

Formulation Design and Characterization of Kollidon SR Based Trimetazidine Dihydrochloride Matrix Tablets

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ABSTRACT

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The purpose of the present study was to formulate sustained release Trimetazidine Dihydrochloride matrix tablets by using Kollidon SR as rate controlling polymer. Each of the formulated tablet contains 35 mg of Trimetazidine Dihydrochloride. The tablets were prepared by direct compression method. The granules were evaluated for angle of repose, bulk density, tapped density and compressibility index. The formulated tablets were evaluated for weight variation, thickness, diameter, hardness, friability and drug content and also in-vitro dissolution studies. Drug content in formulation was determined by UV method. The granules showed satisfactory flow properties. All the tablet formulations showed acceptable pharmacotechnical properties and complied for tested parameters. The in-vitro release study of matrix tablets were carried out in phosphate buffer with pH 7.4 for 7 hours. The drug release from each formulation was analyzed by using release kinetic theories. The results of dissolution studies indicated that all the formulations exhibited drug release pattern very close to theoretical release profile. Applying kinetic equation models, the mechanism of release of the drug from all the formulations were found to be followed Higuchi model, as the plots showed high linearity, with correlation coefficient (r^2) value of 0.93 or more. The 'n' value lies between $0.45 < n < 0.89$ (Korsmeyer-Peppas model) demonstrating that the mechanism controlling the drug release was the anomalous non-Fickian or anomalous release. The mean dissolution time (MDT) was calculated for all the formulations and the highest MDT value was obtained with formulation 1. Therefore, the results generated in this study showed that the formulated sustained release matrix tablets deliver the drug through a combination of both diffusion and erosion controlled mechanism.

Keywords: Trimetazidine Dihydrochloride, Kollidon SR, Matrix Tablet

INTRODUCTION

Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back and arms. It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia. Trimetazidine is an antianginal and anti-ischemic agent that display anti-ischemic effects without inducing haemodynamic changes and improves the status of the ischemic myocardium.¹ It is used therapeutically in the long term treatment of angina pectoris and it is freely soluble in water. It is a unique anti-ischaemic drug, which protects the myocardial cell from the harmful effects of ischemia. The mode of action is trimetazidine is different from beta-blockers, calcium channel blockers and nitrates. Unlike these antianginal agents, which affect haemodynamic determinants of myocardial oxygen supply-demand balance, trimetazidine prevents the damage to the myocardial cell during an ischemic episode. It is absorbed through the intestinal mucosa

with a T_{max} (time to reach maximum concentration) of 5.4 hours. The C_{max} is 89 microg/L. The t_{75} (time during which the plasma concentration remains above 75% of C_{max}) is 11 hours. The bioavailability is 87%, slightly inferior with trimetazidine modified release than with the immediate-release formulation, explaining the increase in the dose of trimetazidine.²

Various types of oral controlled release formulation have been developed to improve the clinical efficacy of drugs having short half-lives as well as to increase patient compliance. These formulations are designed to deliver drugs at a predetermined rate over a wide range of conditions and durations of therapeutic treatments. One of the most commonly used methods of developing sustained release formulations for therapeutic agents is to include it in matrix tablets, as they are easy to manufacture.³ Using a suitable rate controlling polymer, the matrix can be tableted by direct compression or conventional wet granulation method. Because of their simplicity and cost effectiveness, hydrophilic non-cellulosic polymers in an appropriate combination are extensively used for oral controlled release dosage forms. So, there has been a tremendous demand of sustained release product in the pharmaceutical market. The

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rational of the controlled delivery of drugs is to promote therapeutic benefits while at the same time minimizing toxic effects. Sustained release dosage form, a modern approach in the pharmaceutical sciences has proved its importance and compliance.⁴

The aim of the present study is to design sustained release matrix tablets of Trimetazidine Dihydrochloride in Kollidon SR as the rate retarding substance and evaluate the release characteristics of these tablets and mechanism affected by processing conditions and changes of dissolution medium.

MATERIALS AND METHODS

Materials

Trimetazidine Dihydrochloride was obtained as a gift sample from Drug International Ltd, Bangladesh. Polymer Kollidon SR (BSAF Germany) was obtained as a gift sample from BASF Bangladesh Limited. Kollidon SR is insoluble in water but very soluble in N-methylpyrrolidone. Magnesium stearate and Lactose were obtained also as a gift sample from Novo Pharmaceuticals Ltd. All other chemicals used were of analytical reagent grade and distilled water was used throughout the experiments. Standard Trimetazidine Dihydrochloride was also from Drug International Ltd as a gift and the potency of this standard was used in calculation as label claimed from the source.

Preparation of matrix tablet

Matrix tablets, each containing 35 mg Trimetazidine Dihydrochloride were prepared by direct compression method. The composition of various formulations was shown in Table 1. The active ingredient and other excipients were weighed accurately for thirty tablets according to the formulations and collected in mortar pastel. After proper mixing (5 min) passed through the sieve no. 40 and collected in polyethylene bag. Individually weighed the amount of granules for each tablet (200 mg) and compressed the tablet by using a Perkin-Elmer laboratory hydraulic press equipped with a 10 mm flat faced punch and die set. The compression force and compression time were 5 tons and 1.30 min respectively. Before compression, the surface of the die and punch were lubricated with magnesium stearate. All

preparations were stored in airtight photo film containers at room temperature for further study. This method of tablet production has previously been described by several authors⁵⁻⁸ that provided reproducible experimental results in terms of in-vitro release.

Evaluation of Tablet Blends

Angle of repose (θ) of granules was determined by the funnel method. The diameter and height of the powder cone were measured and angle of repose (θ) can be determined by the equation $\tan\theta = h/r$, where h and r are the height and radius of the powder cone.⁹⁻¹⁰ Bulk density (BD) and tapped density (TD) of each formulations were determined. Bulk density and tapped density were calculated using the equation, $BD = \text{weight of the powder}/\text{volume of the packing}$; $TD = \text{weight of the powder}/\text{tapped volume}$.¹¹ Hausner's ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:¹²

$$\text{Carr's Compressibility Index (\%)} = [100 (TD-BD)]/TD$$

Where, TD is the tapped density and BD is the bulk density

Evaluation of Tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Friability test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The instrument used for this test is known as 'Friability Test Apparatus' or 'Friabilator'. Friability of the tablets was determined by using Electrolab EF-2 friability test apparatus. The thickness of a tablet can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of the tablets was determined by using a Digital Caliper (range 0-150 mm). Weight variation test was performed by taking 10 tablets

Table 1: Formulation of Trimetazidine Dihydrochloride loaded Kollidon SR Based Matrix Tablet

Formulation code	Wt. of TMZ/ Tablet (mg)	Wt. of Kollidon SR/ Tablet (mg)	Wt. of Lactose/ Tablet (mg)	Wt. of Mg-stearate/ Tablet (mg)	Total Weight (mg)
F-1	35	150	12	3	200
F-2	35	135	27	3	200
F-3	35	120	42	3	200

using an electronic balance (Adventurer TM electronic balance, Model AR2140, Capacity (Max) - 210 gm, Readability-0.0001 gm).

Compactibility Assessment

For compactibility assessment the force required for diametral breaking of the compacts was determined using a hand operated hardness tester (Electrolab EH-01P). The tensile strength σ_x of the compacts was calculated using the following equation¹³

$$\sigma_x = \frac{2x}{\pi d t}$$

Where, x is hardness in Kgf

d and t is the diameter and thickness of the compacts in mm respectively

Drug Content Assay

An amount of 35 mg Trimetazidine Dihydrochloride was taken in 100 mL volumetric flask and dissolved in phosphate buffer solution (pH 7.4) and make the volume up to 100 mL and measure the absorbance of solution at wavelength 270 nm.

Then, five tablets of formulated tablets from each formulation were weighed accurately and grinded properly. Then 200 mg of grinded powder (equivalent to 35 mg) was taken in 100 mL volumetric flask and dissolved in same pH of phosphate buffer solution and make the volume up to 100 mL. Then measure the absorbance of solution at wavelength 270 nm. Then calculate the percentage content uniformity by the following equation:

$$\text{Percentage content uniformity} = \frac{A_{\text{spl}} \times W_{\text{std}} \times \text{Average Weight} \times P_{\text{std}}}{A_{\text{std}} \times W_{\text{spl}} \times \text{Label claimed of drug in formulation}}$$

Here,

A_{spl} = Absorbance of Sample

A_{std} = Absorbance of standard

W_{spl} = Weight of sample

W_{std} = Weight of Standard

P_{std} = Potency of standard (98.13% as claimed by source)

In-Vitro Dissolution Study

The in vitro release of Trimetazidine Dihydrochloride from the formulated tablets was carried out in USP type II test apparatus (rotating paddle method) using 900 mL of dissolution medium maintained at $37.0 \pm 0.5^\circ\text{C}$ and a stirring rate of 75 rpm. Three tablets from each formulation were tested individually in 900 mL phosphate buffer (pH 7.4) for

the following 7 hours. At specific time interval 5 mL of medium was withdrawn for measuring the drug release and in every case 5 mL of fresh buffer was substituted to maintain the volume constant. After filtration, the amount of Trimetazidine Dihydrochloride in each sample was determined spectrophotometrically at 270 nm. Dissolution studies of the tablets were also carried out in viscous media of different concentration (1%, 2%, 3% HPMC)

Analysis of Release Data

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time (hr)), first order (log cumulative percentage of drug remaining versus time (hr)), Higuchi (cumulative percentage of drug release versus square root of time (hr)), Korsmeyer-Peppas (log cumulative percentage of drug release versus log time (hr)) and Hixson-Crowell (cubic root of percentage drug release versus time (hr)) equation models.

Dissolution data were also fitted according to the well-known exponential equation, which is often used to describe the drug release behavior from polymeric systems introduced by Korsmeyer-Peppas *et al.*¹⁴

$$M_t / M_\infty = k t^n$$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release. A value of n = 0.45 indicates Fickian (case I) release, > 0.45 but < 0.89 for non-Fickian (anomalous) release and > 0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release.¹⁵

Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel and Lippold).¹⁶

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

Where, n is the release exponent and k is the release rate constant.

Statistical analysis

To justify the statistical significance student's t-test was carried out and $p < 0.05$ (at 5% confidence level) was considered as statistically significant.

RESULTS AND DISCUSSION

Evaluation of Tablet Blends

The granules of the different formulations were prepared and evaluated for angle of repose, bulk density, tapped density,

compressibility index and hausner's ratio. The results are presented in the Table 2. The results of angle of repose and compressibility index (%) ranged from (45° to 46.1°) and (36.12 to 39.91) respectively. The results of angle of repose value less than 30 degrees indicates good flow properties.¹⁷ This was further supported by the lower compressibility index. The lowest compressibility index around 21% and below are considered to have fair and excellent flow properties.¹⁷ The results of loose bulk density and tapped bulk density ranged from (0.402 to 0.412) and (0.645 to 0.669) respectively. Although the results of angle of repose and compressibility index were slightly higher, there were no countable problems occurred during the compression of tablets.

Physical Characterization and Drug Content of Matrix Tablets

The prepared tablets were subjected to preliminary characterization such as physical parameters (thickness, diameter, hardness and friability) and weight uniformity of all the fabricated tablets. The values are presented in Table No. 3. Table 3 also shows the drug content of these tablets. All the batches showed uniform thickness and diameter. The percentage of average weight deviation of 10 tablets of each formulation was less than (5%), and hence all formulations passed the test for uniformity of weight as per official requirements. The hardness of all the formulations within the range of limit. In the present study, the percentage friability for all the formulations was below 1% w/w, indicating that the friability is within the prescribed limits. So, all the tablet formulations showed acceptable pharmacopoeial properties and complied with pharmacopoeial specifications for weight variation and friability. All the formulations showed good

uniformity in drug content and the percentage of drug content was 101.92±0.08, 95.63±0.07 and 98.60±0.05 respectively to formulation 1, 2 and 3.

The tensile strength of the compacts is presented in Fig. 1. The values of tensile strength were changed as a function of polymer concentration in the formulation. When compared with F-1, other formulations showed significant changes ($p < 0.05$) in the tensile strength. This result indicates that Kollidon SR is good enough to use to solve the problem, where the tablets showed insufficient tensile strength.

Release Kinetic Studies

The dissolution data (from the values of 0 to 7 hours drug release) of all formulations were fitted into various mathematical models (zero-order, first-order, Higuchi, Korsmeyer-Peppas model, Hixson-Crowell plot) to know which mathematical model will best fit the obtained release profile. The plotted figures of zero-order and Higuchi are

Fig. 1: The tensile strength of Trimetazidine Dihydrochloride sustained release formulations. * $P < 0.05$ compared with the formulation F1.

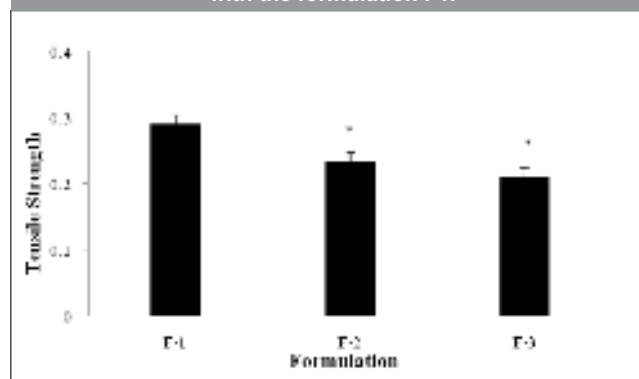


Table 2 : Granule properties of the different formulations of Trimetazidine Dihydrochloride sustained release matrix tablets

Formulation code	Angle of repose (°)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's Ratio
F-1	46.1	0.403	0.650	38.00	1.61
F-2	45.0	0.412	0.645	36.12	1.57
F-3	46.1	0.402	0.669	39.91	1.66

Table 3: Tablet properties of the different formulations of Trimetazidine Dihydrochloride sustained release matrix tablets

Formulation Code	Thickness (mm) (n=3)	Diameter (mm) (n=3)	Hardness (kgf) (n=3)	Friability (%)	Average weight (mg) (n=10)	Drug content (%)
F-1	2.96±0.03	10	13.47±0.03	0.15	201.07±1.25	101.92±0.08
F-2	2.93±0.03	10	10.72±0.28	0.18	201.82±0.57	95.63±0.07
F-3	2.90±0.05	10	9.65±0.11	0.22	200.75±0.89	98.60±0.05

The values are expressed as mean ± SEM; n is specified in each column head

presented in Fig. 2(a) and Fig. 2(b). The release kinetics parameters of all formulations are presented in Table 4. Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. When the data were plotted according to a Higuchi equation, the formulations F-1, F-2 and F-3 showed a fair linearity, with regression values 0.9331, 0.9605 and 0.9479 respectively, while the data were plotted according to a first-order equation, the formulations F-2 and F-3 showed a fair linearity, with regression values 0.9726 and 0.9601 respectively. Based on the 'n' values ranging from $0.45 < n < 0.89$ the drug release was found to follow anomalous or non-Fickian release. This value indicates a coupling of the diffusion and erosion mechanism and indicates that the drug release was controlled

by more than one process. This finding was in accordance with other reported works.¹⁸⁻¹⁹ Moreover, when the Higuchi release rates (Fig. 4) of the formulated tablets were statistically compared with that of F-1, we found a significant ($p < 0.05$) changes of the drug release rate in line with the changes of the polymer concentration in the formulations used in this study.

Release of Drug According to Higuchi Equation and MDT

Based on highest regression coefficient value (r^2) the best-fit model for all formulations was Higuchi model. From this experiment, it was observed that the rate of drug release increases when the amount of polymer decreases and it is

Table 4: Release kinetics parameters of designed sustained release matrix tablets of Trimetazidine Dihydrochloride

Code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Korsmeyer-Peppas (r^2)	Korsmeyer-Peppas (n)	Hixson-Crowell (r^2)
F-1	0.7694	0.8474	0.9331	0.9429	0.461	0.7174
F-2	0.8853	0.9726	0.9605	0.8703	0.737	0.7014
F-3	0.8111	0.9601	0.9479	0.8832	0.599	0.6759

r^2 denote the regression coefficient and n denote the slope of Kosmeyer-Peppas plot

Fig. 2: Release model of Trimetazidine Dihydrochloride sustained release formulations (a) Zero-order release model and (b) Higuchi release model.

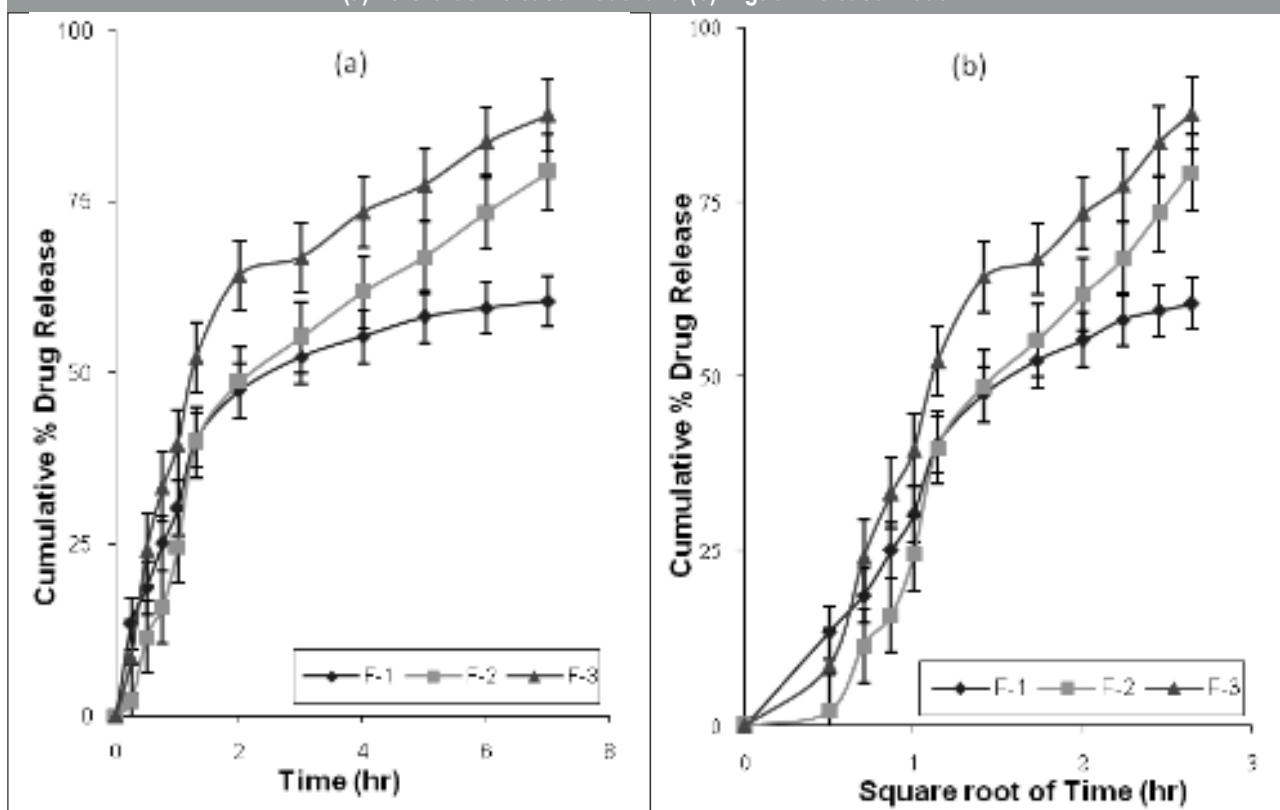
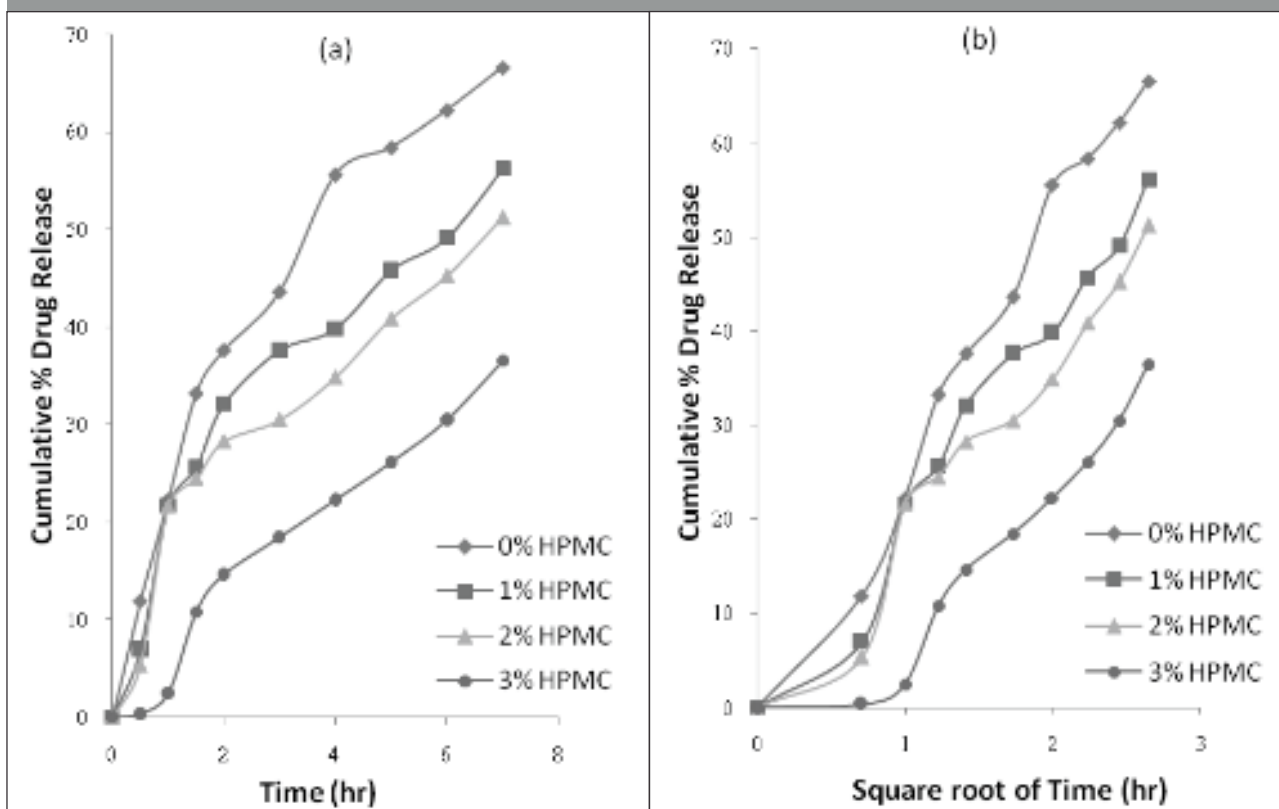


Fig. 3: Release profile of Trimetazidine Dihydrochloride sustained release formulations in different concentration of HPMC (a) Zero-order cruve and (b) Higuchi plot.



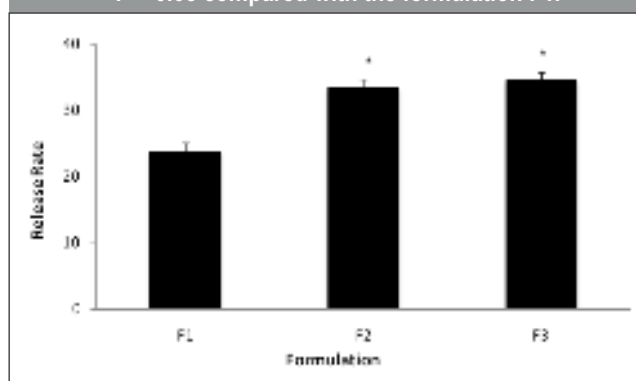
statistically significant and presented in fig.4. Time required for 25, 50 and 75% of drug release was corrected using linear equation of Higuchi plot. From this study, it was observed that formulated tables of formulation 1 took the time more than 8.5 hours for 75% of drug release.

Mean Dissolution Time (MDT) value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability and vice-versa. The MDT value was found to be low for formulation F3 and high for formulation F1 (Table 5). In other words, the formulations containing higher percentage of Kollidon SR exhibited a higher value of MDT. Considering the release kinetic studies, MDT and $T_{75\%}$ of drug release, we concluded that F-1 formulation better one among other formulations.

Effect of Viscosity of Dissolution Medium in Drug Release

With an aim to demonstrate the effect of viscosity of dissolution medium in drug release mechanism, different viscous dissolution medium were prepared by dissolving 1%, 2% and 3% Hydroxypropyl methylcellulose (HPMC) in distilled water. HPMC, a free-flowing powder, is commonly used to provide the hydrophilic matrix. When HPMC comes

Fig. 4: Bar diagram of Higuchi release rate of Trimetazidine Dihydrochloride sustained release formulations. * P < 0.05 compared with the formulation F1.



in contact with water it makes a gel layer.²⁰ Here HPMC was used to evaluate how the gel layer formed by HPMC modify the drug release pattern in aqueous medium. In-vitro release data presented in Fig. 3. shows that drug release was faster in medium without HPMC, but it continuously decreased when the percentage of HPMC incorporation in medium increased. Medium with 3% HPMC contributes around 36.48% drug release after 7 hr while 1% HPMC containing medium

Table 5: Required time for 25, 50 and 75 percentage of drug release

Formulation Code	Time 25% (hr)	Time 50% (hr)	Time 75% (hr)	MDT (hr)
F-1	0.684	3.516	8.544	4.66
F-2	0.891	2.859	5.944	4.37
F-3	0.412	1.858	4.343	2.37

showed 56.15% drug release. From this it was observed that there was a gradually decline in the release rate of Trimetazidine Dihydrochloride with the increase in viscosity (Fig. 3). Increase in the dissolution media viscosity by using HPMC reduced the hydrodynamic activity of the dissolution fluid and thereby decrease the rate of hydration of Kollidon SR matrixes. The formation of rubbery state at the boundary layer and consequent erosion was lower in higher viscosity fluid; therefore release rate was also slower. From this study, its help to predict that if HPMC is incorporated in the Kollidon SR based matrix tablets directly, it may contribute a zero order drug release as Hossain *et al* found a zero order release of theophylline in presence of HPMC from Kollicoat SR 30D and Kollicoat EMM 30D based matrix.⁸

CONCLUSION

From the study, it is possible to conclude that the proposed tablet formulations were suitable for direct compression method. The incorporation of Kollidon SR as a polymer entails the stronger rate-retarding agents. According to the release studies, it was observed that the rate of drug release increases with decrease in total polymeric content of the matrix. Kollidon SR is quite good enough to sustain the drug release from the matrix tablet. However, further investigation is required to establish in-vivo-in-vitro correlation to reveal the accurate pattern of drug release in vivo environment from this polymeric system.

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