. Oral sustained release drug delivery (OSRDD) medication will continue to account for the largest share (up to 80%) of drug delivery systems. The matrix tablet preparation appears to be most attractive approach for the process development and scale-up point of view. A calcium channel blocker, Diltiazem hydrochloride has found its applicability in cardiovascular diseases advised to take the long term treatment of cardiovascular medicaments like anti-anginals, anti-hypertensives, etc. The calcium channel blockers are utilized as the potential agents for the treatment of these diseases. They are considered as a slow calcium channel blockers. The direct compression method was adopted for the preparation of sustained release matrix tablets with the 10mm punches and targeted weight of 350mg. The % drug release studies for combined hypromellose and xanthan gum matrices confirmed the batch H_2X_2 (at the end of 12 hours) as per USP criteria Test 2, which give the 93.78% drug release. Hence, this formulation was optimized and subjected to release kinetic study and accelerated stability studies. The drug release data for batch H_2X_2 were fitted better into an anomalous/non-fickian diffusion mechanism and due to higher erodability of xanthan gum Hixson-Crowell kinetics was concluded. The accelerated stability studies for three months revealed that there were no any remarkable changes in physical properties and % drug released profile.

Keywords: Calcium channel blocker, Diltiazem hydrochloride, Matrix tablet, Sustain release, Control release.

INTRODUCTION

Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal.[1]

Recently, controlled release and sustained release drug delivery has become the standards in the modern pharmaceutical design and intensive research for achieving better drug product effectiveness, reliability and safety. Oral sustained release drug delivery (OSRDD) medication will continue to account for the largest share (up to 80%) of drug delivery systems[2]. The matrix tablet preparation appears to be most attractive approach for the process development and scale-up point of view. [3]

The increased risk of cardiovascular diseases advised to take the long term treatment of cardiovascular medicaments like anti-anginals, anti-hypertensives, etc. The calcium channel blockers are utilized as the potential agents for the treatment of these diseases. They are considered as a slow calcium channel blockers. [4]

A calcium channel blocker, Diltiazem hydrochloride has found its applicability in such a life threatening cardiovascular diseases and widely used as an anti-anginal, anti-hypertensive and an anti-arrhythmic agent. It is a BCS class I (highly soluble, highly permeable) drug with extensive and highly variable hepatic first pass metabolism following oral administration, with systemic bioavailability of between 36-50% and half life of 3.5 ± 1.2 hours. When such a drug administered in conventional immediate release dosage form, the frequency of administration increased up to 3-4 times in day due to its shorter half-life. [5]

In such a case, the sustained release formulation will be beneficial than the immediate release dosage form as therapeutic level is maintained for an extended period of time, eliminating maxima in drug concentration commonly associated with multiple doses.

In the past many sustained release systems for low or sparingly soluble drugs have been developed, but considerable difficulties have been experience in the formulation of freely soluble (class I) drugs. Suppressing the diffusion of embedded drug possess major challenges due to inherent solubility of drug.

Therefore, the aim of the present study was to formulate sustained-release matrix tablets of diltiazem hydrochloride using hydrophilic natural gums (xanthan gum and guar gum) and hydrophobic compritol 888ATO in combination with the selected grade of hypromellose for the economical tablet production.

Hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.[6]

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets. Controlled-release tablets of diltiazem hydrochloride prepared using xanthan gum have been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate. [7]

Guar gum has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose. In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant, in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery. Guar-gum-based three-layer matrix tablets have been used experimentally in oral controlled-release formulations.[8]

MATERIAL AND METHODS

Material

Diltiazem Hydrochloride was provided by Themis Laboratories Ltd., Mumbai. Hypromellose K4M, K15M and K100M, Compritol 888ATO, and Xanthan gum were provided by Colorcon Asia Pvt. Ltd., Goa. Guar gum and Magnesium stearate were provided by Research Fine Labs, Mumbai.

Methods

Formulation of core batches

Various batches (Table no1) of tablets were prepared by combining varying percentages of hypromellose K4M with natural gums and compritol 888ATO in the ratio of 1.0:1.5 (Drug: Polymer ratio). Different tablet formulations were prepared by direct compression method. Table No.3 shows composition of each tablet formulation. All the ingredients were passed through 90µm sieve. The ingredients were accurately weighed and mixed together in a glass mortor for 10 minutes. Finally the magnesium stearate was added and mixed for additional 2 minutes. The lubricated powder blend was then compressed using 10mm standard flat faced punch on a 10 station tablet punching machine. The total tablet weight was set at 350mg. The compression pressure was adjusted during tableting of each formula to get tablet hardness in the range of 5 to 7 kg/cm^3.

Table 1: Formulation of core batches

Formulations	DHZ	HPMC K4M	Xanthan Gum	Guar Gum	Compritol 888 ATO
H3X1	90.0	101.25	33.75	-----	----------
H2X2	90.0	67.50	67.50	-----	----------
H1X3	90.0	33.75	101.25	-----	----------
H3G1	90.0	101.25	---------	33.75	----------
H2G2	90.0	67.50	---------	67.50	----------
H1G3	90.0	33.75	---------	101.25	----------
H3C1	90.0	101.25	---------	-----	33.75
H2C2	90.0	67.50	---------	-----	67.50
H1C3	90.0	33.75	---------	-----	101.25

(Composition of S. R. Matrix Tablet of Diltiazem HCl in milligrams)

(The above formula contains 121.5mg of Cyclocel® (MCC PH102) and 1.0% Magnesium stearate in each tablet, with the targeted tablet weight of 350mg).

Evaluation of Batches

Pre formulation testing

Pre formulation Testing of powder blends all the batches were performed like Bulk Density, Tapped Density, Hausner's ratio, Angele of repose, Compressibility Index shown in Table no 2.

Formulation testing [9-12]

In this Hardness, Thickness, Weight variation, Friability, Drug Content Uniformity tests were performed using 10 tablets of each batch shown in Table no 3.

In-vitro Release Profile Study of Formulated Tablets [13-14]

Method

In vitro drug release studies were carried out using USP 25 (Type II) apparatus in 900ml of dissolution medium (n=3) maintained at 37±1^{0}C at a speed of 100 rpm. Distilled water was used as dissolution medium to avoid the effects of pH change on the solubility of diltiazem hydrochloride as it decreases with the increasing pH. Aliquots of 10ml were withdrawn at predetermined time intervals using calibrated pipette during a 12 hours period and filtered. An equivalent amount of fresh dissolution medium, maintained at 37±1^{0}C was added after withdrawing each sample to maintain the sink conditions. The drug concentrations in the sample analyzed spectrophotometrically (double beam UV, Thermo) at 237nm. The mean of three readings was used to determine concentration. (Table no.4, Fig no.1-3)

Drug Kinetic Study[15]

The release data obtained from various batches were studied with respect to the effect of drug: polymer ratio, diluents ratio. To analyze the mechanism of drug release from the formulation, the dissolution profile of optimized batches was fitted to zero-order, first-order, Higuchi, Hixson-Crowell, Korsemeyer and Peppas to ascertain the kinetic modeling of drug release as shown in (Table no 5).

Water uptake and erosion studies[16,17]

The selected formulations were subjected to the swelling and erosion studies. The results of the swelling studies were shown in Table No. 6 and 7 and Fig No. 4 and 5.Swelling of the tablet excipients particles involves absorption of water resulting in an increase in weight and volume. Water uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecules. The water enters the particles through pores and bind to large molecules breaking the hydrogen bond and swelling of the particle. Three tablets were used per time point. At predetermined time intervals, tablets were removed from the medium and lightly patted using tissue paper to remove excess surface water. The wet weight of tablets was determined and then dried at 70^{0}C until constant weight was achieved before reweighing to determine dry weight.

The following equations were used to determine percent weight gain (water uptake) and percent mass loss:

$$\text{Weight gain (\%)} = \frac{\text{Wet Weight - Dry Weight}}{\text{Dry Weight}} \times 100$$

$$\text{Mass loss (\%)} = \frac{\text{Original Weight - Remaining (Dry) Weight}}{\text{Original Weight}} \times 100$$

FT-IR Spectroscopy

It's important to check any kind of interaction between drug candidate and polymer. The polymers which are to be incorporated into formulation should be compatible with the drug. This compatibility study or interaction study was done using Fourier transformed infrared spectroscopy. IR spectra of pure diltiazem hydrochloride and polymers viz. hypromellose (K4M, K15M, and K100M), xanthum gum, guar gum and compritol 888ATO were taken separately. Then to know if there is any interaction between drug and polymer, IR spectra of diltiazem hydrochloride and other polymers were taken in combination. (Fig no 6, Table no 8.)

Accelerated Stability Studies

The tablets from the selected and optimized batch (H_2X_2) were studied for stability and kept under the accelerated conditions of temperature and moisture (humidity) for the period of three months.The tablets were studied for stability at 40°C and 75% RH conditions for the period of three months. Each tablet was individually weighed and wrapped in an aluminum foil and packed in black PVC bottle and put at above specified conditioned in a heating humidity chamber for 3 months. After each month the, the formulation was observed for changes in physical appearance and analyzed for *in-vitro* drug release. The results were illustrated in (Table No.9 and Fig. No.7).

RESULT AND DISCUSSION

For this study, the hypromellose in various grades like K4M, K15M and K100M were screened firstly in an increasing drug to polymer ratio (1:1, 1:1.5, 1:2) and then selected grade was combined with the natural gums (xanthan and guar) and hydrophobic polymer (compritol 888ATO) in different polymer to polymer ratios (1:3, 2:2, 3:1).

The characterization of drug sample by physical and analytical methodologies revealed that the received drug sample was as per pharmacopoeial standard. Further, the drug and other polymers were subjected to interaction studies by FTIR spectroscopy. No interactions were found between drug and polymer samples.

The powder blend was evaluated for physical properties like bulk density, tapped density, compressibility index, Hausner ratio and angle of repose which shown the results within prescribed compendial limits.

The direct compression method was adopted for the preparation of sustained release matrix tablets with the 10mm punches and targeted weight of 350mg.

The % drug release studies for combined hypromellose and xanthan gum matrices confirmed the batch H_2X_2 (at the end of 12 hours) as per USP criteria Test 2, which give the 93.78% drug release. Hence, this formulation was optimized and subjected to release kinetic study and accelerated stability studies.

The drug release data for batch H_2X_2 were fitted better into an anomalous/non-fickian diffusion mechanism and due to higher erodability of xanthan gum Hixson-Crowell kinetics was concluded. The accelerated stability studies for three months revealed that there were no any remarkable changes in physical properties and % drug released profile.

Table 4: In-vitro Release Profile Study of Formulated Tablets

Time (hr)	In-vitro Release Profile Study of Formulated Tablets								
	Formulation Code								
	H3X1	H2X2	H1X3	H3G1	H2G2	H1G3	H3C1	H2C2	H1C3
1	20.96	17.85	14.69	16.63	19.72	22.94	19.56	21.52	24.03
2	27.47	23.68	19.18	22.42	25.48	27.18	25.14	28.47	30.47
3	33.63	28.26	23.93	30.78	32.72	35.67	28.39	32.58	33.58
4	42.72	37.14	35.76	35.17	41.04	44.34	35.6	38.27	44.66
5	54.19	49.13	47.73	44.08	46.31	51.81	47.78	44.81	50.91
6	63.15	56.68	54.76	52.36	57.06	59.06	53.76	59.62	58.25
7	76.81	68.52	67.34	67.83	71.43	73.24	64.34	67.39	73.18
8	84.72	76.12	74.56	76.92	79.91	81.49	75.52	78.12	81.37
9	87.3	81.42	83.07	84.23	83.32	86.73	82.07	84.43	87.43
10	89.34	88.34	86.27	86.53	88.69	89.59	85.17	87.5	89.82
11	91.49	90.49	88.63	87.48	90.26	91.36	87.3	89.68	91.09
12	94.85	93.78	90.49	91.75	92.58	96.58	90.79	91.75	93.85

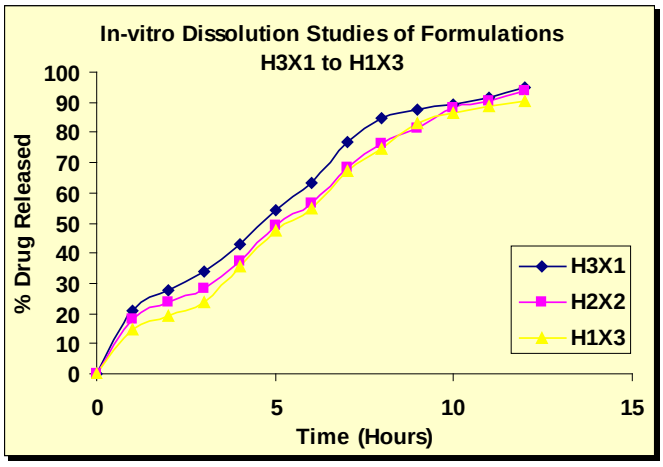

Fig. 1: In-vitro dissolution studies of formulation H3X1 to H1X3

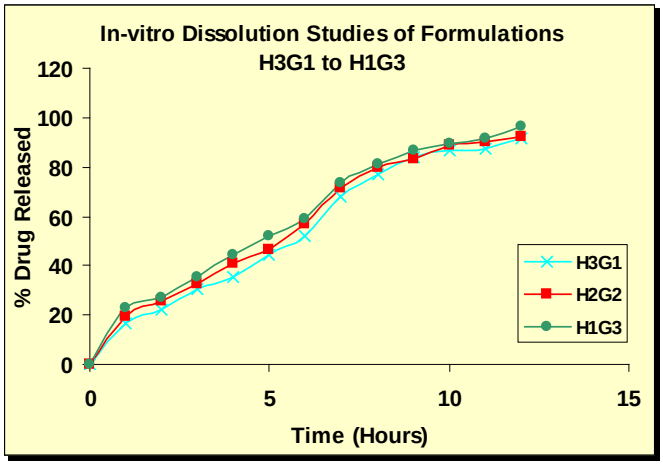

Fig. 2: In-vitro dissolution studies of formulation H3G1 to H1G3

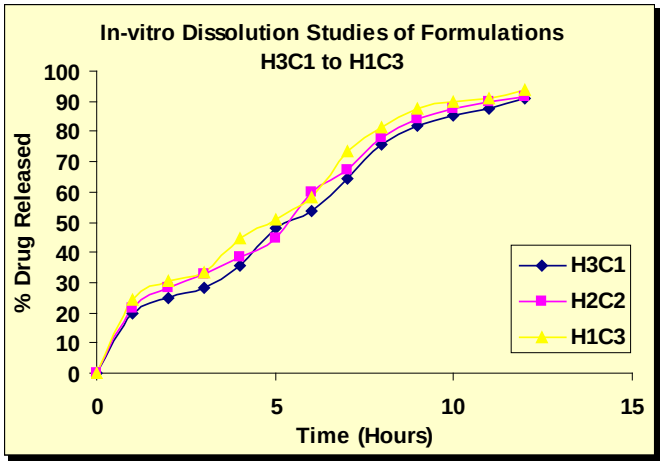

Fig. 3: In-vitro dissolution studies of formulation H3C1 to H1C3

Table 5: Drug Release Kinetic Studies from Formulation II

Formulation	n	Zero-order	First-order	Higuchi	Hixson-Crowell
H3X1	0.628	0.963	0.971	0.985	0.966
H2X2	0.643	0.972	0.963	0.959	0.975
H1X3	0.709	0.983	0.956	0.963	0.988
H3G1	0.515	0.909	0.956	0.994	0.947
H2G2	0.531	0.935	0.969	0.998	0.956
H1G3	0.548	0.916	0.971	0.989	0.963
H3C1	0.574	0.953	0.978	0.987	0.989
H2C2	0.602	0.875	0.939	0.946	0.963
H1C3	0.671	0.847	0.985	0.924	0.970

Table 6: % Water Uptake Studies

Time (Hours)	% Water Uptake					
	X	G	H	H2X2	H2G2	H2C2
0	0	0	0	0	0	0
2	172.28	136.54	110.6	125.1	135.22	86.29
4	248.62	214.55	205.3	185.3	186.39	165.63
6	359.29	295.62	284.3	283.6	285.52	205.79
8	414.64	378.34	344.18	372.62	353.78	293.55
10	475.94	445.76	410.58	415.05	446.14	386.56
12	541.61	532.92	469.84	489.19	524.58	425.68

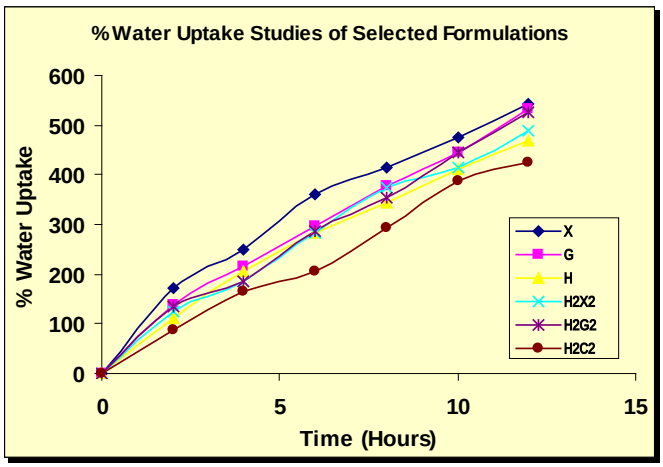

Fig. 4: % Water uptake studies of selected formulations.

Table 7: % Mass Loss Studies

Time (Hours)	% Mass Loss					
	X	G	H	H2X2	H2G2	H2C2
1	15.26	11.38	10.68	12.57	12.74	14.87
2	22.63	16.56	13.74	14.68	15.23	16.37
4	34.74	19.67	20.18	22.8	21.83	23.48
6	52.06	27.08	30.98	33.48	35.18	36.38
8	57.32	36.18	43.36	45.18	47.58	49.18
10	74.22	53.84	51.93	54.96	60.97	62.07
12	80.93	60.34	57.48	59.38	64.86	70.76

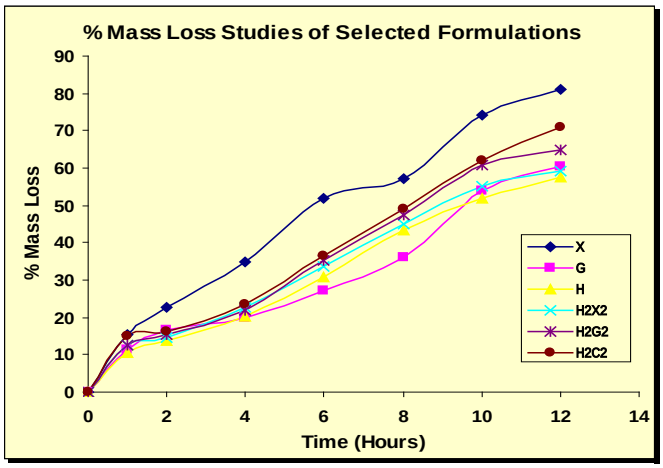

Fig. 5: % Mass loss studies of selected formulations

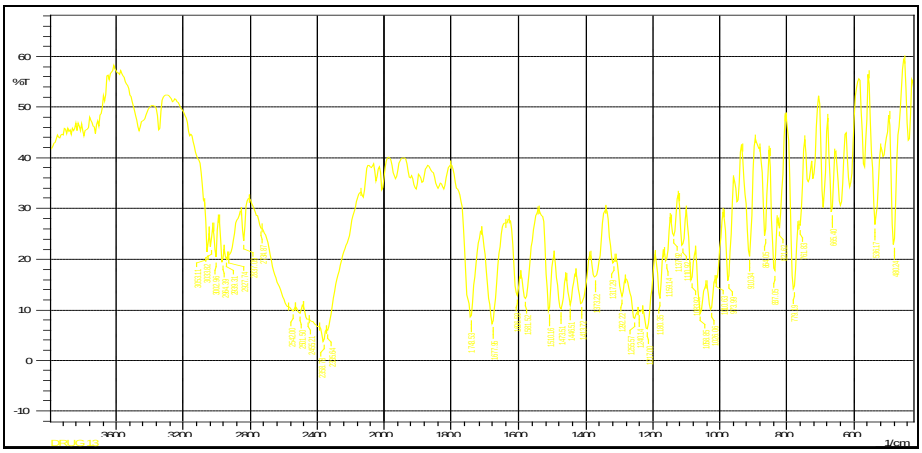

Fig. 6: FTIR of Diltiazem Hydrochloride

Table 8: Interpretation of studied FTIR peaks with their characteristics functional groups

Peaks (cm^{-1})	Characteristic Functional Groups
1700-1650	-CO str
1750	Esteric –CO str
3350-3200	-NH str
3000-2900	Aliphatic (CH3,CH2,CH) str
3100-3000	Aromatic CH str

Table. 9: Effect of temperature and humidity on *in-vitro* drug release

Time (Hours)	% Drug Released			
	0 Month	1 Month	2 Months	3 Months
2	23.68	23.16	24.06	24.92
4	37.14	36.75	37.28	37.75
6	56.68	56.64	57.14	58.42
8	76.12	76.32	76.74	77.96
10	88.34	87.26	87.65	88.32
12	92.78	91.48	92.08	92.46

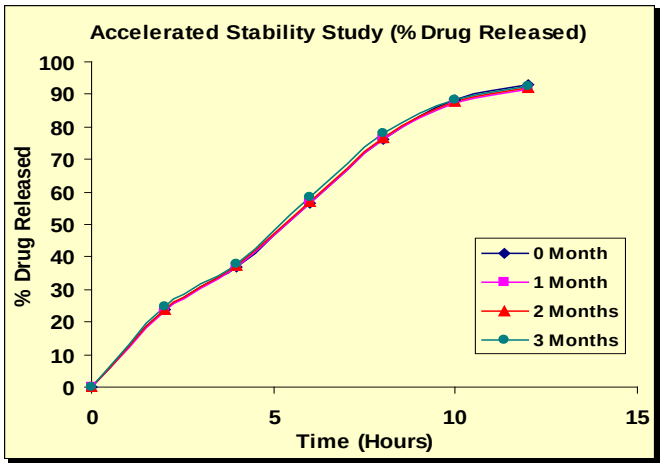

Fig. 7: % Drug release study of optimized formulation at accelerated Conditions

CONCLUSION

In the above view of findings it can be suggested that hypromellose when combined with the hydrophilic natural gums shows the synergistic effects and hence can be utilized as matrix forming agent to prolong the release of Diltiazem HCl. The overall release rate from combined hypromellose and guar flour matrices was significantly higher than that for xanthan gum and compritol 888ATO matrices. Xanthan gum has higher release retarding ability than guar flour. Hypromellose when combined with hydrophobic polymer provides greater release retarding effects than hydrophilic natural gums. The overall frequency of administration of a drug candidate like Diltiazem HCl was successfully reduced to 2 times a day, which generally requires dosing in 3 to 4 times a day in conventional tablet dosage form.

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