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Design, Development and Evaluation of Modified Release Trimetazidine Dihydrochloride Matrix Tablet

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ABSTRACT

Trimetazidine Dihydrochloride is chemically known as 1-(2, 3, 4-trimethoxybenzyl) piperazine. It is a safe drug in the treatment of chronic ischemic disorders. So, for achieving continuous and constant plasma levels it is import to change immediate release dosage form into a modified release dosage form of Trimetazidine Dihydrochloride. The experiment revealed that Methocel K4M CR in varying concentrations control the Trimetazidine Dihydrochloride release effectively for 8 hours; hence the formulation F4 can be considered as the desired formulation for a twice daily sustained release tablet of trimetazidine dihydrochloride. Drug release kinetics indicated that the drug release of formulation F-1, F-2 and F-3 were best explained by First Order pot as the plot showed the highest value of linearity and the drug release of formulation F-4 and F-5 was best explained by First Order, Higuchi and Hixson-Crowell equations as these plots showed the highest value of linearity. Formulation F-6 to F-8 was best fitted in terms of Higuchi model. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism from all proposed formulations (F-1 to F-8) showed exponent n values ranging from 0.358 to 0.697 indicating that both Fickian diffusion (F1 to F3) and non-Fickian diffusion or anomalous transport (F-4 to F-8) as if n = 0.45 the release mechanism follows Fickian diffusion and if $0.45<n<0.89$ the release mechanism follows anomalous diffusion or non-Fickian diffusion. This study reveals that the release of Trimetazidine Dihydrochloride critically depends on the rate retarding polymer level in the matrices. Proper adjustment of polymer with drugs enabled a desirable release characteristic of active ingredient.

Keywords: Trimetazidine Dihydrochloride, Matrix tablets

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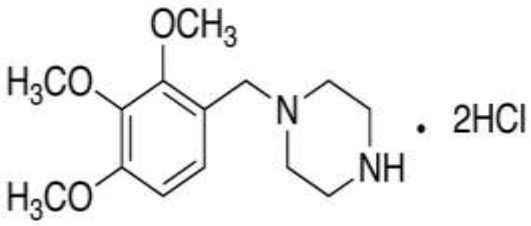
INTRODUCTION

Trimetazidine Dihydrochloride is chemically known as 1-(2, 3, 4-trimethoxybenzyl) piperazine.



Molecular formula: $C_{14}H_{22}N_2O_3$•2HCl

Molecular weight: 339.26

Trimetazidine Dihydrochloride is used therapeutically in the long term treatment of angina pectoris and administered orally in doses of 40 to 60mg daily in divided doses as an immediate release preparation. It has short plasma half-life of around 0.6 – 1.4 hours because of having quick absorption and elimination. For this reason 20mg preparation is given twice or thrice a day in order to ensure relatively constant plasma levels. Multiple daily dosing is often inconvenient and causes missed dosing and patient non-compliance with therapeutic regimen. Consedering manufacturing easiness and cost effectiveness hydrophilic polymers are mostly used and among hydrophilic polymers,polysaccharides are appropriate choice of materials beacause of having non toxicity and wide regulatory acceptance.

MATERIALS AND METHOD

Materials:

Table 1: List of ingredients used in the preparation of trimetazidine dihydrochloride matrix tablet:

Ingredients	Functions	Source
Trimetazidine Dihydrochloride	API	JPN Pharma Pvt. Ltd., India
Methocel K4M CR	Polymer	Colorcon Asia Pvt. Ltd.
Dibasic Calcium Hydrogen Phosphate	Diluent	Commercial Source (Local)
Povidone (Kollidone 30)	Binder	BSF, South East Asia Pvt. Ltd. Singapore
Colloidal Silicon Dioxide (Aerosil 200)	Glidant	Evonik Degussa Germany
Magnesium Stearate	Lubricant	Novochem GmbH

Table 2: List of reagents used in the preparation of trimetazidine dihydrochloride MR tablet:

Reagents	Source Company name	Country
HPLC grade Methanol	J. T. Baker	USA
Distilled water	In house	

Table 3: List of instruments used in the preparation of trimetazidine dihydrochloride matrix tablet:

Instruments	Source
Rapid mixer granulator	Thailand
Fluid bed processor	Thailand
Pilot Press Compression Machine	India
Binder Stability Chamber for 40°C + 75% RH	Germany
Sartorius Electronic Balance	Germany
PHARMATEST Friability Tester	Germany
PHARMATEST Hardness Tester	Germany
Vernier Caliper	China

Methods:

Preparation of matrix tablets:

Matrix tablets, each containing 35 mg Trimetazidine Dihydrochloride, were prepared by wet granulation technique. The drug polymer concentration was developed to adjust drug release and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 210 mg with different drug polymer (HPMC) concentration. A batch of 1000 tablets was prepared in each formula. The composition of tablets is shown in Table 1. Dibasic calcium phosphate (anhydrous) was incorporated as filler excipient to maintain tablet weight constant. This filler was incorporated also for counterbalance the faster solubility of the drug in presence of hydrophilic polymer and to provide a stable monolithic matrix. The ingredients Trimetazidine Dihydrochloride, HPMC, Dibasic calcium phosphate (anhydrous) were passed through sieve no. 30 and mixed in a polybag. The powder blend was granulated using granulating fluid PVP-K30 dissolved in IPA and passed the wet mass through sieve no. 12. The wet granules were dried into a Fluid bed dryer at 65^0c until LOD reaches in the range of 2.5% to 3.5% w/w. The dried granules were passed through sieve no. 24. The granules was then lubricated with magnesium stearate and Aerosil 200 passed through sieve no. 40 and compressed into tablets on a 10-station single rotary Polit Press machine using 8.0 mm Standard concave punches plain on both side.

Formulations of trimetazidine dihydrochloride matrix tablets (F-1 to F-8)

Table 4: The active ingredient, polymers and excipients used in the proposed formulations coded as (F-1to F-8):

Ingredients (mg/Tab.)	Formulations							
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Trimetazidine Dihydrochloride	35	35	35	35	35	35	35	35
HPMC K4M	90	100	110	120	130	135	140	145
Dibasic Calcium Phosphate (Anhydrous)	72.5	62.5	52.5	42.5	32.5	27.5	22.5	17.5
Povidon (Kollidon 30)	6	6	6	6	6	6	6	6
Aerosil 200	1	1	1	1	1	1	1	1

Magnesium Stearate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
IPA	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Total	210	210	210	210	210	210	210	210

Evaluation of physical properties of formulation granules:

Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of granules lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume observed, the cylinder was allowed to fall under its own height onto hard surface from the height of 2.5 cm at 2 seconds interval. The tapping was continued until no further change in the volume was noted. (LBD) and (TBD) were calculated by using the following formulas[1].

LBD = Weight of the powder / volume of the packing.

TBD = Weight of the powder /tapped volume of the packing

The compressibility index

The compressibility index of the granules was determined by Carr's compressibility index[2].

Hausner's Ratio

Hausner found that the ratio D_F/D_o was related to inter particle friction and as such, could be used to predict powder flow properties[3].

Hausner's factor = Tapped bulk density/Loose bulk density. According to Hausner ratio, less than 1.25 indicates Good type of flow property and more than 1.5 indicates Poor type of flow property.

Angle of Repose

Static angle of repose of the granules were determined by the funnel method. The accurately weighed granules were taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[4].

$\tan \theta = h/r$

Where "h" and "r" are the height and radius of the powder cone.

Moisture content:

Moisture content of granules was determined using Mettler Karl Fischer Titrator. About 120mg granules was weighed and added into the reagent solutions of the instrument, which was stirred and the tare weight was fed into the instrument. Then after certain duration of time the moisture content as %w/w was read on the monitor.

Evaluation of physical properties of matrix tablets:

Weight variation test:

To study weight variation, 20 tablets from each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness:

For each formulation, the hardness of 6 tablets was determined using the PHARMA TEST Hardness Tester Machine.

Thickness:

The thicknesses of the tablets were determined by using a digital slide calipers. Five tablets from each batch were used and average values were calculated.

Friability:

Friability of 20 tablets of each proposed formulations were determined using the PHARMA TEST Friability Tester.

Drug Content

Assay of Trimetazidine Dihydrochloride after preparation of tablets:

Drug content of each of eight proposed formulation tablets were determined by HPLC analysis. For drug content assay, about 25 mg of working standard of trimetazidine dihydrochloride were taken in five separate 100ml volumetric flasks, which were then diluted up to the mark with Phosphate buffer solution pH 6.8 and sonicated for 10 minutes to dissolve the active Trimetazidine Dihydrochloride in the diluting solvent. Dilute 10 ml of this solution to 50 ml with Phosphate buffer solution pH 6.8. Then each solution was filtered using 0.2µ disk filter and the filtrate was taken in HPLC vials.

20 tablets were weighed and the average weight was determined. The tablets of eight proposed formulations (F-1 - F-8) were crushed and the powder equivalent to 100 mg was taken into 200 ml volumetric flask which contain 120 ml previously boiled Phosphate buffer solution pH 6.8 (Temperature up to 90^{o}C), sonicated for 20 minutes followed by cooling to room temperature. Filtration was done through Whatman 1 filter paper and 5 ml of the filtrate was diluted with Phosphate buffer solution pH 6.8. Then each solution was filtered using 0.2µ disk filter and the filtrate was taken in HPLC vials. Finally, vials were placed into the tray of the auto sampler of HPLC, then the instrument was run and chromatograms were recorded by injecting 50µl from each of the vials. Trimetazidine Dihydrochloride content was then measured by using following equation

Trimetazidine Dihydrochloride content per tablet,

$$= \frac{P_{sample} \times W_{standard} \times 10 \times 200 \times 50 \times Y \times \text{Average wt. of tablet}}{P_{standard} \times 100 \times 50 \times 5 \times W_{sample} \times 100}$$

Where;

P_{sample} = Peak area of Trimetazidine Dihydrochloride in sample

$P_{standard}$ = Peak area of Trimetazidine Dihydrochloride in standard

$W_{standard}$ = Weight of standard in mg

Y = Potency of standard

W_{sample} = Weight of sample in mg

***In-vitro* release studies of Trimetazidine Dihydrochloride MR Tablets**

***In-vitro* dissolution Studies:**

The *in vitro* dissolution studied was carried out using USP 24 dissolution apparatus type II (USP 24) (paddle method) at 75 rpm. Dissolution test was carried out for a total period of 8 h using 0.1N HCl (pH 1.2) solution (900 ml) as dissolution medium at 37 ± 0.5^0C for 1 hr, and pH 6.8 phosphate buffer solution (900 ml) for the rest of the period. Ten milliliters of the sample was withdrawn at regular intervals and replace with the same volume pre-warm (37 ± 0.5^0C) fresh dissolution medium. The samples withdrawn were filtered through 0.45µ membrane filter, and drug content in each sample was analyzed after suitable dilution by Shimadzu HPLC-Prominence at 240 nm.

***In vitro* release kinetic models**

The *in vitro* drug release kinetic data were tested with the following mathematical models:

Zero order equation:

The equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows:

$$\mathbf{C = K_0 t} \quad \text{---------- (1)}$$

Where, $K_0$is the zero order rate constant expressed in unit concentration/time and *t* is the time in hour. A graph of concentration *vs* time would yield a straight line with a slope equal to $K_0$and intercept the origin of the axes.

First order equation:

The release behavior of first order equation expressed as log cumulative percentage of drug remaining *vs.* time. The equation may be as follows (Wagner, 1969):

$$\mathbf{\log C = \log C_0 - kt / 2.303} \quad \text{---------- (2)}$$

Where, *C* is the amount of drug undissolved at time t, the C_0 is drug concentration at $t = 0$, *k* corresponding release rate constant.

Higuchi square root law:

The Higuchi release model describe as cumulative percentage of drug release *vs* square root of time. The equation may be as follows[5]:

$$Q = K\sqrt{t} \quad \text{---------- (3)}$$

Where, Q = the amount of drug dissolved at time t. K is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Hixson-Crowell cube root law:

It is the law that provides idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles/tablets. It is mentioned as the cube root of the percentage of drug remaining in the matrix *vs* time. The equation may be as follows:

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} \times t \quad \text{---------- (5)}$$

Where Q_0 is initial amount of the drug in the tablets, Q_t is the amount of drug release in time t and k_{HC} is rate constant for the Hixson-Crowell cube root law.

Comparison of Dissolution Data:

For assessment of the best formulation difference factor (f1) and similarity factor (f2) (Moore *et al*., 1996) were calculated to compare the dissolution profile with innovator brand. Difference factor f1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves.

The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

Stability Studies:

Stability studies were done according to ICH guidelines to assess the drug content and formulation stability[6]. One selected fabricated tablet batch was strip packaged (Alu-Alu Blister) and kept at at 40 ± 2°C and 75 ± 5% RH. Samples were withdrawn at 30, 60 and 90 days for evaluation of appearance, hardness, drug content and percentage drug release during the stability studies.

RESULTS AND DISCUSSION

Evaluation of physical properties of formulation granules

In this study cellulose derivative i.e. Methocel K4M CR was used for the development of Trimetazidine Dihydrochloride modified release tablet by wet granulation method. Formulations were designed in such a way to evaluate the impact of polymers on drug release (F-1 to F-8) for different concentrations of hydrophilic matrix.

Table 5: Physical properties of trimetazidine dihydrochloride granules (F-1 to F-8)

Formulation	Loose Bulk Density (LBD)(gm/ml	Tapped Bulk Density (TBD)(gm/ml	Carr's Index (%)	Hausner ratio	Angle of Repose (^{0})	Moister Content (%)
F-1	0.328±0.02	0.383 ±0.06	14.360±0.05	1.168±0.01	28.14±0.04	3.09
F-2	0.325±0.01	0.375 ±0.05	13.333±0.04	1.154±0.02	27.18±0.08	2.95
F-3	0.318±0.02	0.379 ±0.04	16.095±0.07	1.192±0.01	29.82±0.05	3.12
F-4	0.310±0.01	0.360 ±0.03	13.89±0.03	1.161±0.01	29.81±0.03	3.42
F-5	0.309±0.03	0.357 ±0.02	13.445±0.05	1.155±0.02	30.06±0.05	3.23
F-6	0.304±0.03	0.355 ±0.04	14.366±0.04	1.167±0.05	32.15±0.08	3.06
F-7	0.301±0.04	0.348 ±0.05	13.506±0.07	1.156±0.06	34.42±0.17	3.10
F-8	0.300±0.05	0.350 ±0.02	14.286±0.10	1.166±0.05	33.97±0.14	2.98

*Results are expressed as mean±SD

As the angle of repose 20^o to 30^o specified for good flow properties, the results of angle of repose (<30^0) indicated good flow properties of the trimetazidine dihydrochloride granules of the formulations F-1 - F-4 and the angle of repose of F-5 – F-8 is between 30-34 which means passable flow properties. This was further supported by lower Carr's index and Hausner ratio values. Generally, Carr's index values up to 16% and Hausner ratio values less than 1.25 results in good to excellent flow properties. The properties of granules of all the formulations indicated that the granules possessed satisfactory flow properties and compressibility (Table 5).

Evaluation of physical properties of matrix tablets

Table 6.: Evaluation of physical properties of Trimetazidine Dihydrochloride Matrix tablets (F-1 to F-8)

Formulation	Average weight (mg) ± SD (n = 20)	Diameter (mm)	Thickness (mm) ± SD (n = 5)	Hardness (Kp) ± SD (n = 6)	Friability (%) (n = 20)	Drug Content (%) ± SD (n = 5)
F-1	210.04±1.21	8.0	4.20±0.05	8.1±0.27	0.05	100.14±1.17
F-2	211.3±0.89		4.25±0.04	8.2±0.39	0.12	99.92±1.54
F-3	210.64±1.79		4.22±0.05	8.0±0.57	0.09	100.00±0.72
F-4	209.20±1.50		4.26±0.04	8.8±0.22	0.08	99.86±0.97
F-5	209.72±1.03		4.27±0.03	8.5±0.25	0.17	100.01±1.73
F-6	211.50±0.95		4.38±0.11	8.2±0.64	0.20	100.0±1.08
F-7	211.86±1.05		4.32±0.10	8.0±0.19	0.18	100.28±2.15
F-8	210.09±2.12		4.40±0.14	7.9±0.30	0.15	99.56±1.65

*Results are expressed as mean±SD

It was found that all the formulations showed uniform thickness. The average percentage of deviation of all tablet formulations was found to be within the limit. Good uniformity in drug content was found among different formulations of the tablets and the percentage of drug content was more than 98%. In this study the percentage friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits. Good uniformity of content of Trimetazidine Dihydrochloride showed uniform drug distribution.

Drug Content:

Assay of Trimetazidine Dihydrochloride in the matrix tablet:

The assay of Trimetazidine Dihydrochloride matrix tablet was carried out by High Performance Liquid Chromatography (HPLC) method. The drug was extracted in Phosphate buffer pH 6.8. The solution was filtered through 0.2µ disc filter. The absorbance was measured at 240 nm after suitable dilution by using a HPLC

***In vitro* release study**

The dissolution studies of Trimetazidine Dihydrochloride matrix tablet were also carried out by High Performance Liquid Chromatography (HPLC) method. The retention time of principal peak (Trimetazidine Dihydrochloride) was found at 21 minutes (Approximately). Peak area obtained from the dissolution studies were converted into percent release of drug from the formulations of matrix tablets.

As per the result of dissolution study formulation F1, F2, F3, F4, F5,F6, F7 and F8 showed 99.0%, 98.22%, 97.45%, 94.58%, 91.77%, 72.82%, 69.58% and 56.75% drug release in 8 hours respectively. This showed that drug release from the tablets was sustained for 8 hours. Drug release decreased with increase of polymer loading as HPMC polymers form viscous gelatinous layer (gel layer) upon exposure to aqueous medium by undergoing rapid hydration and chain relaxation and this gel layer acts as the barrier to release of drug and as a result drug release is prolonged.

Effect of Methocel K4M CR on release pattern of Trimetazidine Dihydrochloride MR Tablet:

Eight different concentrations of Methocel K4M CR (42.85%, 47.62%, 52.38%, 57.14%, 61.90%, 64.28%, 66.66% & 69.04%) were used to form matrix tablet of Trimetazidine Dihydrochloride. Six tablets from each formulation were used and the release profile of Trimetazidine Dihydrochloride from the matrix in the dissolution medium was monitored at 0 hour, 1 hour, 2 hour, 4 hour and 8 hour. The results of *in vitro* dissolution studies of the formulations F-1 to F-8 are shown in Table 5. Which indicates that release rate gradually decreased with increase in polymer load in the matrix tablet.

Table 7: Effect of Methocel K4M CR (F-1 to F-8) on trimetazidine dihydrochloride release.

Time (hr)	Cumulative amount of drug released (%)							
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
0	0	0	0	0	0	0	0	0
1	46.03	43.05	38.5	32.20	26.77	22.5	18.2	12.75
2	74.70	70.19	64.35	51.18	45.70	39.45	32.25	30.14
4	90.14	88.02	83.06	74.50	67.50	50.55	48.72	42.95

8	99.00	98.22	97.45	94.58	91.77	72.82	69.58	56.75

Drug release kinetics

To evaluate the release kinetics and mechanism the release of Trimetazidine Dihydrochloride was fitted with the following different models and the results obtained are described below.

- The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets.
- The model that best fits the release data is selected based on the correlation coefficient (r) value in various models.
- The model that gives high 'r^2' value is considered as the best fit of the release data.

Zero Order Plot

Graph 1. : Zero order release profile of eight formulations (F-1 to F-8) of trimetazidine dihydrochloride Matrix Tablets

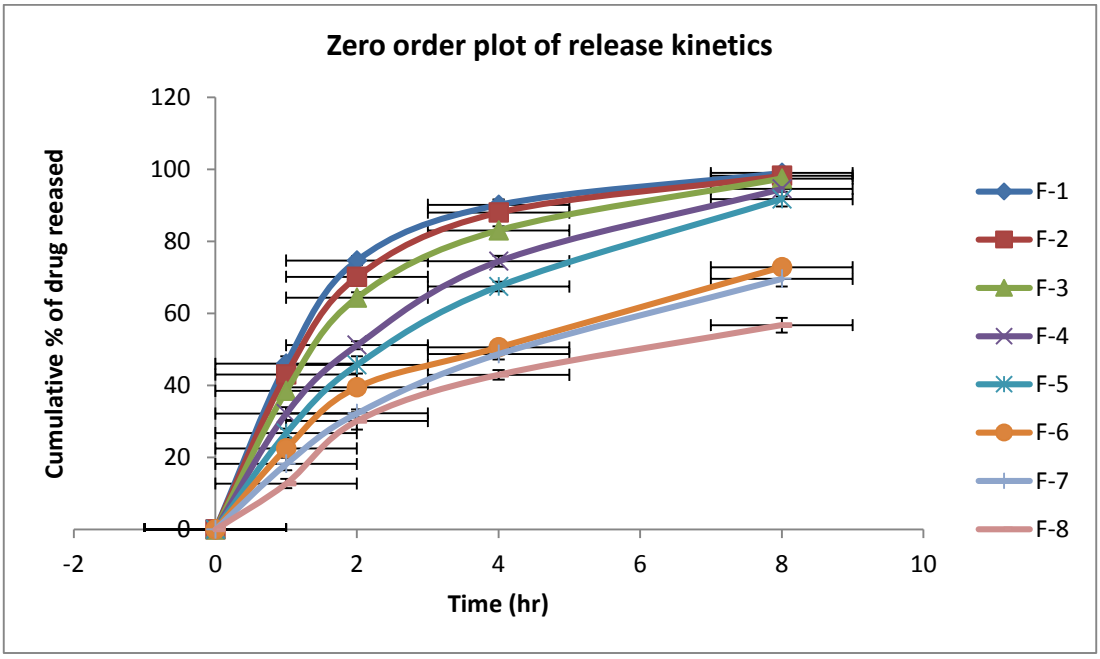


Figure: Zero order plot of release kinetics of eight formulations (F-1 to F-8) of Trimetazidine Dihydrochloride Matrix tablets.

Graph 2: First order release profile of eight formulations **(F-1 to F-8)** of trimetazidine dihydrochloride Matrix Tablets.

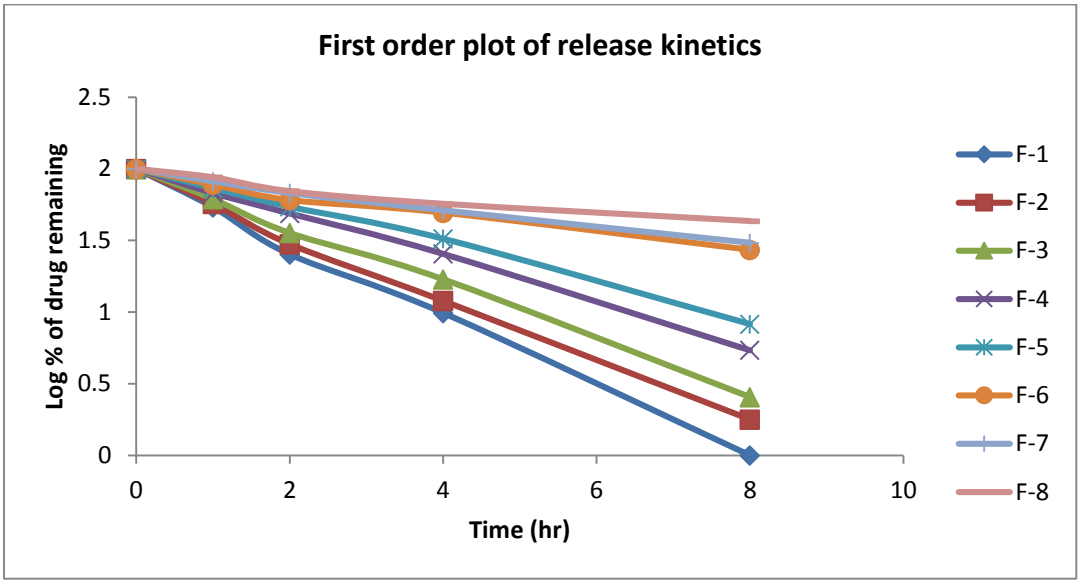


Figure: First order plot of release kinetics of eight formulations (F-1 to F-8) of trimetazidine dihydrochloride matrix tablets

Graph 3: Higuchi release profile of eight formulations (F-1 to F-8) of trimetazidine dihydrochloride Matrix tablets.

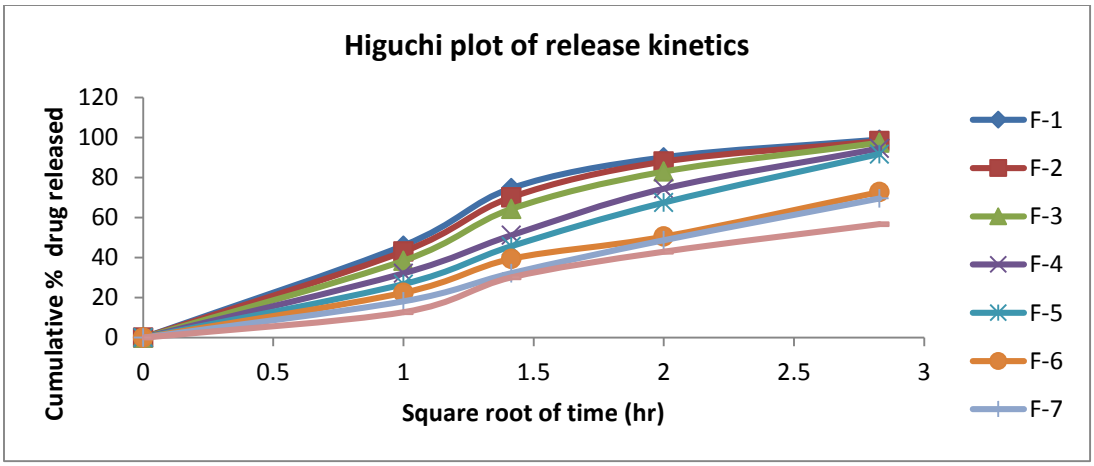


Figure: Higuchi plot of release kinetics of eight formulations (F-1 to F-8) of trimetazidine dihydrochloride matrix tablets.

Graph 4: Korsmeyer-Peppas release profile of eight formulations **(F-1 to F-8)** of trimetazidine dihydrochloride Matrix tablets.

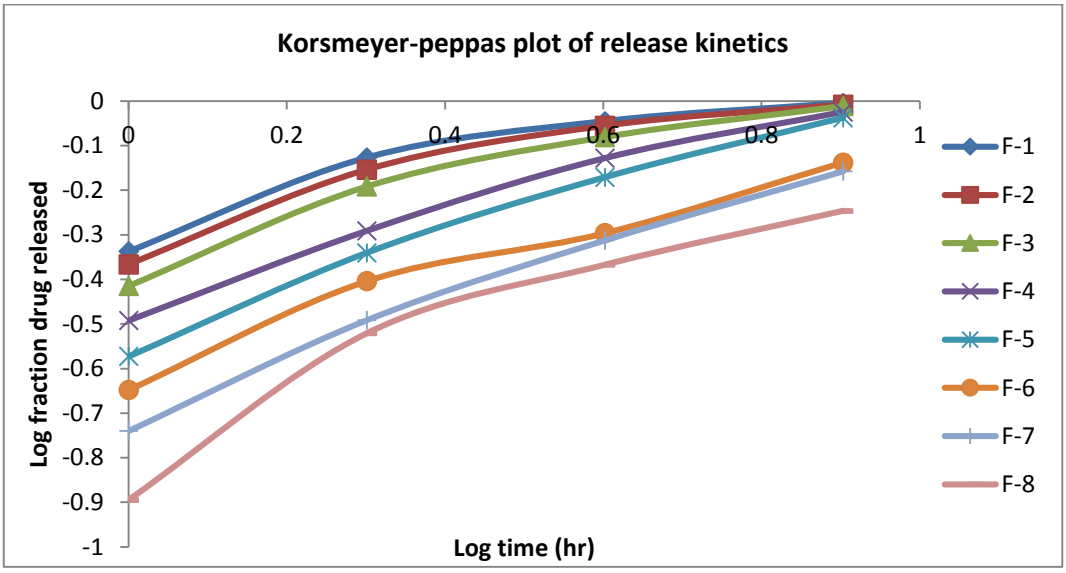


Figure: Korsmeyer-Peppas plot of release kinetics of eight formulations (F-1 to F-8) of trimetazidine dihydrochloride matrix tablets.

Hixson-Crowell Plot

Graph 5: Hixson-Crowell release profile of eight formulations **(F-1 to F-8)** of trimetazidine dihydrochloride Matrix tablets.

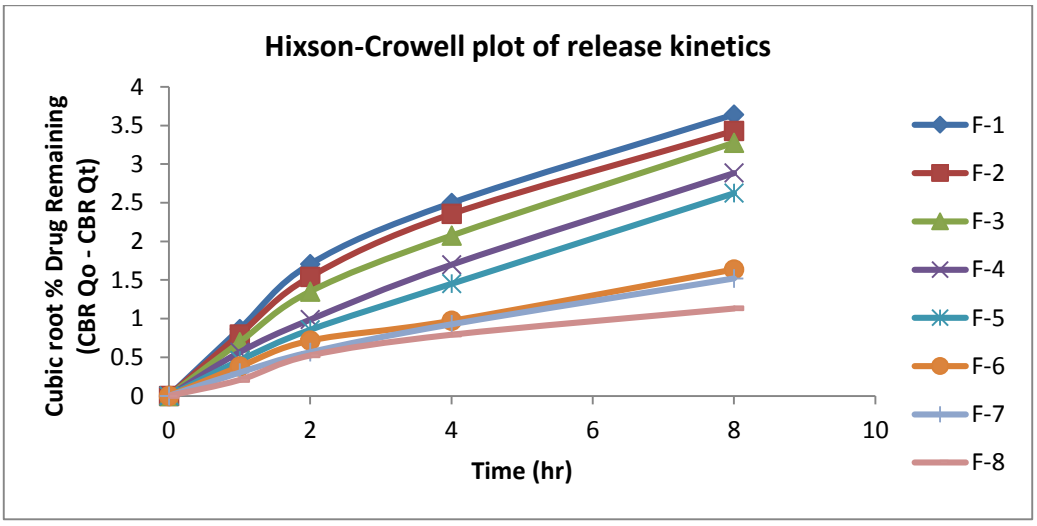


Figure: Hixson-Crowell plot of release kinetics of eight formulations (F-1 to F-8) of trimetazidine dihydrochloride matrix tablets

Interpretation of Release rate constants and R-square values for different release kinetics of F-1 to F-8:

Table 8: Release rate constants and R^2 values for different release kinetics of eight formulations of trimetazidine dihydrochloride Matrix tablets.

Formulation	Zero order		First order		Higuchi		Korsmeyer-Peppas		Hixson-Crowell	
	K_0	R^2	K_1	R^2	K_h	R^2	n	R^2	K_{HC}	R^2
F-1	10.46	0.681	-0.246	0.997	36.17	0.918	0.358	0.886	0.431	0.933
F-2	10.57	0.716	-0.216	0.997	36.00	0.937	0.389	0.907	0.409	0.940

F-3	10.72	0.771	-0.196	0.998	35.66	0.962	0.438	0.933	0.392	0.964
F-4	10.79	0.862	-0.156	0.998	34.46	0.991	0.520	0.981	0.350	0.986
F-5	10.67	0.904	-0.134	0.997	33.33	0.993	0.589	0.984	0.319	0.992
F-6	8.255	0.893	-0.067	0.980	25.93	0.993	0.544	0.974	0.191	0.960
F-7	8.199	0.930	-0.063	0.992	25.19	0.990	0.639	0.987	0.184	0.978
F-8	6.776	0.887	-0.044	0.949	21.12	0.972	0.697	0.925	0.137	0.931

The best fitted model and mechanism of drug release from the matrix tablets of trimetazidine dihydrochloride Table 9.

Table 9: The best fitted model and mechanism of drug release

Formulation	Best fitted model	n value (Korsmeyer-Peppas model)	Release Mechanism
F-1	First order	0.358	Fickian diffusion
F-2	First order	0.389	Fickian diffusion
F-3	First order	0.438	Fickian diffusion
F-4	First order and Higuchi	0.520	Anomalous / non-Fickian transport
F-5	First order, Higuchi and Hixson-Crowell	0.589	Anomalous / non – Fickian transport
F-6	Higuchi	0.544	Anomalous / non-Fickian transport
F-7	Higuchi	0.639	Anomalous / non – Fickian transport
F-8	Higuchi	0.697	Anomalous / non – Fickian transport

The data from Table 9. shows that F-1, F-2 and F-3 was best fitted in terms of 1st order release kinetics (r^2=0.997), (r^2=0.997) and (r^2=0.998). F-4 was best fitted in terms of 1st order and Higuchi model (r^2 = 0.998) and (r^2 = 0.991). F-5 was best fitted in terms of 1st order, Higuchi and Hixson-Crowell model (r^2 = 0.997), (r^2 = 0.993) and (r^2 = 0.992). F-6 to F-8 were best fitted in terms of Higuchi model (r^2 = 0.993), (r^2 = 0.990) and (r^2 = 0.972). To confirm the drug release mechanism, the data were fitted into Korsmeyer- Peppas equation. Formulation F-1to F-8 showed exponent n values ranging from 0.358 to 0.697.

Successive fractional dissolution time:

Successive fractional dissolution time of eight formulations (F-1 to F-8) of trimetazidine dihydrochloride matrix tablets are summarized in the following table.

Table 10: Successive fractional dissolution time of eight formulations (F-1 to F-8) of trimetazidine dihydrochloride Matrix tablets:

Formulation	MDT	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$
F-1	1.702	0.1344	0.932	3.462
F-2	1.873	0.1894	1.1255	3.7676
F-3	2.153	0.2984	1.4522	4.2468
F-4	2.717	0.5523	2.0946	5.1717
F-5	3.133	0.8032	2.6056	5.7871

F-6	4.799	1.0653	3.8091	9.0375
F-7	5.108	1.4969	4.4287	9.2409
F-8	6.207	2.0680	5.5904	10.9724

MDT, $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ values were determined to characterize the drug release rate from the matrix tablets and the retaining efficiency of drug of the polymers. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa (Table 10).

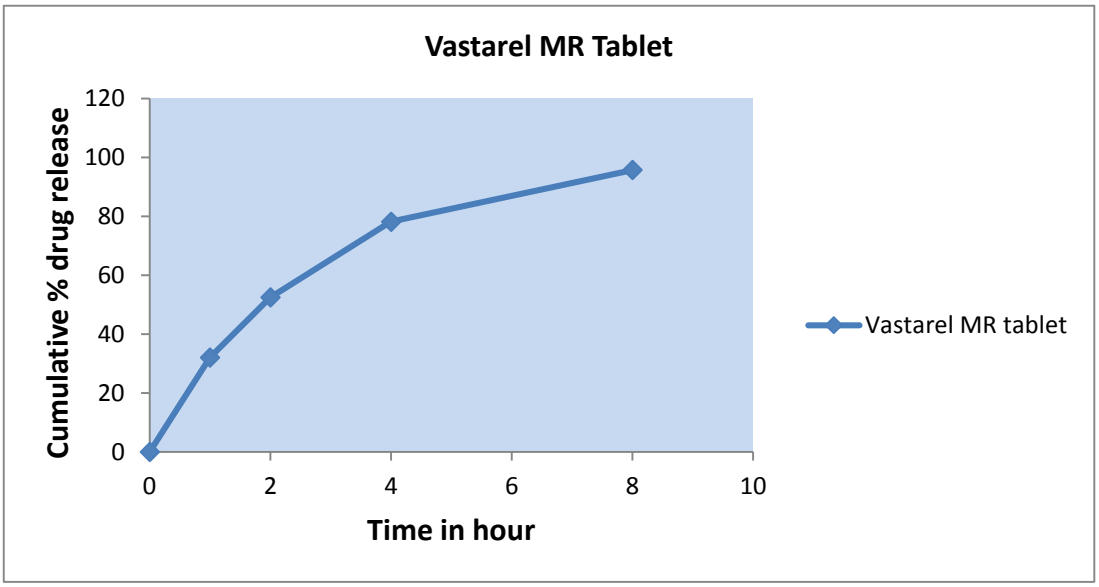
Comparison of Dissolution Data

Dissolution data of Innovator brand (Vastarel MR Tablet)

The formulations obtained in evaluation studies were compared with marketed product (Vastarel MR Tablet). Difference factor (f1) and similarity factor (f2) were calculated to compare the dissolution profile with innovator brand.

Table 11: Dissolution data of Innovator brand (Vastarel MR Tablet)

Time (hr)	Cumulative amount of drug released (%)
0	0.00
1	32.10
2	52.50
4	78.20
8	95.70



Graph 6: Release profile of Innovator Brand (Vastarel MR Tablets).

Table 12: Comparison of dissolution (f1 and f2) data with innovator brand (Vastarel MR Tablet)

Pair Comparison	Similarity factor (f2)	Difference factor (f1)
F-1	41.88	19.87
F-2	46.72	15.85
F-3	56.88	9.62
F-4	82.15	2.34
F-5	57.07	10.35

F-6	35.26	28.31
F-7	31.70	34.72
F-8	26.03	44.84

The table has shown the f1 and f2 values of different formulations in respect of innovator brand. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100 (FDA, 1997), **F4 seems to be best similar to the innovator brand for the higher f2 (82.15) and lower f1 (2.34) value.**

Comparison of release of F-4 and Innovator brand (Vastarel MR Tablet)

The formulations obtained in evaluation studies were compared with marketed product (Vastarel MR Tablets). The results showed that formulation F4 is the best similar to the innovator brand.

The Analytical parameters of formulation F-4 and marketed product (Vastarel MR Tablet) are given in the following tables and is constructed graphically.

Table 13. : Comparison of dissolution data with innovator brand (Vastarel MR Tablet)

Time (hr)	Cumulative amount of drug released (%)	
	Vastarel	F-4
0	0.00	0.00
1	32.10	32.20
2	52.50	51.18
4	78.20	74.50
8	95.70	94.58

Stability Studies

Tablets of formulation F4 was packaged in Alu-Alu blister and kept at 40^{o}C ± 2^{o}C with 75% ± 5% RH for 90 days. Drug release and potency of this formulation F4 was almost similar with the initial value as summarized in Table 4.15. Which indicates that there is no interaction between drug and polymer and the formulation is suitable for commercial manufacturing.

Table 14: Summary of accelerated stability study of formulation F4 after 90 days.

Tests	Results			
	Initial	After 30 days	After 60 days	After 90 days
Appearance	White round tablet	Complies	Complies	Complies
Hardness (Kp)	8.72± 0.49	8.6 ± 0.76	8.4 ± 0.85	8.58 ± 0.68
Dissolution				
1st hour	31.72%	30.59%	31.45%	32.29%
2nd hour	54.65%	53.12%	51.35%	52.39%
4th hour	70.18%	72.20%	73.76%	71.33%
8th hour	95.11%	94.02%	93.90%	92.95%
Assay	99.89%	99.80%	99.06	98.32%

Drug release and potency of formulation F-4 after 90 days are summarized in table 15. Potency and drug release were almost similar with the initial values which indicates that the there is no

interaction between drug and polymer and the formulation F-4 is suitable for commercial manufacturing

CONCLUSION

This study reveals that the release of Trimetazidine Dihydrochloride critically depends on the rate retarding polymer level in the matrices. Proper adjustment of polymer with drugs enabled a desirable release characteristic of active ingredient.

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