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Research Article

IN-VITRO EVALUATION OF ORAL EXTENDED RELEASE DRUG DELIVERY SYSTEM FOR TRIMETAZIDINE DIHYDROCHLORIDE USING METHOCEL POLYMERS

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ABSTRACT

Objective: In the present study an attempt has been made to evaluate the effect of hydrophilic, pH independent polymers on the release profile of drug from matrix system.

Methods: Trimetazidine Dihydrochloride, an anti-anginal agent was used as model drug to evaluate their release characteristics from different matrices. Matrix tablets [1] of Trimetazidine Dihydrochloride were prepared by direct compression process using METHOCEL K15M CR, METHOCEL K4M CR and METHOCEL K100M CR. Release kinetics of Trimetazidine Dihydrochloride from these controlled extended release matrices at 0.1 N HCl using USP paddle method with sinker was conducted for 10 hours and examined.

Results: Statistically significant differences were found among the drug release profile from different classes of polymeric matrices. Higher polymer content (50%) in the matrix decreased the rate of the drug due to increased tortuosity and decreased porosity. At lower polymeric level (25%), the rate of drug release [10] was elevated. METHOCEL K4M CR was found to cause the retardation of drug. On the other hand, highest release was found from METHOCEL K100M CR, while other formulations gave an intermediate release profile of Trimetazidine Dihydrochloride. METHOCEL K15M CR and METHOCEL K4M CR extended the release of Trimetazidine Dihydrochloride up to 10 hours. The release mechanism was explored and explained with zero order, first order, Higuchi and Korsmeyer equation.

Conclusion: The result generated in this study showed that the profile and kinetics of drug release were functions of polymer type, polymer level and physicochemical properties of drug. A controlled plasma level profile of Trimetazidine Dihydrochloride drug can be obtained by exact combination of polymers [9] and modulation of polymer content in the matrix.

Keywords: Trimetazidine Dihydrochloride, Polymer, Methocel K4M CR, Methocel K15MCR, Methocel K100M CR.

INTRODUCTION

Extended release drug delivery system becoming more popular for designing solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target tissue. So that, the controlled and reproducible extended release technology in the formulation of pharmaceutical product has become increasingly important during last few years. For formulating sustain release dosage form, matrix tablets are becoming very easier option. The use of polymers in controlling the release of drugs has become important in the formulation of pharmaceuticals.

Trimetazidine Dihydrochloride chemically described as 1-(2,3,4-Trimethoxybenzyl) piperazine dihydrochloride 1. It is known as 3-KAT inhibitors. It exerts antianginal properties[3] due to reduce the metabolic damage caused during ischemia, by acting on β-oxidation. This is made possible by a selective inhibition of an enzyme of fatty thiolase (3-KAT) 2.This inhibition result in-Reduction of fatty acid oxidation & stimulation of glucose oxidation [13].

The purpose of the present study is to develop a controlled and reproducible extended release dosage form of Trimitazidine Dihydrochloride using water swellabe pH independent hydrophilic matrix polymer to evaluate in-vitro release characteristics of Trimitazidine Dihydrochloride from formulated tablets [4]. The retarding effect of different types of matrix forming agents of METHOCEL grades was compared in this study.

MATERIALS AND METHODS

Trimetazidine Dihydrochloride was produced from Drug International Ltd (DIL). Methocel K4M, Mehtocel K15M and Methocel K100M were collected from Colorcon, USA. Avicel PH 102 was collected from Switzerland. Magnesium stearate was collected from Germany and Aerosil from India. All other reagents employed were of analytical or pharmaceutical grade.

Preparation of matrix tablets

Matrix tablets were prepared by direct compression process. At first active and excipients were weighed properly. During granulation Active, Methocel and Avicel PH 102 first pass through the sieve and then mixed the dry mass up to 5 minutes manually. After that, Aerosil 200 is passed through the 0.5 mm sieve and then mixed with previous mixer for 5 minutes. Finally, Magnesium is added and mixed for 3 minutes. **(Table 1)** represents the formulation of co-matrix tablets with their formulation code. In all cases the amount of active was 35 mg & the total weight of tablet was 200 mg. Co-matrix tablets were prepared by Manesty 3 station rotary press applying a compression force 1.5 ton. All the tablets were then stored in air tight containers at room temperature for further investigation.

In vitro dissolution study [12]

All dissolution studies were carried out for extended release Trimetazidine Dihydrochloride formulations in a USP XXII dissolution apparatus II (paddle). The dissolution study was performed for 10 hours in 900 ml of 0.1N HCl dissolution medium with 100 rpm. 5 milliliter of sample was withdrawn at a regular intervals and replace with the same volume pre-warm (37°c ± 0.5°c) fresh dissolution medium. The withdrawn samples were filtered and the amount of drug dissolved in the medium was determined by UV spectrophotometer at 270 nm 3.

Release kinetics

After completing 10 hours in vitro dissolution study [6], the results of all batches were treated by different kinetic models (zero-order, first order, Higuchi's equation and Korsmeyer's equation) to evaluate the drug release kinetics from matrix system. The data were evaluated by the following equation:

Zero-order model 4:

$$Mt = M0 + K0t \quad \ldots\ldots (1)$$

First-order model 5:

Ln M1 = Ln M0 + K1t ..... (2)

Higuchi model 6-7:

Mt = M0 + KH t1/2 ..... (3)

Korsmeyer-Peppas model 8:

Mt / M∞ = K tn ..... (4)

In these equations, Mt is the cumulative amount of drug released any specified time point and M0 is the dose of the drug incorporated in the delivery system. K0, K1, KH, K are the rate constant for Zero order, First order, Higuchi and Korsmeyer-Peppas model respectively.

For a cylinder shaped matrix the value of n ≤ 0.45 indicates Fickian release; > 0.45 but <0.89 for non-Fickian (anomalous) release. This case generally refers to the erosion of polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release9. Mean dissolution Time (MDT) can be calculated from dissolution data according to equation 5, where n is the release exponent and k is release rate constant.

MDT = (n/n +1)k-1/n ..... (5)

A higher value of MDT indicates a higher drug retaining ability of polymer and vice-versa.

Table 1: Formulation of Trimetazidine Dihydrochloride tablets containing Methocel K4M, Methocel K15M, Methocel K100M

Ingredients (mg)	Formulation code																	
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Trimetazidine Dihydrochloride	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35
Methocel K4M	50	60	70	80	90	100	-	-	-	-	-	-	-	-	-	-	-	-
Methocel K15M	-	-	-	-	-	-	50	60	70	80	90	100	-	-	-	-	-	-
Methocel K100M	-	-	-	-	-	-	-	-	-	-	-	-	50	60	70	80	90	100
Avicel PH102	113	103	93	83	73	63	113	103	93	83	73	63	113	103	93	83	73	63
Aerosil 200	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mg-stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total weight	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Drug release kinetics of Trimetazidine Dihydrochloride from tablets containing Methocel K4M CR, Methocel K15M CR, Methocel K100M CR matrices

Formulation code	% of drug release after 10 hrs	Zero Order		First Order		Higuchi		Korsmeyer	
		r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
F1	97.30	0.898	8.900	0.970	0.148	0.992	31.620	0.976	0.489
F2	92.87	0.884	8.435	9.986	0.111	0.990	30.160	0.968	0.548
F3	87.34	0.895	8.070	0.990	0.088	0.991	28.690	0.970	0.591
F4	85.13	0.921	7.779	0.991	0.078	0.996	27.340	0.995	0.595
F5	80.71	0.926	7.465	0.993	0.069	0.996	26.160	0.998	0.605
F6	77.39	0.945	7.286	0.992	0.063	0.994	25.250	0.990	0.586
F7	98.40	0.868	8.189	0.886	0.144	0.986	29.500	0.993	0.382
F8	95.08	0.874	8.024	0.953	0.111	0.988	28.820	0.991	0.408
F9	90.66	0.892	7.941	0.988	0.095	0.993	28.320	0.995	0.458
F10	87.34	0.913	7.772	0.991	0.083	0.998	27.450	0.999	0.471
F11	84.03	0.919	7.617	0.993	0.074	0.998	26.820	0.997	0.505
F12	79.60	0.926	7.398	0.993	0.066	0.997	25.950	0.995	0.539
F13	96.19	0.883	8.542	0.978	0.137	0.990	30.550	0.992	0.432
F14	95.08	0.907	8.552	0.978	0.125	0.994	30.250	0.994	0.466
F15	95.08	0.925	8.640	0.972	0.123	0.994	30.260	0.996	0.505
F16	87.34	0.919	7.879	0.994	0.084	0.995	27.720	0.994	0.503
F17	82.92	0.916	7.439	0.991	0.071	0.993	26.170	0.987	0.503
F18	80.71	0.936	7.398	0.994	0.067	0.995	25.770	0.993	0.542

RESULTS AND DISCUSSION

Effect of METHOCEL K4M CR on release pattern of Trimetazidine Dihydrochloride

For this experiment, different METHOCEL K4M matrix tablet containing Trimetazidine Dihydrochloride as active ingredient having METHOCEL K4M CR polymer 25%, 30%, 35%, 40%, 45% and 50% respectively of total tablet weight in the matrix tablet with the formulation code TDK4MF1, TDK4MF2, TDK4MF3, TDK4MCRF4, TDK4MF5, TDK4MF6 were prepared. After preparation according to formulation shown in the **(Table 1)**, their dissolution studies were carried out in paddle method with a sinker at 100 rpm in 0.1 N HCl medium at 37^{0}c (±0.5^{0}c). Three tablets from each formulation were used for the dissolution study. The release profile of Trimetazidine Dihydrochloride was monitored up to 10 hours. The zero order[5] release pattern is shown in **(Fig. 1)**. **(Fig. 2)** represents the Higuchi impact that is obtained by plotting the % of cumulative drug release vs Square Root of Time (SQRT). First order release profile is shown in **(Fig. 3)** and Korsmeyer in **(Fig. 4)**. The percent of drug release from these six formulations at different time intervals is shown at the **(Table 3)**.

From the graphs, a release profile of Trimetazidine Dihydrochloride containing METHOCEL K4M CR matrix tablet of six formulations was obtained. The total % of Trimetazidine Dihydrochloride release from the formulation TDK4MF1, TDK4MF2, TDK4MF3, TDK4MCRF4, TDK4MF5, TDK4MF6 were 97.30%, 92.87%, 87.34%, 85.13%, 80.71% and 77.34% respectively. It has been observed that the release rate has been extended with the increase of polymer % and with the decrease of Avicel PH102 %. The highest percent of drug release within 10 hours is obtained from TDK4MF1 where polymer content is 25% and that of lactose is 56.5%. But in TDK4MF6, the polymer content is 50% and lactose content is 31.5%, the release of drug is controlled with 77.34 % within 10 hours.

The rate of drug release was found to be inversely related to the amount of METHOCEL K4M CR present in the matrix structure, i.e. the drug release increased with decrease in the polymer content of the matrix tablet. Such increase in polymer content results in a

decrease in the drug release rate due to a decrease in the total porosity i.e. release is extended to long period. Lactose causes a decreased tortuosity of the path of the drug due to its preferential solubility than METHOCEL K4M CR, by its swelling effect, additionally weakened the integrity of the matrix (Nixon, Patel and Tong, 1995).[10]

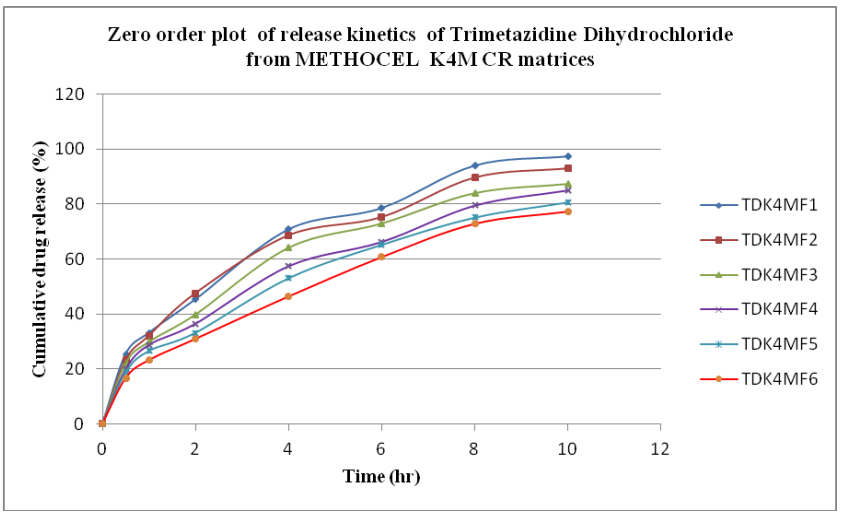

Fig. 1: Zero order plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K4M CR matrices.

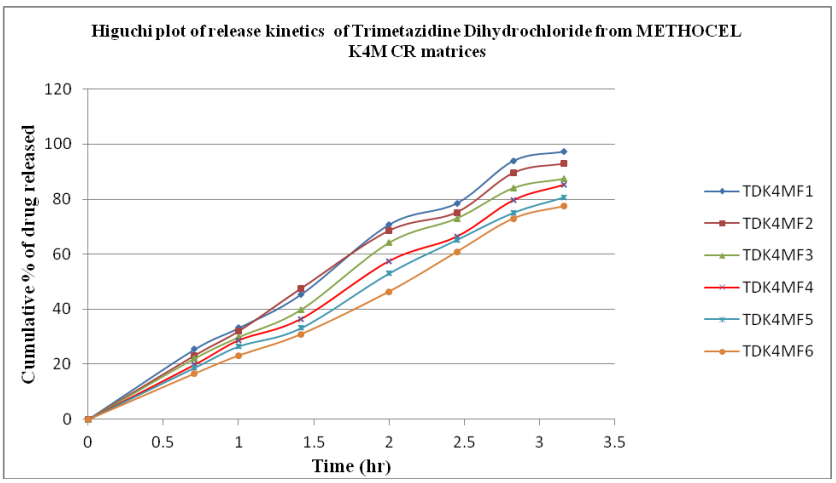

Fig. 2: Higuchi plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K4M CR matrices.

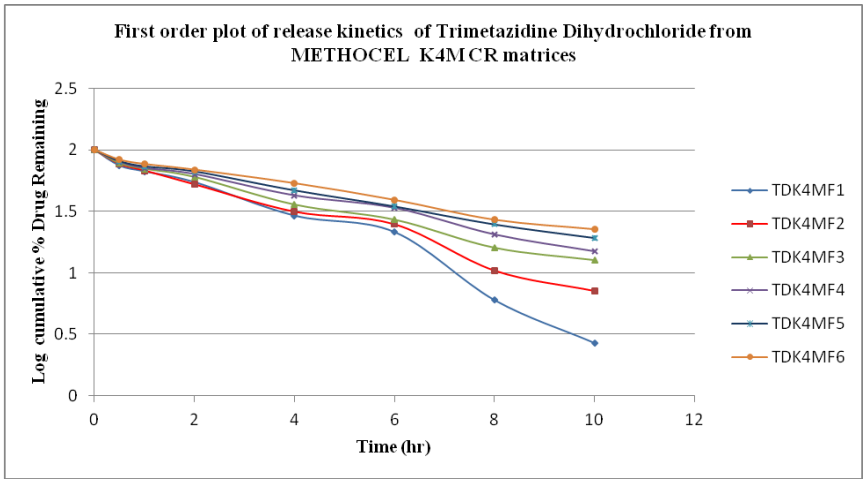

Fig. 3: First order plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K4M matrices.

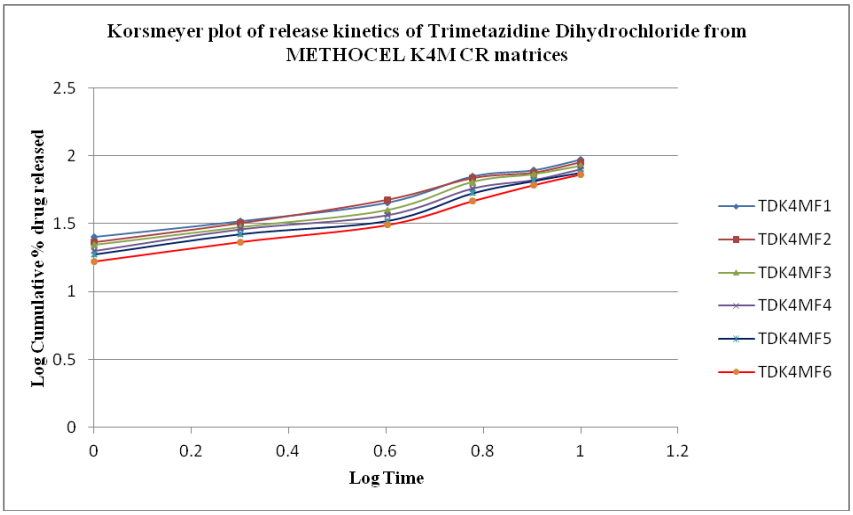

Fig. 4: Korsmeyer plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K4M CR matrices.

Table 3: Release kinetics of Trimetazidine Dihydrochloride from METHOCEL K4M CR matrices

Formulation code	Zero order		First order		Higuchi		Korsmeyer	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	N
TDK4MF1	0.898	8.900	0.97	0.148	**0.992**	31.62	0.976	**0.489**
TDK4MF2	0.884	8.435	0.986	0.111	**0.990**	30.16	0.968	**0.548**
TDK4MF3	0.895	8.070	0.99	0.088	**0.991**	28.69	0.970	**0.591**
TDK4MF4	0.921	7.779	0.991	0.078	**0.996**	27.34	0.995	**0.595**
TDK4MF5	0.926	7.465	0.993	0.069	0.996	26.16	**0.998**	**0.605**
TDK4MF6	0.945	7.286	0.992	0.063	**0.994**	25.25	0.990	**0.586**

The kinetics data are mentioned in **(Table 3)**. The formulation TDK4MF1 best fits with Higuchi (r^2= 0.992) kinetic model. Similarly, TDK4MF2, TDK4MF3, TDK4MF4 & TDK4MF6 also follow Higuchi model where the rate of release are 0.990, 0.991 and 0.996. TDK4MF5 follows Korsmeyer kinetic model.

The value of release exponent (n) for Korsmeyer release for the formulation TDK4MF1 & TDK4MF2, TDK4MF3, TDK4MF4, TDK4MF5 & TDK4MF6 are 0.489, 0.548, 0.591, 0.595, 0.605 & 0.586 respectively. Korsmeyer represent good linearity and indicates that all the formulations containing polymer Methocel K4M CR follow Anomalous diffusion or non-Fickian (0.45 < n < 0.89) release pattern. This means that the drug being released by both diffusion and erosion controlled mechanism.

Effect of METHOCEL K15M CR on release pattern of Trimetazidine Dihydrochloride

Different METHOCEL K15M CR matrix tablet containing Trimetazidine Dihydrochloride as active ingredient having METHOCEL K15M CR polymer 25%, 30%, 35%, 40%, 45% and 50% respectively of total tablet weight in the matrix tablet with the formulation code TDK15MF1, TDK15MF2, TDK15MF3, TDK15MCRF4, TDK15MF5, TDK15MF6 were prepared to evaluate the effect of this polymer. After preparation according to formulation shown in the **(Table 1)**, their dissolution studies were carried out in paddle method with a sinker at 100 rpm in 0.1 N HCl medium at 37^{0}c (±0.5^{0}c). Three tablets from each formulation were used in dissolution study. The release profile of Trimetazidine Dihydrochloride was monitored up to 10 hours. The average release pattern is shown in **(Fig. 5)**. **(Fig. 6)** represents the Higuchi impact that is obtained by plotting the % of drug release vs Square Root of Time (SQRT). First order release pattern has been shown in **(Fig. 7)**. Korsmeyer release pattern has been obtained by plotting log cumulative percent drug release vs log time **(Fig. 4)**. The percent of drug release from these six formulations at different time intervals are shown at the **(Table 4)**.

A release profile of Trimetazidine Dihydrochloride containing METHOCEL K15M CR matrix tablet of six formulations was obtained from the graphs. The total % of Trimetazidine Dihydrochloride release from the formulation TDK15MF1, TDK15MF2, TDK15MF3, TDK15MCRF4, TDK15MF5, TDK15MF6 were 99.26%, 96.00%, 94.69%, 89.32%, 79.20% and 74.69%respectively. It has been observed that the release rate has been extended with the increase of polymer % and with the decrease of Avicel PH %. The highest percent of drug release within 10 hours is obtained from TDK15MF1 where polymer content is 25% of total tablet weight and that of Avicel PH 102 is 56.5 %. But in TDK15MF6, the polymer content is 51.50% of total tablet weight and Avicel PH 102 content is 31.5%, the release of drug is controlled with 79.60 % within 10 hours.

Table 4: Zero order release profile METHOCEL K15M CR based Trimetazidine Dihydrochloride Matrix Tablets

Time (hrs)	TDK15MF1	TDK15MF2	TDK15MF3	TDK15MF4	TDK15MF5	TDK15MF6
0	0	0	0	0	0	0
0.5	29.85	28.75	26.53	23.22	19.90	17.69
1	40.91	37.59	32.06	29.85	26.53	23.22
2	49.75	46.44	43.12	40.91	37.59	35.38
4	68.55	66.34	63.02	57.49	56.39	53.07
6	79.60	78.50	75.18	68.55	66.34	63.02
8	86.24	82.92	81.82	80.71	76.29	74.08
10	98.40	95.08	90.66	87.34	84.03	79.60

The rate of drug release was found to be inversely related to the amount of METHOCEL K15M CR present in the matrix structure, i.e. the drug release increased with decrease in the polymer content of the matrix tablet. Such increase in polymer content results in a decrease in the drug release rate due to a decrease in the total porosity i.e. release is extended to long period. Avicel PH 102 causes a decreased tortuosity of the path of the drug due to its preferential solubility than METHOCEL K15M CR, by its swelling effect, additionally weakened the integrity of the matrix (Nixon, Patel and Tong, 1995).

The release kinetics data has been mention in the **(Table 5)**. From the table it has been seen that TDK15MF1, TDK15MF2, TDK15MF3 & TDK15MF4 formulations of this class follows Korsmeyer release model; whereas TDK15MF5 & TDK15MF6 follow Higuchi kinetic model although Korsmeyer also represent good linearity.

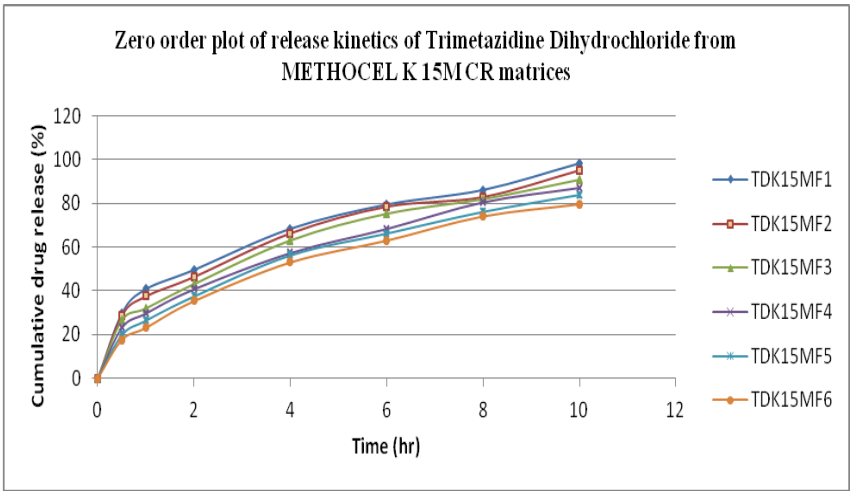

Fig. 5: Zero order plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K15 M CR matrices.

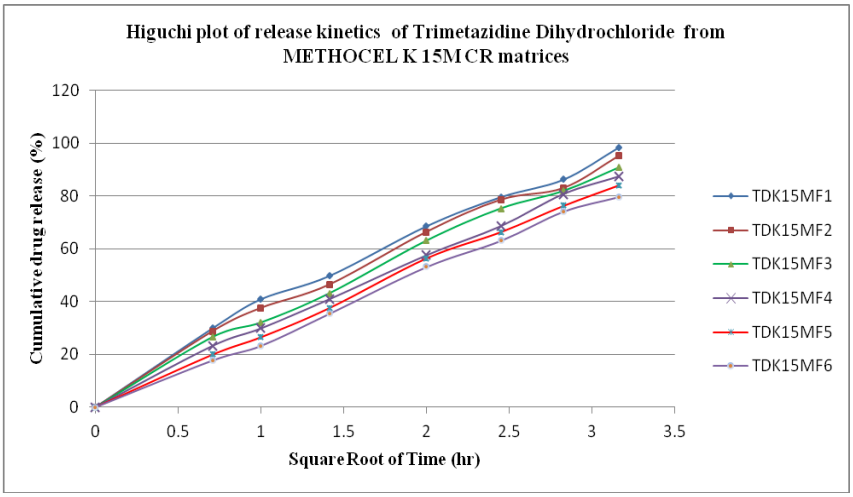

Fig. 6: Higuchi plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K15 M CR matrices.

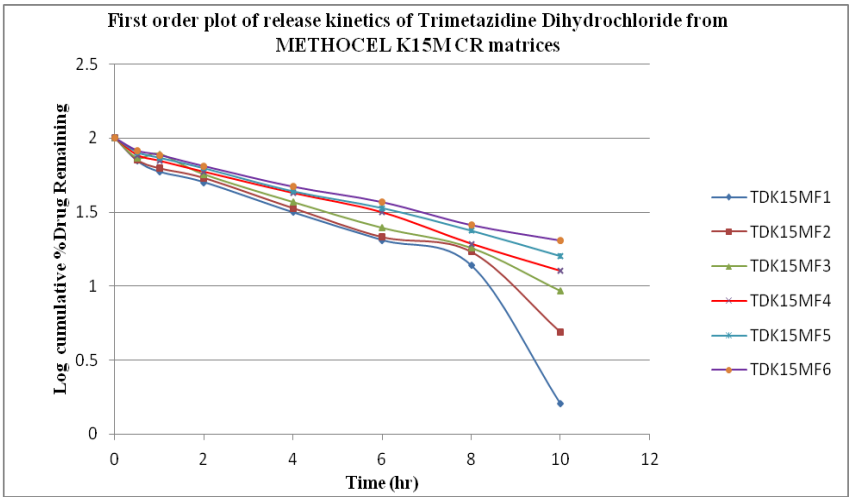

Fig. 7: First order plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K15M CR matrices.

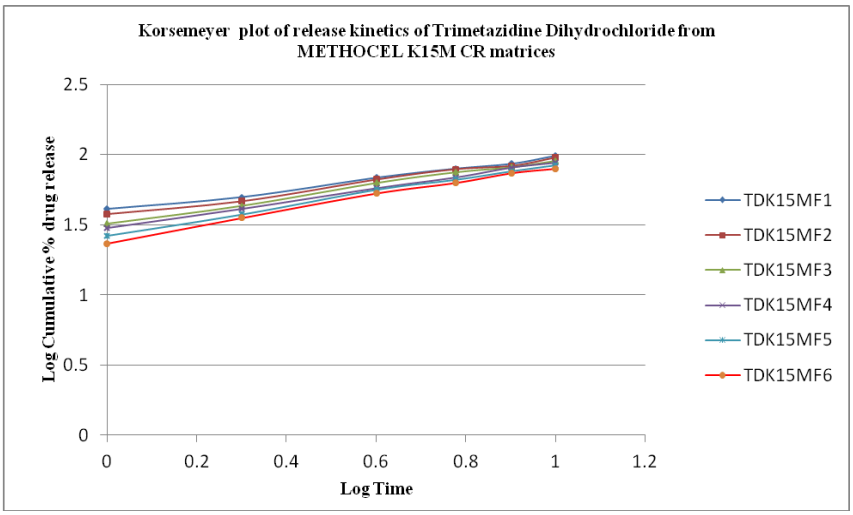

Fig. 8: Korsmeyer plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K15M CR matrices.

Table 5: Release kinetics of Trimetazidine Dihydrochloride from METHOCEL K15M CR matrices.

Formulation code	Zero order		First order		Higuchi		Korsmeyer	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
TDK15MF1	0.868	8.189	0.886	0.144	0.986	29.5	**0.993**	**0.382**
TDK15MF2	0.874	8.024	0.953	0.111	0.988	28.82	**0.991**	**0.408**
TDK15MF3	0.892	7.941	0.988	0.095	0.993	28.32	**0.995**	**0.458**
TDK15MF4	0.913	7.772	0.991	0.083	0.998	27.45	**0.999**	**0.471**
TDK15MF5	0.919	7.617	0.993	0.074	**0.998**	26.82	0.997	**0.505**
TDK15MF6	0.926	7.398	0.993	0.066	**0.997**	25.95	0.995	**0.539**

It is seen that no significant difference in release pattern in METHOCEL K4M CR and METHOCEL K15M CR matrices though the viscosity of second one is very much higher than that of first one. Both polymers showed almost linear and reproducible release pattern. The kinetics data are mentioned in **(Table 5)**. The formulation TDK15MF1 best fit with Korsmeyer (r^2= 0.993) kinetic model. Similarly, TDK15MF2, TDK15MF3, TDK15MF4 also follow Korsmeyer kinetic model where rate of release kinetic (r^2) are 0.991, 0.995 & 0.999 respectively. On the otherhand, TDK15MF5 & TDK15MF6 follow Higuchi model where r^2 value are 0.998 and 0.997 respectively.

The value of release exponent (n) for Korsmeyer release for the formulation TDK15MF1 & TDK15MF2 are 0.382 & 0.408 respectively. These indicate that the formulations follow Fickian release pattern, more specifically diffusion controlled release mechanism which means the zero order release rate was changed over time. The release can be poorly explained by zero order release profile which supported by the r^2values (for, TDK15MF1=0.382 & TDK15MF2 = 0.408). Again, the value of release exponent (n) for Korsmeyer release for the formulations TDK15MF3, TDK15MF4, TDK15MF5 & TDK15MF6 are 0.458, 0.471, 0.505 and 0.539 respectively. The values of slope for Korsmeyer indicates that all the formulations containing polymer Methocel K15M CR follow Anomalous diffusion or non - Fickian ($0.45 < n < 0.89$) release pattern. This means that the drug being released by both diffusion and erosion controlled mechanism.

Effect of METHOCEL K100M CR on release pattern of Trimetazidine Dihydrochloride

METHOCEL K100M polymer was used as matrix forming agent to prepare the tablet containing Trimetazidine Dihydrochloride as active ingredient having METHOCEL K100M polymer 25%, 30%, 35%, 40%, 45% and 50% of total drug weight in the matrix tablet with the formulation code TDK100MF1, TDK100MF2, TDK100MF3, TDK100MF4, TDK100MF5, TDK100MF6. After preparation according to formulation shown in the **(Table 1)**, their dissolution studies were carried out in paddle method (USP apparatus II) with a sinker at 100 rpm in 0.1 N HCl medium at 37^{0}c (±0.5^{0}c). Three tablets from each formulation were used in dissolution study. The release profile of Trimetazidine Dihydrochloride was monitored up to 10 hours. The average release pattern is shown in **(Fig. 9)**. **(Fig. 10)** represents the Higuchi impact that is obtained by plotting the % of drug release vs Square Root of Time (SQRT). **(Fig. 11)** represents the first order release profile. Log cumulative percent drug release vs time gives Korsmeyer plot **(Fig. 12)**. The cumulative percent of drug release from these six formulations at different time intervals is shown at the **(Table 6)**.

A release profile of Trimetazidine Dihydrochloride containing METHOCEL K100M matrix tablet of six formulations was obtained from the graphs. The formulation TDK100MF1, TDK100MF2 and TDK100MF3 exerts 95-96% release at time 10 hour respectively. It has been observed that the release rate has been extended with the increase of polymer percent. The highest percent of drug release within 10 hours is obtained from TDK100MF1 where polymer content is 25% of total tablet wt. But in TDK100MF6, the polymer content is 50% of total tablet weight, the release of drug is 80.71 % within 10 hours. The rate of drug release was found to be inversely related to the amount of METHOCEL K100M present in the matrix structure, i.e. the drug release increased with decrease in the polymer content of the matrix tablet. The formulation containing 40%, 45% and 50 % polymer extended to 10 hours.

From the graphs, it is seen that that the release pattern from the formulation TDK100MF1, TDK100MF2 and TDK100MF3 are not reproducible where as the last three formulations show reproducible release pattern. In case of formulation TDK100MF4, TDK100MF5, TDK100MF6, the release is extended (sustained) up to 10 hrs. The formulation TDK100MF1 and TD100MF2 follow Korsmeyer kinetic model whereas the remaining follows Higuchi model. The formulation TDK100MF1 indicates Fickian diffusion mechanism **(Table 7).**

Table 6: Zero order release profile of Trimetazidine Dihydrochloride from METHOCEL K100M CR matrices.

Time (hrs)	TDK100MF1	TDK100MF2	TDK100MF3	TDK100MF4	TDK100MF5	TDK100MF6
0	0	0	0	0	0	0
0.5	29.85	27.64	26.53	24.32	23.22	19.90
1	37.59	34.27	30.96	28.75	27.64	24.32
2	47.54	44.23	42.01	37.59	34.27	32.06
4	67.44	63.02	59.70	57.49	55.28	50.86
6	80.71	77.39	75.18	70.76	67.44	64.13
8	93.98	91.77	90.66	80.71	75.18	72.97
10	96.19	95.08	95.08	87.34	82.92	80.71

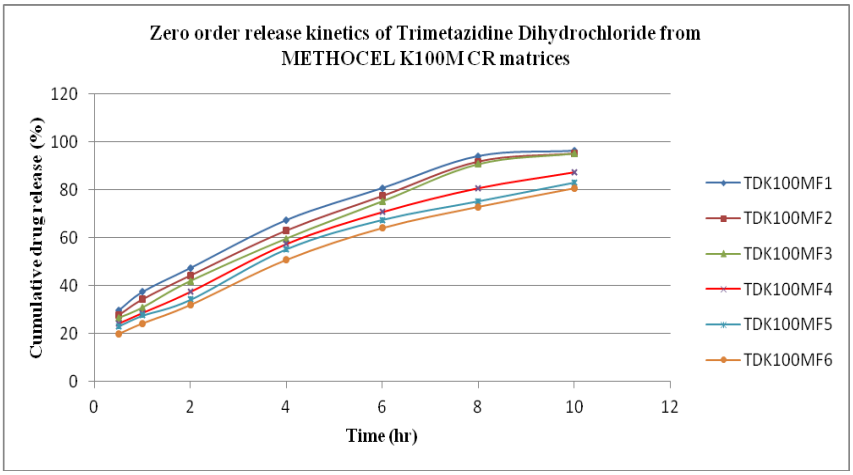

Fig. 9: Zero order plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K100M CR matrices.

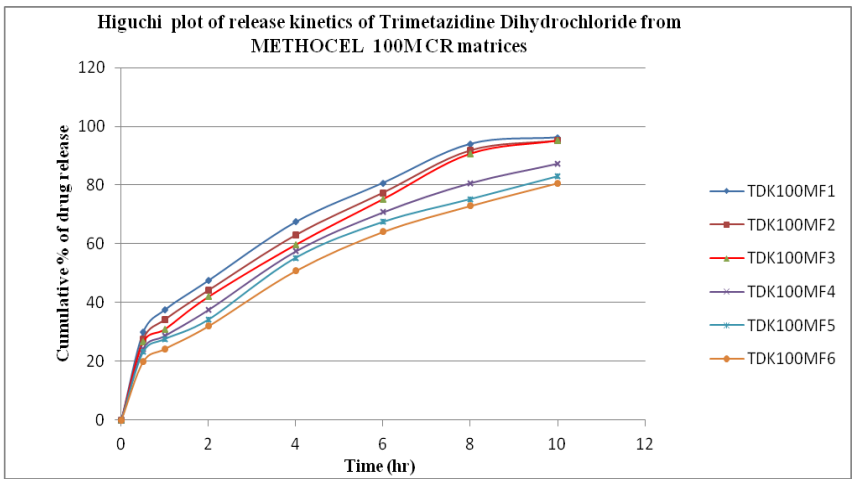

Fig. 10: Higuchi plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K100M CR matrices.

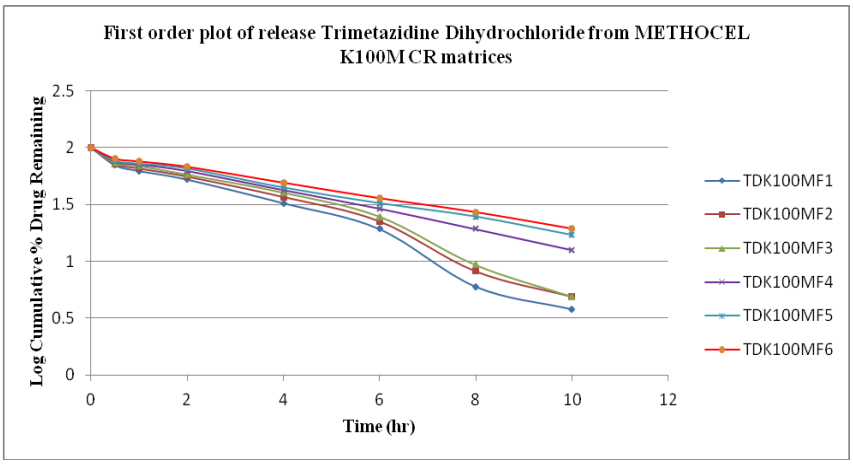

Fig. 11: First order plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K100M CR matrices.

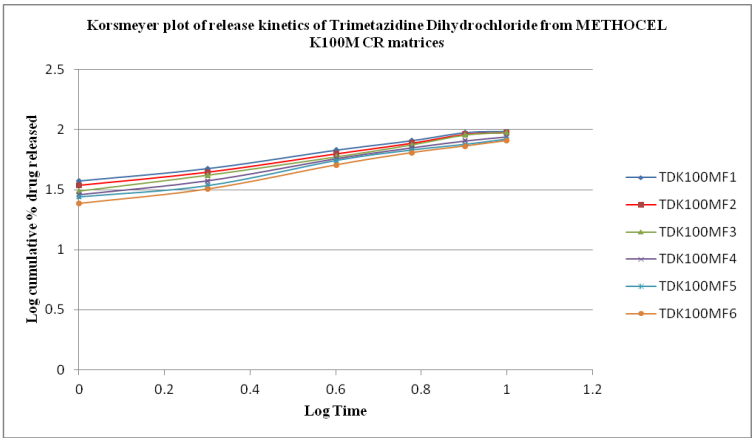

Fig. 12: Korsmeyer plot of release kinetics of Trimetazidine Dihydrochloride from METHOCEL K100M CR matrices.

Table 7: Release kinetics of Trimetazidine Dihydrochloride from METHOCEL K100M CR matrices

Formulation code	Zero order		First order		Higuchi		Korsmeyer	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
TDK100MF1	0.883	8.542	0.978	0.137	0.990	30.55	**0.992**	**0.432**
TDK100MF2	0.907	8.552	0.978	0.125	**0.994**	30.25	**0.994**	**0.466**
TDK100MF3	0.925	8.64	0.972	0.123	**0.994**	30.26	0.996	**0.505**
TDK100MF4	0.919	7.879	0.994	0.084	**0.995**	27.72	0.994	**0.503**
TDK100MF5	0.916	7.439	0.991	0.071	**0.993**	26.17	0.987	**0.503**
TDK100MF6	0.936	7.398	0.994	0.067	**0.995**	25.77	0.993	**0.542**

The kinetics data are mentioned in **(Table 7)**. The formulation TDK100MF1 best fits with Korsmeyer (r^2= 0.990) kinetic model and same for TDK100MF2 (r^2= 0.994). Formulation TDK100MF2 also follows Higuchi (r^2= 0.994); whereas TDK100MF3, TDK100MF4, TDK100MF5, TDK100MF6 follow Higuchi kinetic model where the rate of release [7] are 0.994, 0.995, 0.993, 0.995 respectively.

The value of release exponent (n) for Korsmeyer release for the formulation TDK100MF1 is 0.432. This indicates that the formulations follow Fickian release pattern, more specifically diffusion controlled release mechanism which means the zero order release rate was changed over time. Again, the value of release exponent (n) for Korsmeyer release for the formulations TDK100MF2, TDK100MF3, TDK100MF3, TDK100MF4, TDK100MF5 & TDK100MF6 are 0.466, 0.505, 0.503, 0.503 & 0.542 respectively. The values of slope for Korsmeyer indicates that these formulations containing polymer Methocel K100M CR follow Anomalous diffusion or non - Fickian ($0.45 < n < 0.89$) release pattern. This means that the drug being released by both diffusion and erosion controlled mechanism.

Higuchi release rate of Trimetazidine Dihydrochloride from different matrices

The slope of the Higuchi plot was calculated from their release rate of Trimetazidine Dihydrochloride. The formulations those contain least amount of polymer show highest percentage of release of Trimetazidine Dihydrochloride. For example, the formulation which contains 25 percent of METHOCEL K100M CR polymer results highest release rate (30.55%).

On the other hand, the formulation those contain highest amount of polymer results least amount of release of Trimetazidine Dihydrochloride. Lowest percentage of release and release rate was found with Trimetazidine Dihydrochloride from the formulation TDK4MF6 (77.39 % and the release rate is 25 mg / $hr^{1/2}$) among all the formulations of Trimetazidine Dihydrochloride matrices [8] used in the experiment. This can be attributed to the basic nature of METHOCEL K4M CR. Higher amount of polymer loading caused an extensive gel layer to form through which it was difficult for the drug to be released into the dissolution medium. Is this cases an elevated amount of METHOCEL K4M CR in this formulation increases the thickness of the gel layer around the matrix tablet that the consecutively increases the path length of diffusion. As a result, small amount of drug is released from the formulation that contains the highest proportion of METHOCEL K4M CR. The formulation TDK15MF4, TDK15MF5 and TDK15MF6 shows highest linearity and reproducibility.

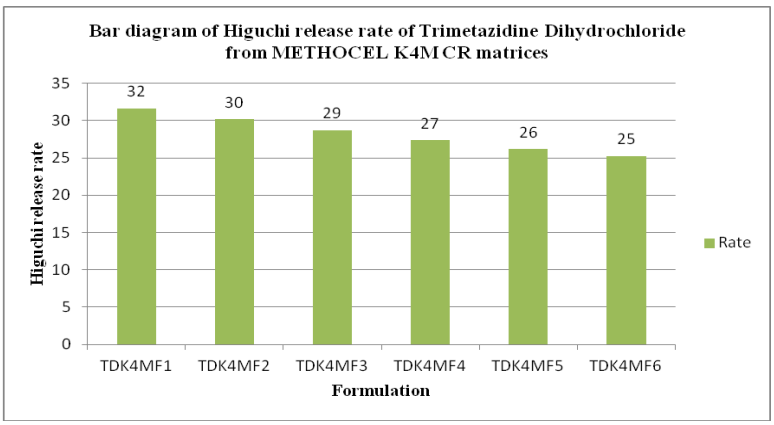

Fig. 13: Bar diagram of Higuchi release rate of Trimetazidine Dihydrochloride from METHOCEL K4M CR matrices.

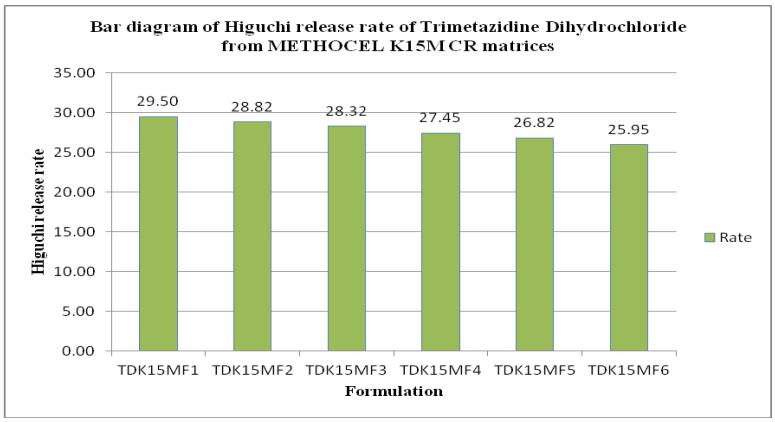

Fig. 14: Bar diagram of Higuchi release rate of Trimetazidine Dihydrochloride from METHOCEL K15M CR matrices.

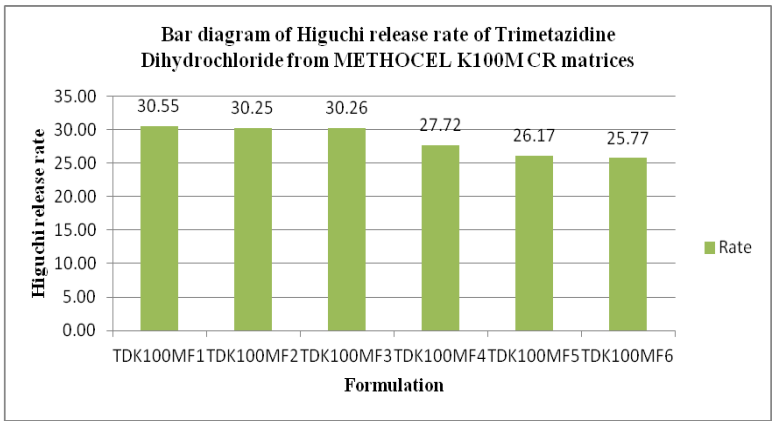

Fig. 15: Bar diagram of Higuchi release rate of Trimetazidine Dihydrochloride from METHOCEL K100M CR matrices.

Effect of Different polymer and formulation variables on release rate of Trimetazidine Dihydrochloride

It has been observed that the formulation that contains higher percent of polymer, releases the drug at slower rate i.e. extend the release of drug for long time. The extension of release is directly related to percentage of polymer. On the other hand, Avicel PH 102 is a good filler and most widely used in tablet formulations. The formulation that contains higher percentage of Avicel PH 102 results immediate release of drug because the swelling behavior of Avicel PH 102 allowed further penetration of the aqueous medium, resulting in rapid erosion of the polymer matrices. Drug release is controlled by penetration of water through the gel layer around the matrix system when they come into contact of dissolution medium. Drug release is controlled by penetration of water through the gel layer produced by hydration [11] of polymer and diffusion of drug through the swollen, hydrated matrix in addition to erosion of the gelled layer. In case of plastic polymer, the release of drug is controlled through porous channel. High drug polymer ratios result in formulation from which drug release is controlled by attrition (Salmon and Doelker, 1980). As the water absorption rate increases, the radial and axial dimensions of the matrix diminish along with a reduction in the matrix's weight when the lactose concentration is high and polymer viscosity is low. The diminishment furthers the matrix's passage from the swelling front to the erosion front where the polymer chains are cleaved off. These findings are in accordance with works reported by Gao and Meury, Lee and Kim and Ju et al (1996).

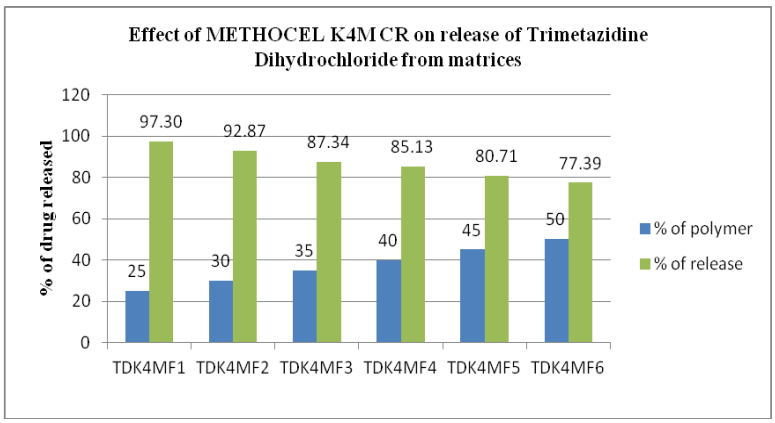

Fig. 16: Effect of METHOCEL K4M CR on release of Trimetazidine Dihydrochloride from matrices.

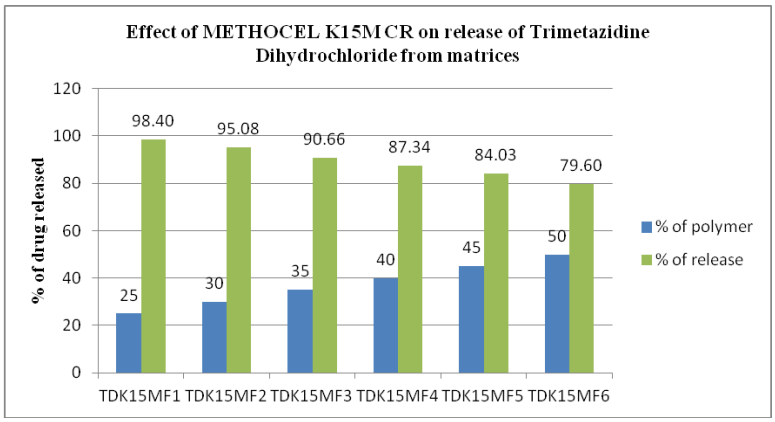

Fig. 17: Effect of METHOCEL K15M CR on release of Trimetazidine Dihydrochloride from matrices.

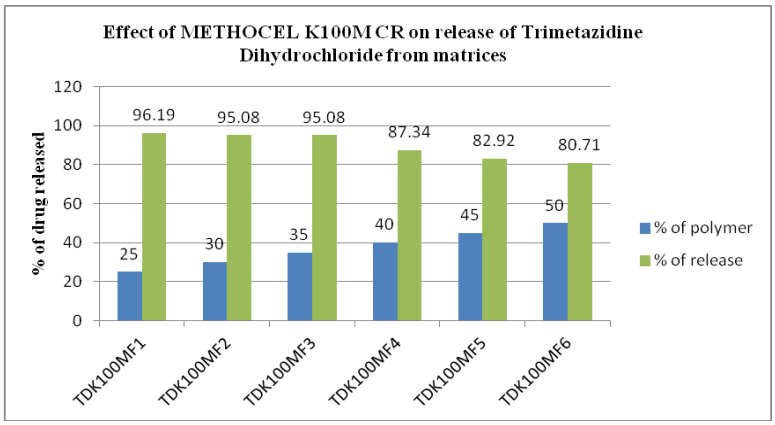

Fig. 18: Effect of METHOCEL K100M on release of Trimetazidine Dihydrochloride from matrices.

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CONCLUSION

The present research was undertaken to develop extended release solid dosage form of Trimetazidine Dihydrochloride. For this reason, different water swellable pH independent hydrophilic and water insoluble pH dependent solubility polymers have been used during the course of experiment to find out the release pattern. Different polymers have been planned to modify the drug release and Avicel PH 102 amount variation is used as a parameter to identify the best release formulation. Trimetazidine Dihydrochloride matrix tablets were prepared utilizing pH independent hydrophilic polymer as a carrier. Physical properties of all formulations were found to be satisfactory for the manufacturing process. The cumulative percent of release of Trimetazidine Dihydrochloride from all these polymeric matrices were plotted against time to get zero order plot **(Fig. 1**, **Fig. 5** and **Fig. 9)**. The cumulative percent of release of Trimetazidine Dihydrochloride were plotted against Squre Root of Time (SQRT) to obtain Higuchi kinetics **(Fig. 2**, **Fig. 6** and **Fig. 10)**. The log % remaining was plotted against time to get first order kinetics **(Fig. 3, Fig. 7** and **Fig. 11)**. Again Log cumulative percent drug released were plotted against log time to get Korsmeyer plot **(Fig. 4, Fig. 8** and **Fig. 12)**.

The release data were treated in different fashion and their kinetic values were calculated to evaluate the release pattern **(Table 7)**. The slope of Higuchi plots were calculated to get their release rate. The effect of polymer loading was also calculated. The best fit release kinetics with highest correlation coefficients was achieved with Higuchi model followed by zero order, first order and Korsmeyer equation. The data generated from this experiment showed that the release pattern of drug from high viscosity METHOCEL grades is mostly followed anomalous or non-Fickian transport process. Compared to conventional tablets, release of Trimetazidine Dihydrochloride from matrices prepared with these polymers was prolonged.

From the experimental point of view, it is clear that there is a chance of modulate the rate and extend of drug release with these polymers and formulations prepared in this experiment could be useful for the preparation by judicious combination between drug and release modifiers. A further advance study in the in-vitro condition can justify the release pattern observed from this current work and a standard drug release profile of Trimetazidine Dihydrochloride extended release tablet could be commercially justified.

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