Formulation, *In-vitro* and *In-vivo* X-ray evaluation of sustained release matrix tablets of Diltiazem HCL using hydrophilic hydrophobic polymer blend

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ABSTRACT

The SR matrix tablets were formulated by directly compressible hydrophilic hydrophobic polymeric blend of HPMC K100LV and Eudragit L100-55. Here Diltiazem hydrochloride was used as model drug. Tablets were prepared by direct compression method. The pre and post compression parameters were evaluated. Drug polymer interaction was checked by comparing the FTIR spectra of the physical mixture of drug with the excipients used with pure drug. This established the stability of the drug in the formulation which was further confirmed by Differential Scanning Calorimetry thermograms. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release. The results of dissolution studies indicated that formulation F11 the most successful of the study, exhibited drug release pattern very close to marketed product release profile. The mechanism of drug release from F11 was diffusion coupled with erosion (anomalous). Scanning electron microscopy was used to visualize the effect of dissolution medium on matrix tablet surface. In vivo X-ray studies were conducted by X-ray analysis which shows sustaining activity by adhering to various sites in the gastrointestinal tract. The long term stability results show no significant change in the dissolution profile. In conclusion, SR matrix tablet formulation is successfully formulated which can lead to improve efficacy and better patient compliance.

Key words: Diltiazem Hydrochloride, HPMC K100LV, Eudragit L100-55, X-ray, SR Matrix tablets.

INTRODUCTION

Development of oral sustained release drug delivery systems is of much interest to the pharmaceutical scientists as these systems provide prolonged duration of action of drugs having short biological half-life, and reduce dose-related toxicity, dosing frequency, and patient non-compliance (1-2). Among the various sustained release drug delivery systems, pharmaceutical industries prefer sustained release tablet dosage form because of the ease of production using the existing tablet manufacturing infrastructure (3-5). Of these, matrix systems have gained wide-spread importance in controlled drug delivery due to cost-effective manufacturing technology. Matrix drug delivery systems are of two types: diffusion/ swellable systems and dissolution systems. In diffusion systems, drug release is mainly governed by the hydration of matrices followed by diffusion of the drug molecules from the hydrated layer to the surrounding bulk solution, and sometimes, partially by erosion/dissolution(6).

Cellulose ethers (7) Eudragit L100-55s (8) and Carbopols (9) are the best examples of such systems. Hypromellose (HPMC) is the compound most commonly used to control drug release, and the drug-release properties of HPMC have been widely investigated (10-14).
In the present study, matrix tablet containing different proportion of various polymers like HPMC K100LV, Eudragit L100-55 alone and in combination were evaluated for the oral sustained drug release of water-soluble diltiazem hydrochloride in the form of a matrix tablet by using in vitro dissolution studies and in vivo X-ray studies.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride (DTZ) was a gift sample form Wockhardt (Aurangabad, India). HPMC K100LV was gifted by Glenmark (Mumbai, India), Eudragit L100-55 was gifted by Evonik (Mumbai,India). Microcrystalline cellulose (Avicel, FMC Type pH-102), lactose and Magnesium Stearate where obtained as gift samples from Cipla (Kurkumbh,India). All other reagents were of analytical grade.

Preparation of Diltiazem HCL matrix tablets

Diltiazem HCL polymeric matrix tablets were prepared by direct compression method as follows. The formulation of each tablet is shown in Table 1.

Table 1: Formulation development of Diltiazem HCl Sustained release matrix tablets containing 90mg of drug & HPMC K100LV/Eudragit L100-55

Ingredients (mg)	**All batches' quantity in mg/tablet's**											
	F1	F2	F3	F4	F5	F5	F7	F8	F9	F10	F11	F12
Diltiazem Hydrochloride	90	90	90	90	90	90	90	90	90	90	90	90
HPMC K100LV	45	90	180	270	-	-	-	-	22.5	45	90	135
Eudragit L100-55	-	-	-	-	45	90	180	270	22.5	45	90	135
Microcrystalline cellulose	155.25	132.75	87.75	42.75	155.25	132.75	87.75	42.75	155.25	132.75	87.75	42.75
Lactose	155.25	132.75	87.75	42.75	155.25	132.75	87.75	42.75	155.25	132.75	87.75	42.75
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Total weight	450	450	450	450	450	450	450	450	450	450	450	450

All materials were passed through a sieve no.60 except Magnesium stearate and blend in polythene bag and mixed for 10 min. Magnesium stearate was accurate weighted, sieve through sieve no.60 and added to the polythene bag and mixed for additional 2 min. The powder mix was compressed into tablets by using 7 mm rough punch on 10 station tablet punching machine (M/s Cadmach Machinaries Pvt Ltd., Ahmedabad, India). In this study, the total tablet size was fixed at 450 mg. Matrix tablets of each composition were compressed (100 No.) and tested for their hardness, drug content, and drug release characteristics with the required number of tablets for each test. Matrix tablet formulations were coded as F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12.

Evaluation of the prepared tablets

Tablets were evaluated for both its pre-compression parameters like bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose as well as their post

compression parameters tablet hardness (15), friability, uniformity of weight and content uniformity of drug as per IP 2007 (16).

Tablet weight variation

Twenty matrix tablets were randomly selected and accurately weighed using an electronic balance (Shimadzu Corporation, Japan). The results are expressed as mean values of 20 determinations.

Tablet hardness

The hardness of the matrix tablets was determined by using a Monsanto hardness tester.

Drug content uniformity

Ten tablets were weighed individually, crushed and the drug was extracted in water. The solution was filtered through a cellulose acetate membrane (0.45 µm) and the drug content was determined by UV spectroscopy (Evolution 201, UV-visible spectrophotometer, Thermo Fisher Scientific, Shanghai, China) at a wavelength of 237 nm after a suitable dilution.

Tablet friability

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). 20 tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W_f). The % friability was then calculated by

$$\% \text{ Friability} = (1-W_f / W_0) \times 100$$

Where, W_0 -Weight of tablet before test, W_f -Weight of tablet after test.

Fourier-transform infrared (FTIR) spectroscopy

FTIR spectra of DTZ, HPMC K100LV+ Eudragit L100-55 and DTZ with HPMC K100LV+ Eudragit L100-55 were recorded in a FTIR spectrometer (FTIR-4100, Jasco, Japan). The spectra were recorded within 4000–400cm−1 wave numbers.

In vitro drug release from the matrix tablets

To understand the release profiles of the drug from the tablets, dissolution experiments were performed in simulated gastric (0.1 N HCl, i.e., pH 1.2) and intestinal (pH 7.4) conditions. The release of Diltiazem hydrochloride from the tablet was studied using USP XXIII paddle apparatus (Electrolab, Bangalore). Drug release profile was carried out in 750 ml of 0.1N HCl for 2h and then in 900ml of phosphate buffer solution (PBS) pH 7.4 maintained at 37 ± 0.5˚C temperature at100rpm.Ten ml of samples were withdrawn at predetermined time intervals of every 1 h up to 12 h. The samples were replaced by its equivalent volume of dissolution medium and were filtered through 0.45 µm Whattman filter paper and assayed at 237 nm by UV spectrophotometer (Evolution 201, UV-visible spectrophotometer, Thermo Fisher Scientific, Shanghai, China).

The dissolution similarity (f2 similarity factor) was assessed by using FDA recommended approach for comparison of optimized formulation (F11) with marketed formulation (17). The similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles.

$$f2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} x100\right\}$$

Where: n = number of sample points
Rt = percent of marketed product release profile
Tt = percent of test formulations release observed

FDA has set a public standard of f2 value between 50-100 to indicate similarity between two dissolution profiles.

Kinetics of Drug Release

The in vitro release data were treated according to zero order, first order, Higuchi's, Hixson-and Crowell cube root law to find out whether the drug release from the formulations was providing a constant drug release. The data were also fitted to the model developed by Korsmeyer et al. (18) in order to find out the drug release mechanism from the formulations. The correlation coefficients were calculated and used to find the fitness of the data.

Scanning electron microscope studies

The optimized formulation (Batch F11) was removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The specimen was then positioned on the sample holder so as to present a cross-section of the tablet to the microscope. Samples were coated with gold and visualized under scanning electron microscope (SEM) (DSM 950, Zeiss, Germany) at suitable magnifications using a voltage of 10 kV. Processing parameters were optimized to obtain the best possible micrographs

Differential Scanning Calorimetry (DSC)

The stability of the drug in the formulation was confirmed by Differential Scanning Calorimetry (DSC) thermograms. DSC thermograms of the drug, excipient as HPMC K100LV+ Eudragit L100-55 and optimized formulation (F11) were derived from a DSC-60 (Shimadzu, Kyoto, Japan) with a thermal analysis data station system, computer, and plotter interface. The instrument was calibrated with an indium standard. The samples of (1mg) were heated (20 -300-C) at a constant scanning speed (10-C/min) in sealed aluminum pans, using nitrogen atmosphere.

In vivo X-ray Studies

In vivo X-ray studies were conducted by X-ray analysis (19) to study the behavior of the optimized formulation in New Zealand rabbits. The drug was replaced with barium sulfate and other ingredients were kept constant. The F11 formulation was used for X-ray examination. After overnight fasting, healthy New Zealand rabbits weighing 1.5–2 kg was fed with a little low calorie food given some water. The matrix tablets were administered by oral route through a stomach tube and flushing 15ml of water from the syringe through the tube. The animals were held on a board. Radiographs were obtained at 1h, 3 h, 6h, 9h and up to 12 h. The X-ray parameters were kept constant throughout. The movements of the matrix tablet was identified and observed. Permission was obtained from the Animal Ethics Committee (CPCSEA/C/01/448/11-12/21) for the use of experimental animals prior to the experiment.

Stability Studies

Stability studies were carried out as per ICH (Q1A (R2), 2003) guidelines. The long term stability was carried out on optimized matrix tablets at temperature and relative humidity (RH) conditions (30^{o} C and 75 % RH) in stability chambers (Thermo lab, Mumbai, India) for 3 months. Test samples were withdrawn every month and subjected to various tests like weight, hardness, effect of storage on Diltiazem Hydrochloride release from HPMC K100LV/Eudragit L100-55 matrix tablets for F11batch.

RESULTS AND DISCUSSION

Evaluation of the prepared tablets

Evaluation of pre-compression parameters

All formulation batches were evaluated for pre-compression parameters like bulk density, tapped density, compressibility index, Hausner ratio and angle of repose (Table 2). The Compressibility Index for all formulation was in range of 8.07 to 13.20%, bulk density 0.490-0.521 g/cm^3.

Table 2: Pre-compression parameters of Diltiazem Hydrochloride containing HPMC K100LV/Eudragit L100-55

FORMULATION	BULK DENSITY (G/CM^3)	TAPPE DENSITY (G/CM^3)	COMPRESSIBILITY INDEX (%)	HAUSNER RATIO	ANGLE OF REPOSE (^{O})*
F1	0.517	0.564	8.33	0.92	23.62 ± 1.12
F2	0.510	0.555	8.17	0.92	23.89 ± 0.26
F3	0.513	0.575	10.68	0.89	22.84 ± 0.62
F4	0.521	0.564	7.52	0.92	25.64 ± 0.21
F5	0.500	0.553	9.57	0.90	21.58 ± 0.15
F6	0.526	0.555	5.19	0.95	22.46 ± 0.21
F7	0.490	0.565	13.20	0.87	23.76 ± 0.10
F8	0.516	0.567	8.89	0.91	25.26 ± 1.20
F9	0.526	0.572	8.07	0.92	24.29 ± 0.32
F10	0.515	0.566	9.04	0.91	26.48 ± 0.12
F11	0.515	0.573	10.22	0.90	22.15 ± 0.21
F12	0.494	0.576	14.16	0.86	24.35 ± 0.23

Evaluation of post-compression parameters

Sustained release tablets were prepared by punching 400F5 mg of the drug-loaded polymer under a pressure of 400 kgf/cm2 and tablets contained 90 mg of diltiazem hydrochloride.

The post compression parameters tablet hardness, friability, uniformity of weight and content uniformity of drug in Table 3.

Hardness, weight variation, friability and content uniformity for all batches manufactured were tested. The hardness values of DTZ formulations were within range of 4.6 ± 0.04472-5.4 ± 0.04472. It was observed that hardness was strongly influenced by the type of polymer. The hardness of tablets containing HPMC K100LV was higher than that of tablets containing only Eudragit L100-55. The major reason for this may be that Eudragit L100-55 has a rigid structure but HPMC K100LV exhibits plastic deformation properties (Cameron et. al. 1987). The higher hardness of HPMC K100LV is the result of relatively low methoxy and the high hydroxypropyl group

content and also the high moisture content which may contribute to the development of relatively strong hydrogen bonds within the tablets. The friability of DTZ formulation observed within the range of 0.28 ± 0.0185-0.84 ± 0.0265. Results showed that the percent of the DTZ in the compressed tablets as within the 98.6 ± 0.0532 - 99.8 ± 0.0324% of the theoretical label claim.

Table 3: Evaluation of Diltiazem hydrochloride sustained release matrix Tablets Containing HPMC K100LV/ Eudragit L100-55

FORMULATION	HARDNESS^ (KG/CM^2)	WEIGHT VARIATION*	FRIABILITY # %	CONTENT UNIFORMITY^ (%)
F1	5.0 ± 0.04472	449 ± 2.5726	0.80 ± 0.0265	98.6 ± 0.0532
F2	5.2 ± 0.05477	449 ± 2.2820	0.51 ± 0.0399	99.5 ± 0.0326
F3	5.2 ± 0.08366	448 ± 3.5703	0.43 ± 0.0268	99.5 ± 0.0243
F4	5.4 ± 0.04472	446 ± 2.3951	0.42 ± 0.0378	97.7 ± 0.0326
F5	4.6 ± 0.04472	439 ± 2.1343	0.38 ± 0.0089	98.5 ± 0.0326
F6	4.8 ± 0.04472	441 ± 2.5808	0.45 ± 0.0190	99.1 ± 0.0134
F7	4.8 ± 0.05477	440 ± 2.3004	0.30 ± 0.0348	98.9 ± 0.0709
F8	5.2 ± 0.08366	431 ± 2.5808	0.38 ± 0.0157	99.0 ± 0.0435
F9	5.2 ± 0.08944	449 ± 2.5726	0.28 ± 0.0185	99.4 ± 0.0219
F10	5.2 ± 0.05477	439 ± 2.3004	0.40 ± 0.0377	99.6 ± 0.0219
F11	5.2 ± 0.07071	450 ± 2.4767	0.38 ± 0.0157	99.8 ± 0.0324
F12	5.4 ± 0.04472	439 ± 2.1343	0.84 ± 0.0265	98.8 ± 0.0435
Marketed DILZEM SR	5.0 ± 0.08944	188 ± 2.5726	0.28 ± 0.0185	99.4 ± 0.0219

*All values are expressed as mean ±SD (n=3)
^ All values are expressed as mean ± SD (n=5)
# All values are expressed as mean ± SD (n=3).

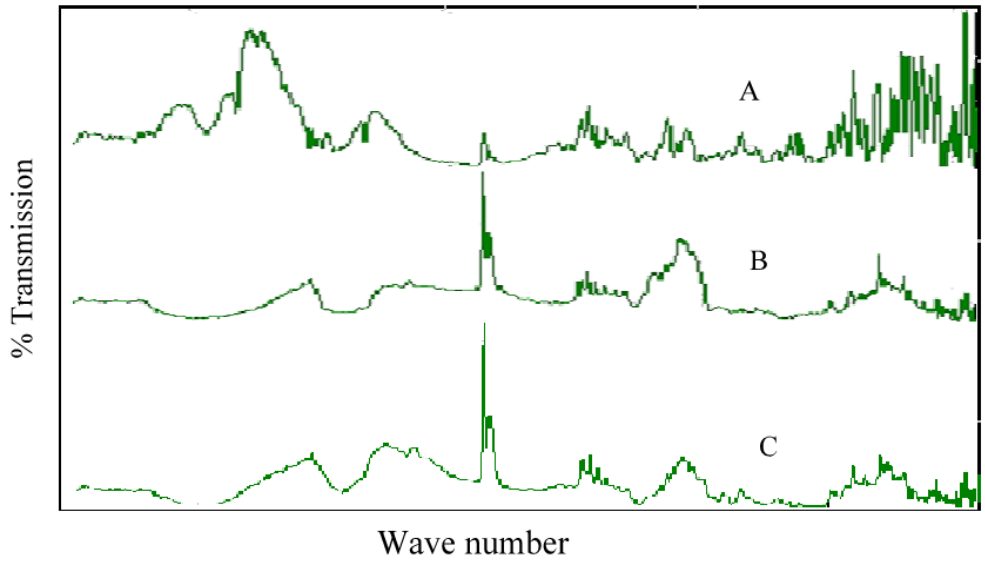

Figure 1: FTIR spectra of Diltiazem HCl (A), HPMC K100LV + Eudragit L100-55 (B), Diltiazem HCl+ HPMC K100LV+ Eudragit L100-55 (C)

FTIR Study

Drug polymer interaction was checked by comparing the FTIR spectra of the physical mixture of drug with the excipients used with the IR spectrum of pure drug. IR

Spectral assignments for Diltiazem HCl reveals that it gives characteristic peaks at 3056 cm-1, 3035 cm-1, 2966 cm-1, 2837 cm-1, 2393 cm-1, 1740 cm-1, 1679 cm-1, 839 cm-1, and 781 cm-1 frequencies in the region of 400 cm-1 to 4000 cm-1. Frequencies of functional groups of pure drug remained intact in physical mixture containing different polymers. So it was concluded FTIR spectra obtained indicated no change in chemical identity of the drug and polymers.

In vitro Release Studies

The varying concentration of HPMC K100LV, Eudragit L100-55 and combination of both on release profile of DTZ was studied. The DTZ release decreased with increased in concentration of HPMC K100LV (Figure 2) for F1, F2, F3and F4. DTZ release is control by the hydration of HPMC K100LV, which forms a gel like barrier layer at the surface of the matrix. Also, the resistance of such a gel layer to erosion is controlled by the viscosity grade of the HPMC K100LV. Matrix tablets containing varying concentration of Eudragit L100-55 showed fast release of DTZ (Figure 3) for F5, F6, F7, F8 which means that Eudragit L100-55 does not promote sustained release. The formulations of DTZ containing combinations of HPMC K100LV and Eudragit L100-55 at 20% and 30% individual level showed a slow release of drug comparable to the formulations containing only HPMC K100LV at 40% and 60% level. It was observed that the combination of HPMC K100LV at 5% and 10% and Eudragit L100-55 at 5% and 10% polymer levels did not retard the drug release (Figure 4). The release pattern of DTZ from marketed tablet and from different batches of formulated matrix tablet i.e. F11 and F12 is illustrated in Figure 5. The formulations of the HPMC K100LV and Eudragit L100-55 combination blends at 20% individual level matrix tablets (i.e. F11) show similar release profile to the marketed product.

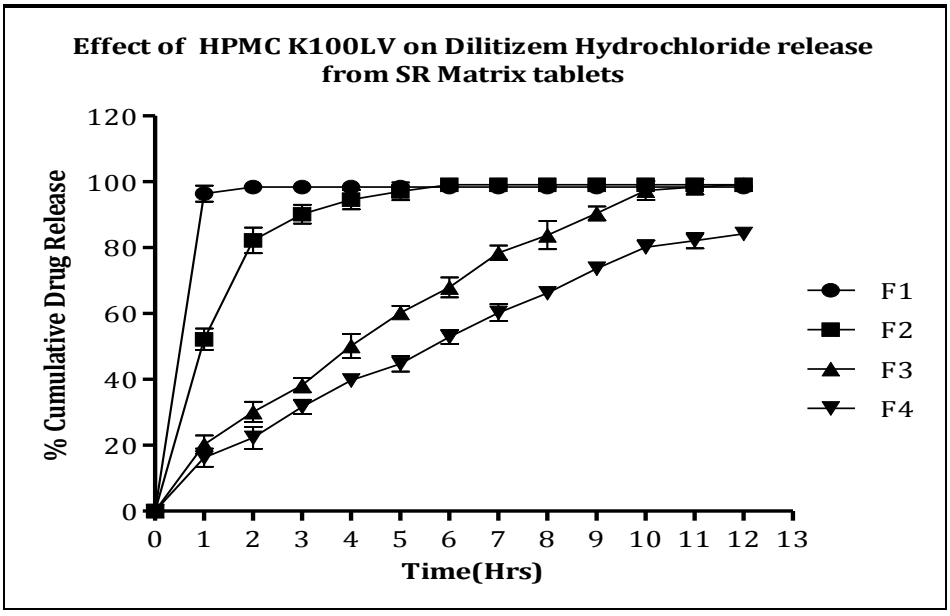

Figure 2: Effect of HPMC K100LV on DTZ release from matrix tablets.

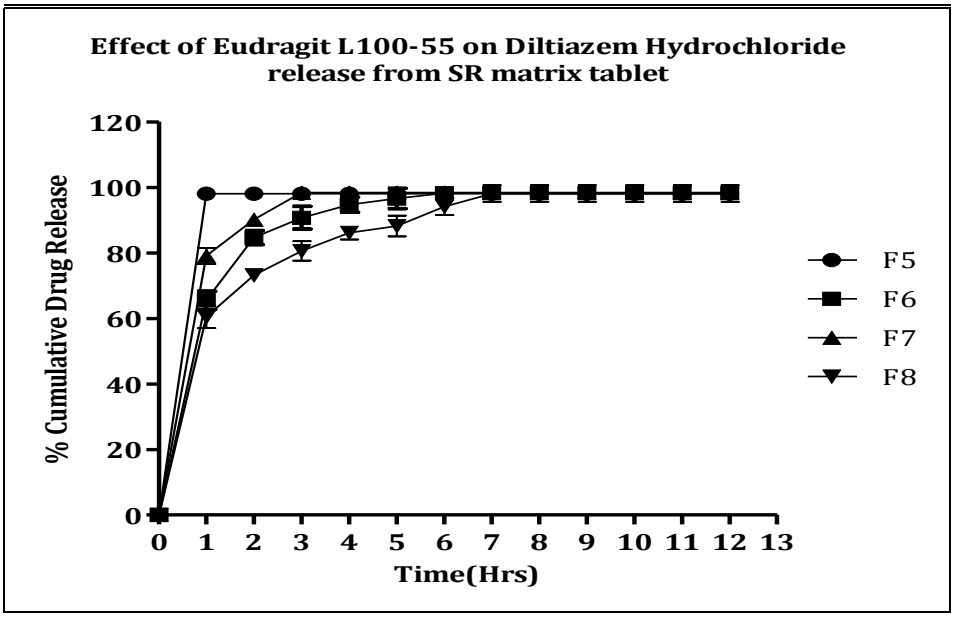

Figure 3: Effect of Eudragit L100-55 L 100-55 on DTZ release from matrix tablets.

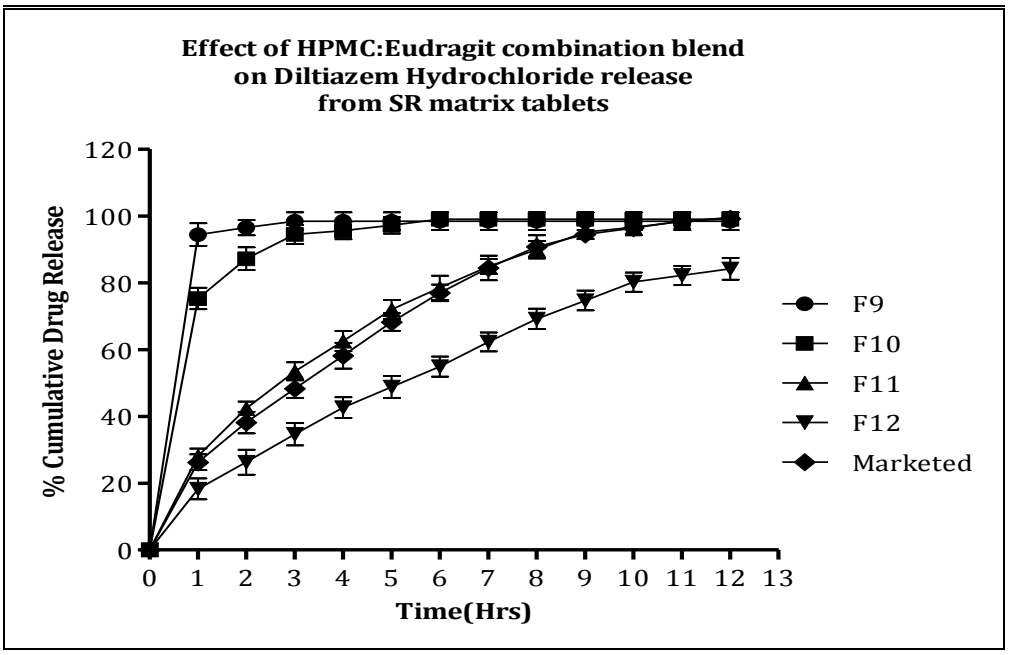

Figure 4: Effect of HPMC K100LV: Eudragit L100-55 combination on DTZ release from matrix tablets.

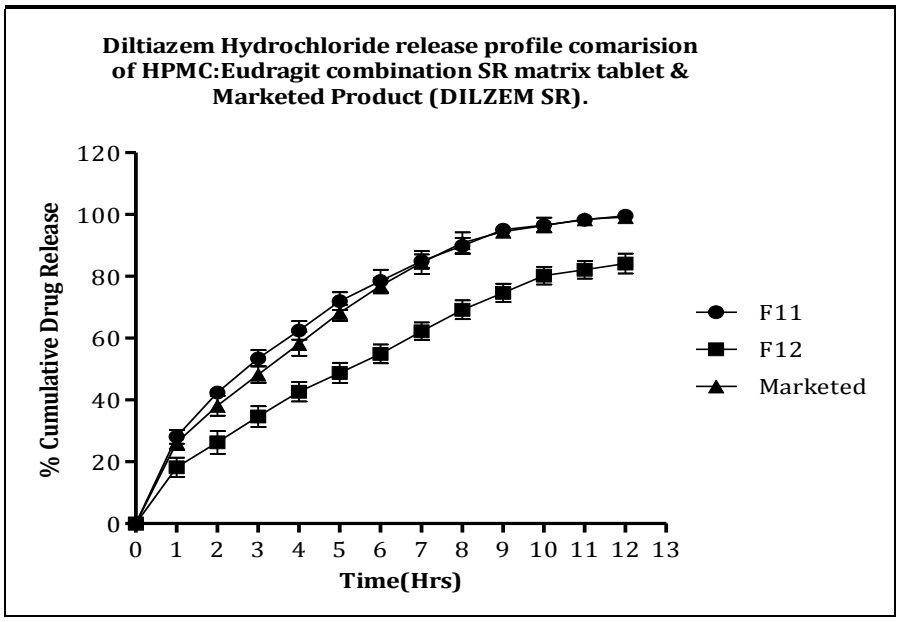

Figure 5: Effect of HPMC K100LV: Eudragit L100-55 combination on DTZ release from matrix tablets compared with marketed preparation.

Dissolution profiles of the HPMC K100LV and Eudragit L100-55 combination blends at 20% individual level SR matrix tablets were comparable to the profile obtained by the marketed product. The f2 value of 77.23 for F11.The f2 values for F11 of the HPMC K100LV and Eudragit L100-55 combination blends at 20% individual level for SR matrix tablets shows its similarity to the marketed product.

Drug Release Kinetics

To describe the drug release kinetics in the 12 formulations and marketed formulation, the in vitro release data were treated according to zero order, first order, Higuchi's, Hixson-Crowell cube root law and Korsmeyer et al's. The release rate kinetic data for all the models can be seen in Table 4. In present study, the in vitro release profiles of drug from F11 and Marketed formulation could be best expressed by Higuchi's equation, as correlation coefficient value (r^2): 0.9927 and 0.9911 shows high linearity respectively. To confirm the diffusion mechanism, the data were fit into Korsmeyer equation. The n value of 0.5208 for F11, and n value of 0.6514 for marketed formulation shows a coupling of diffusion and erosion mechanisms so-called anomalous (non-fickian) diffusion. The complexity of various formulations and its components is indicative of drug release which is controlled by more than one process (dissolution and diffusion).

To confirm the diffusion mechanism, the data were fit into Korsmeyer et al's equation. The mechanism of release of DTZ from batches F1, F2, F6 to F10 was quasi (Fickian) diffusion, while F3, F4, F11, F12 and Marketed showed behaviour of Fickian diffusion (Table 4). Formulation F-11 showed average linearity (R^2 value 0.9870), with slope (n) value of 0.542. This n value appears to indicate a coupling of diffusion and erosion mechanism (known as anomalous non-Fickian diffusion). Hence, diffusion coupled with erosion may be the mechanism of DTZ release from F-V.

Table 4: Correlation coefficient [r^2] and Diffusion exponent [n] after fitting of dissolution data into various releases kinetic models of all formulation of Diltiazem containing HPMC K100LV /Eudragit L100-55.

FORMU-LATION	CORRELATION COEFFICIENT [r^2]					FOR KROSMEYER -PEPPAS EQUATION
	ZERO ORDER	1ST ORDER	HIGUCHI	HIX. CROW.	KORSMEYER PEPPAS	RELEASE EXPONENT [n]
F1	0.6720	0.8072	0.9134	0.7425	0.9065	0.0197
F2	0.6795	0.9614	0.9557	0.9561	0.9384	0.3440
F3	0.9509	0.8803	0.9795	0.9728	0.9918	0.6892
F4	0.9711	0.9842	0.9730	0.9940	0.9953	0.7142
F5	0.8367	0.8574	0.9562	0.8432	0.3333	0.0002
F6	0.5091	0.9132	0.9203	0.8763	0.9524	0.2211
F7	0.8117	0.9695	0.9686	0.9600	0.9840	0.1979
F8	0.5217	0.9200	0.9335	0.9072	0.9896	0.2416
F9	0.6892	0.9028	0.9203	0.8259	0.8790	0.0369
F10	0.3066	0.9617	0.8810	0.8432	0.9694	0.1519
F11	0.8303	0.9363	0.9927	0.9919	0.9906	0.5208
F12	0.9481	0.9875	0.9823	0.9907	0.9911	0.6514
Marketed	0.8763	0.9126	0.9910	0.9888	0.9901	0.5675

Scanning electron microscope studies

SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix (Figure 6C-F). SEM study confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of matrix tablet. The tablet containing HPMC K100LV shows erosion after 1 hour on their surface early in the process, so the active agent placed in this area is immediately released to dissolution medium (Figure 6B). SEM photomicrographs of tablet surface at different time intervals also showed that erosion of matrix increased with respect to time. SEM photomicrograph of the surface of fresh tablet (Figure 6A) did not show any pores. Photomicrographs at 3, 6, 9 and 12 hours revealed pores with increasing diameter. These photomicrographs also revealed formation of gelling structure indicating the possibility of swelling of matrix tablets (Figure 6D). Hence, the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of DTZ from formulated matrix tablets.

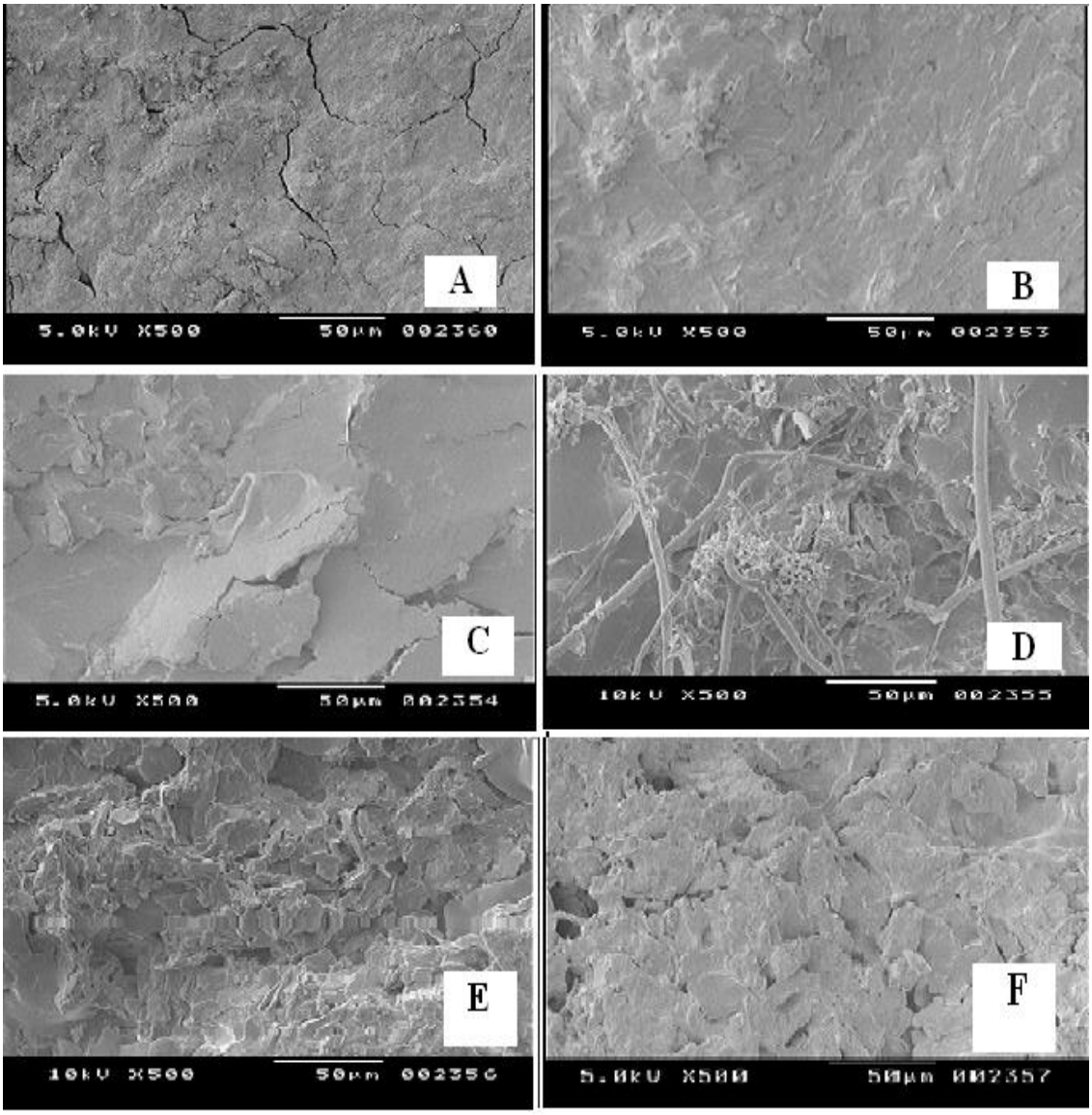

Figure 6: SEM photomicrographs of optimized matrix tablet (batch F11) showing surface morphology after 0 hours (A, 500×), 1 hours (B, 500×), 3 hours (C, 500×), 6 hours (D, 500×), 9 hours (E, 500×), and 12 hours (F, 500×) of dissolution study.

Differential Scanning Calorimetry (DSC)

The DSC study confirmed that the presence of other excipients did not affect the drug nature and it was well maintained in the selected formulation. Thermograms of the DTZ, HPMC K100LV+ Eudragit L100-55 and the optimized formulation F11 are shown in figure 7. A sharp melting transition of Diltiazem hydrochloride pure drug was observed at 216.4°C. In formulation F11 melting endotherm at 213.9°C was observed. This confirmed that the presence of other excipients did not affect the drug nature and it was well maintained in the selected formulation.

Stability studies

The F11 SR Matrix batch were observed for changes in physical properties (Table No: 5). The long term stability results show a significant change in hardness at the 3 month, 6 month and 9 month period. However, there was no significant change in the

dissolution profile (Figure 8) for tablets stored under long term stability conditions for up to 9 months.

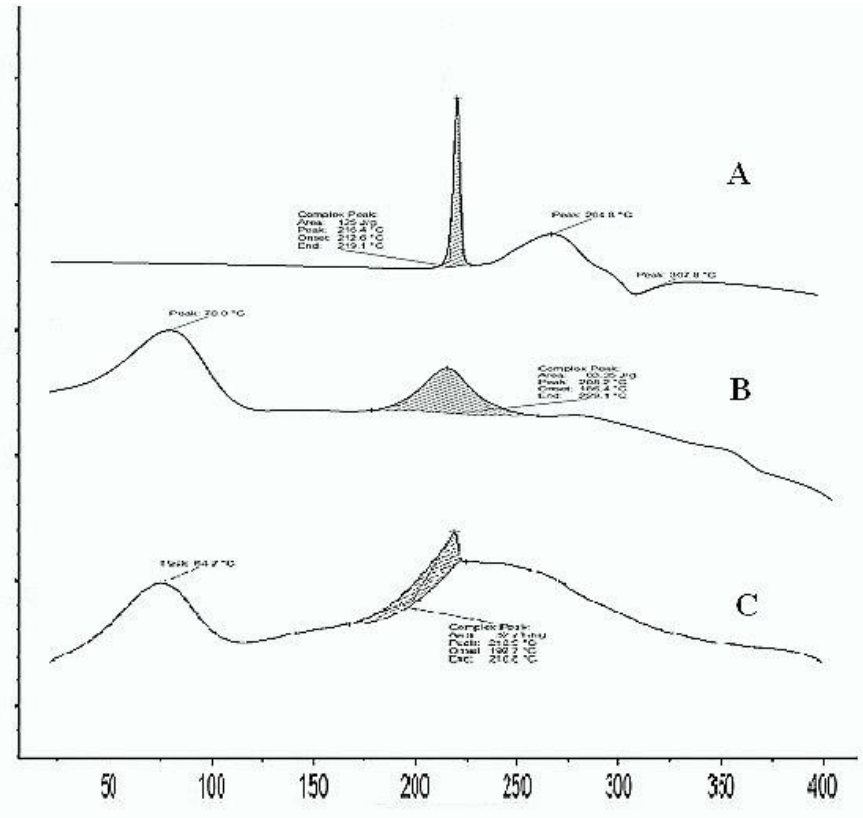

Figure 7: DSC Thermograms of Diltiazem HCl (A), HPMC K100LV + Eudragit L100-55 (B), Formulation 11 (F11) (C)

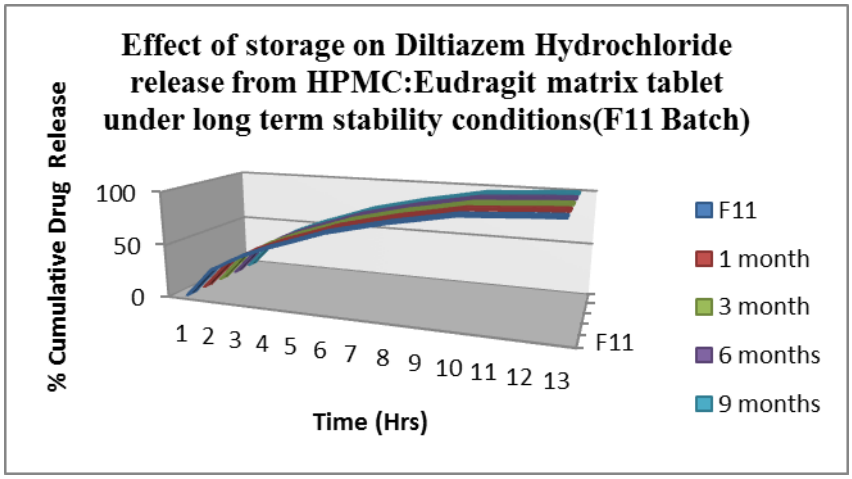

Figure 8: Effect of storage on Diltiazem Hydrochloride release from HPMC K100LV/Eudragit L100-55 matrix tablets under long term stability conditions (F11 Batch)

Table 5: Effect of long term stability storage on the physical properties of HPMC K100LV/Eudragit L100-55 tablets

Physical Property	Initial	1 month	3 months	6 months	9 months
Weight	450 ± 2.4767	449 ± 2.5726	450 ± 2.5726	451 ± 2.2820	451 ± 3.5703
Hardness	5.2 ± 0.07071	5.2 ± 0.0836	5.3 ± 0.0894	5.4 ± 0.0447	5.5 ± 0.0894

(*) significantly different from initial at 0.05 level

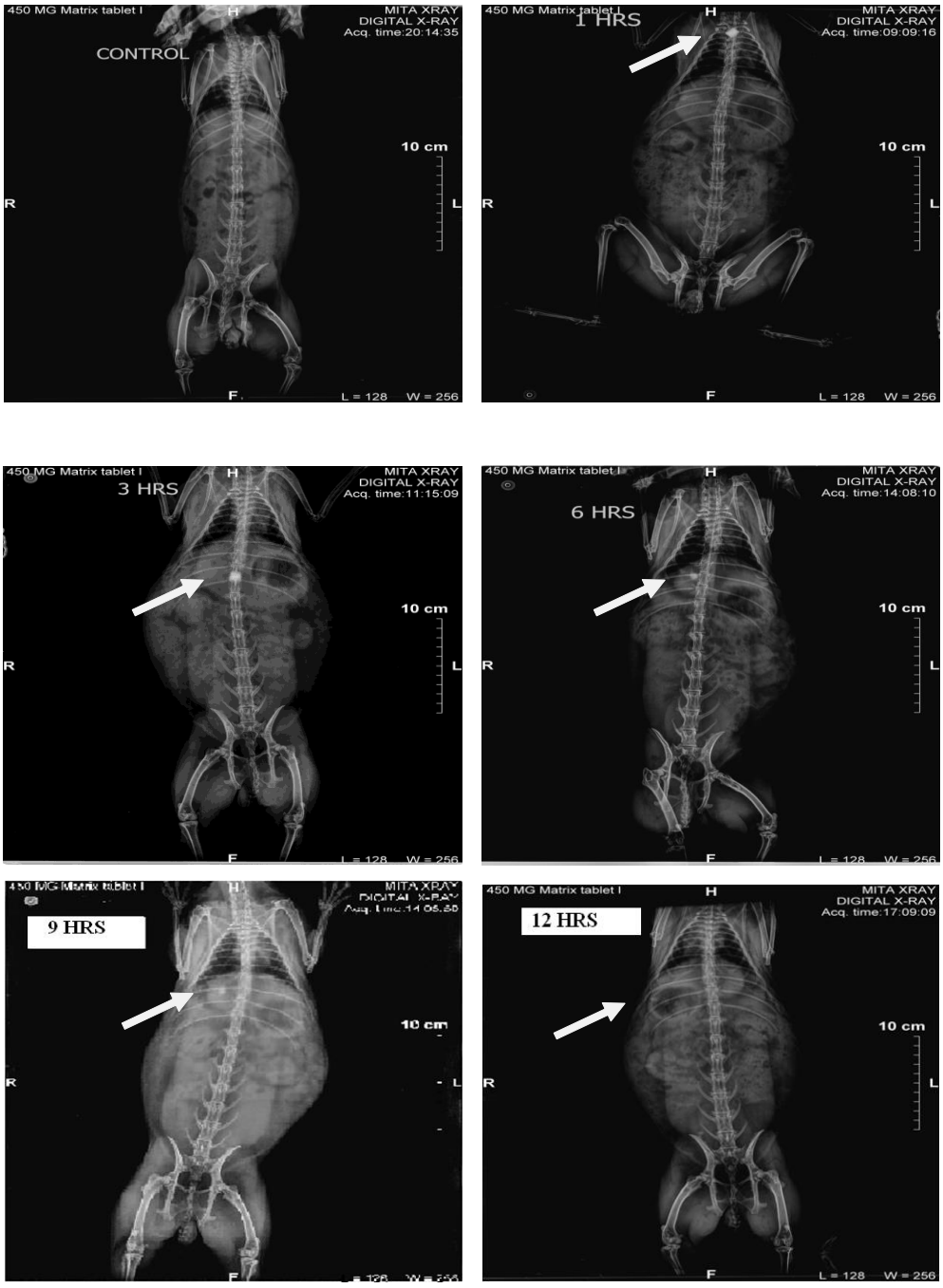

Figure 9: X-rays indicating the position of the barium sulfate-labeled matrix tablets in the gastrointestinal tract of New Zealand rabbits at different time periods X-ray taken at 1 h, 3 h, 6 h, 9 h and 12 h (Arrow indicates the position of tablets).

In vivo X-ray studies

The in vivo X-ray studies were carried out in New Zealand rabbit using soft X-ray analysis. The polymer utilized for the optimization of the formulation showed the sustaining activity in vivo in rabbit by adhering to various sites in the gastrointestinal tract. F11 formulation showed sustaining effect for 12 h as shown in Figure 9.

CONCLUSION

Results of the present study demonstrated that combination of both HPMC K100LV and Eudragit L100-55 polymers could be successfully employed for formulating sustained-release matrix tablets of DTZ. The investigated sustained-release matrix tablet was capable of maintaining constant DTZ concentration through 12 hours. The mechanism of drug release for optimized formulation F11 and for marketed formulation shows a coupling of diffusion and erosion mechanisms so-called anomalous (non-fickian) diffusion. This can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional DTZ tablets.

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