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Research Article

FORMULATION AND EFFECT OF VISCOSITY AND CONCENTRATION OF METHOCEL ON RELEASE CHARACTERISTICS OF TRIMETAZIDINE MATRIX TABLETS

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ABSTRACT

Trimetazidine dihydrochloride is absorbed quickly from immediate release dosage form and attains very low concentration in plasma at time of next dose. To maintain constant drug plasma level, matrix tablets were prepared with varying Methocel E grades and concentrations, and followed by their *in vitro* drug releases studies. The formulated products were also compared with marketed product for release behavior. Low viscosity Methocel formulated matrix tablets, F1 to F3 showed fast release of drug. F6 was best formulation which released drug for 12 h while high viscosity Methocel in F7 to F9 showed very slow drug release which extended for more than 12 h. release rate was also extended as concentration of Methocel was increased. Model fitting of the *in vitro* drug release studies suggests that formulations best fitted in first order release kinetics. Drug release from the matrix occurred by combination of two mechanisms, diffusion of drug from tablet matrix and erosion of drug from tablet surface, which was reflected from Higuchi's model.

Keywords: Trimetazidine dihydrochloride, Matrix tablets, *In vitro,* Methocel E, Higuchi's model

INTRODUCTION

Angina pectoris is the most frequent symptom of ischemic heart disease and results from a temporary relative imbalance of oxygen supply and demand in myocardium[1]. When symptom of angina is not adequately controlled by mono-therapy of nitrates, β-blockers or calcium channel blockers, these drugs are used in combinations, but these drugs have adverse effects. In this case Trimetazidine (TMZ) dihydrochloride can be used to control angina. TMZ controls symptoms of myocardial ischemia by metabolic changes with fewer side effects. TMZ is used therapeutically as coronary vasodilator for prophylactic treatment of angina chest pain and for treatment of giddiness of vascular origin[2].

TMZ is administered orally in dose of 40 to 60 mg daily as an immediate release preparation. It is quickly absorbed and eliminated with plasma half life of around 6.0±1.4 h and T_{max} of around 1.8±0.7 h. Since it has shorter plasma half life, in practice 20 mg preparation is given twice or thrice a day in order to ensure relatively constant plasma level. But due to the fact that it is absorbed quickly, these immediate release forms lead to maximum plasma level immediately after administration and to a very low plasma level at time of next dose, resulting in great difference in peak and trough plasma levels at steady state. This compelled the necessity of fabricating the immediate release dosage form into sustained release preparation for achieving regular and constant plasma levels, which is also favorable for compliance of the patient to his treatment.[2] Polymeric matrix tablets, offer a great potential as oral controlled drug delivery systems. Often hydroxypropyl methyl cellulose is used as matrix former[3]. It excludes complex production procedure such as specialized coating during manufacturing and drug release rate from the dosage form is controlled mainly by the type & proportion of polymers used in the preparations[4].

MATERIAL and METHODS

Trimetazidine dihydrochloride was generously gifted by Synmedic Labs, Faridabad, Haryana. Methocel E100 LV, E4M CR Premium, E10M CR Premium were provided by Colorcon Asia Pvt Ltd, Verna, Goa, India. Polyvinyl Pyrrolidone K25 and Lactose were provided by Hi-Media Laboratories Pvt. Ltd, Mumbai. Isopropyl Alcohol was provided by Merck Ltd, Mumbai. Magnesium stearate and talc were provided by S.D. chem. Ltd, Mumbai. All other chemicals were of analytical grade used as received.

Preparation of matrix tablets

Different tablet formulations (Batch size of 100 tablets) were prepared by wet granulation technique [Table 1]. Accurately weighed quantities of pre-sieved drug, lactose and matrix materials (Methocel) were mixed uniformly and wetted with Polyvinyl Pyrrolidone K25 (PVP) in Isopropyl Alcohol (IPA): water (9:1) as granulating fluid. The cohesive mass thus obtained was screened through a sieve no. 12 and granules were air dried at room temperature. The coarse granules so obtained were once again screened using same sieve. Talc and magnesium stearate were finally added as anti-frictional agents to the uniformly sized granules and granules were compressed (8 mm diameter, biconvex punches) using a rotary press (Rimek Ahmedabad).

Evaluation of granules[5]

Both loose bulk density (LBD) and tapped bulk density (TPD) were determined by using bulk density apparatus (Shital Scientific Ind. Mumbai). After 300 taps, the tapped volume of packing was noted. LBD and TPD were calculated by using formulae:

LBD = weight of the powder/volume of packing

TBD = weight of the powder/ tapped volume of packing

The compressibility index volume was determined by

$$\text{Carr's index (\%)} = [(\text{TBD-LBD})]/\text{TBD}$$

The angle of repose of granules was determined by funnel method. Angle of repose was calculated using the equation

$$\theta = \tan^{-1}(h/r)$$

where, θ is angle of repose, h is height of powder cone in cm and r is radius of powder cone base in cm. Moisture content of granules was determined using Karl Fischer instrument (Spectra Lab. Mumbai). The moisture content %w/w was read on the monitor[6,7,8].

Evaluation of matrix tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, diameter, friability and drug content. Tablet hardness was determined for 10 tablets using a Monsanto hardness tester (Campbell electronics, Mumbai). The weight variation was evaluated on 20 tablets using an electronic balance and the test was performed according to the official method[9].

The thickness and diameter was determined for 10 tablets with the help of a digital Vernier caliper. Friability was determined taking 20 tablets in a Roche friabilator (Campbell electronics, Mumbai) for 4 min at 25 rpm. Swelling characteristics and mass degree of swelling of 10 tablets were evaluated[10]. Drug content of the matrix tablets was determined by weighing and finely grinding 10 tablets of each batch. Aliquot of this powder equivalent to 35 mg of TMZ was accurately weighed, suspended in approximately 50 ml of phosphate

buffer pH 6.8 and shaken for 15 min. Final volume was adjusted to 50 ml with phosphate buffer and filtered. Absorbance of this solution was recorded at 270 nm using UV/VIS spectrophotometer (Shimadzu, Japan) against a reagent blank and the content was compared from a calibration curve prepared with standard TMZ in the same medium[11].

Table 1: Table shows formulations to prepare matrix tablets 250mg

Sr. No.	Ingredients	Quantity (mg)								
		F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
1	TMZ	35	35	35	35	35	35	35	35	35
2	E100LV	35	52.5	70	-	-	-	-	-	-
3	E4M	-	-	-	35	52.5	70	-	-	70
4	E10M	-	-	-	-	-	-	35	52.5	8
5	PVP K30	8	8	8	8	8	8	8	8	3
6	Mag. Stearate	3	3	3	3	3	3	3	3	3
7	Talc	3	3	3	3	3	3	3	3	131
8	Lactose	166	148.5	131	166	148.5	131	166	148.5	qs
9	IPA::water (9:1)	qs	Qs	qs	qs	qs	qs	qs	qs	

Scanning electron microscopy

The dried samples were coated with gold using Auto Coating Unit e5, 200 coater (London, English), for about 2 min to obtain a coating thickness of about 200 A°. Surface morphologies of tablets were characterized. Micrographs were taken at an accelerating voltage of 15 KV with Cambridge Stereo Scan 200 (London, England).

Swelling and erosion characteristics

Matrix tablets were introduced into vessel of dissolution apparatus having 500 ml of dissolution media (pH 1.2). The tablets were removed using a small basket at interval of 1 h for 8 h then thickness, radius and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were dried in a vacuum oven at 45°C to a constant weight.

***In vitro* release studies**

The *in vitro* release rate studies were carried out by using USP dissolution test apparatus Type II in simulated gastric fluid (pH 1.2±0.1) from 0 to 2 h and simulated intestinal fluid (pH 6.8±0.1) from 2 h to 12 h. Rotation speed of 50 rpm at temperature of 37±0.5°C of 500 ml dissolution medium was maintained throughout the experiment. At interval of 1h, 10 ml of sample was withdrawn and replaced with the same volume of pre-warmed (37±0.5°C) fresh dissolution medium. The samples withdrawn were filtered through 0.45 µ membrane filter and drug content in each sample was analyzed after suitable dilution by UV/VIS spectrophotometer at wavelength 270 nm. The actual content in samples was read from a calibration curve prepared with standard TMZ. All dissolution studies were carried out in duplicate and repeated thrice. The rate and mechanism of drug release from prepared matrix tablets was analyzed by fitting dissolution data into Zero-order, First order, Higuchi and Korsemeyer Peppas model. The promising formulation was compared with marketed product (Esvedon CR 35mg) formulation for drug release study.

Stability studies

Stability study of optimized formulation was carried out at 40°C, 75 % RH for 3 months. Formulation was analyzed for its appearance, thickness, diameter, weight variation, friability, hardness, drug content and *in vitro* dissolution analysis.

RESULT AND DISCUSSION

A successful attempt has been made to formulate controlled release matrix tablets of TMZ using Methocel as polymer. Effect of Methocel concentrations was studied. Total nine formulations were prepared.

Granules are the key factor in tablet production. Various physical parameters of granules significantly affect tablet production and dissolution of drug. Thus granules of all formulations were evaluated for LBD, TBD, compressibility index, angle of repose and moisture content [Table 2]. The LBD and TBD of granules ranged from 0.231±0.02 g/ml to 0.282±0.03 g/ml and 0.269±0.04 g/ml to 0.333±0.05 g/ml respectively. The LBD and TBD of granules were decreased as viscosity and concentration of Methocel were increased in formulation F1 to F9. It indicated that as viscosity and concentration of Methocel increases size of granules also increases. Compressibility index values were ranging from 14.10±0.12 % to 15.31±0.39 %. Generally, compressibility index values up to 15 % result in good to excellent flow properties[6]. Angle of repose values of all formulations ranged from 25.41±0.59° to 29.39±0.29° which indicated good flow properties[12]. The moisture content of all the formulations was found to be satisfactory.

The results of hardness and friability of the prepared matrix tablets were ranged from 4.8±0.30 kg/cm^2 to 5.6±0.5 kg/cm^2 and 0.11±0.05 % to 0.19±0.03 % respectively. The tablet formulations in all the prepared batches contained TMZ ranging from 99.4 % to 100.3 %. The results of thickness and diameter of tablets were ranged from 3.4±0.2 mm to 3.7±0.2 mm and 8.0±0.1 mm to 8.2±0.1 mm, respectively. Swelling characteristics were observed by measuring the initial radius and thickness of all the formulations and the change in radius and thickness after hydrating for 8 hours in water. Swelling characteristics of formulations indicated that tablet surface area was increased with increase of concentration and viscosity of Methocel. It was observed that swelling in axial direction was faster than radial direction [Fig. 1 (a) and (b)]. More increase in axial swelling might be due to compression force and gravitational force acting in axial direction of tablets[13].

Table 2: Pre-Compression evaluation of granules F1 to F9

Formulation No.	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Angle of	27°13′	26°36′	25°41′	29°39′	27°36′	28°26′	27°42′	26°38′	28°19′
Repose	±0.32′	±0.31′	±0.59′	±0.29′	±0.41′	±0.42′	±0.49′	±0.37′	±0.34′
LBD (g/ml)	0.282	0.280	0.278	0.261	0.259	0.258	0.237	0.235	0.231
	±0.03	±0.09	±0.012	±0.014	±0.026	±0.021	±0.031	±0.026	±0.02
TBD (g/ml)	0.333	0.329	0.327	0.308	0.305	0.303	0.274	0.27	0.269
	±0.05	±0.03	±0.06	±0.04	±0.01	±0.02	±0.03	±0.02	±0.04
Carr's compressibility index.	15.31	14.89	14.98	15.25	15.08	14.85	14.44	14.44	14.10
	±0.39	±0.31	±0.19	±0.48	±0.35	±0.21	±0.37	±0.35	±0.12

SEM images Fig. 2 (a) and (b) of matrix tablet surface at 100X and 500X resolutions were crude and rough, showing aggregated particles and rough crusts, cracks and pores.

The *in vitro* dissolution studies were conducted in duplicate and repeated thrice; the mean values were plotted versus time with SD of less than 3, indicating the reproducibility of the results. The effect of three viscosity grades of Methocel (E100LV, E4M, E10M) on the dissolution is shown in Fig. 3. Release rate varied among Methocel viscosity grades as the viscosity of Methocel was increased the release rate extended from 4 h to more than 12 h. The E100LV formulations (F1, F2 and F3) were the fastest releasing products and showed complete release of TMZ in only 4 h to 6 h while the formulations with the higher viscosity grades (E4M and E10M) showed slower release rates.

Table 3: Evaluation parameters of compressed tablets

Formulation No		F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Hardness (kg/cm^2)		5.4	5.1	5.2	5.6	5.1	4.9	5.1	4.8	5.6
		±0.7	±0.8	±0.3	±0.5	±0.8	±0.6	±0.4	±0.3	±0.5
Friability (%)		0.19	0.16	0.12	0.11	0.16	0.14	0.14	0.15	0.17
		±0.03	±0.04	±0.02	±0.05	±0.02	±0.04	±0.03	±0.03	±0.04
Drug content (%)		99.4	99.7	99.4	100.3	100.0	99.7	100.3	99.1	99.7
Thickness (mm)		3.5	3.6	3.5	3.7	3.4	3.5	3.4	3.6	3.4
		±0.1	±0.2	±0.1	±0.2	±0.2	±0.1	±0.2	±0.1	±0.2
Diameter (mm)		8.1	8.0	8.1	8.0	8.1	8.0	8.2	8.1	8.0
		±0.1	±0.1	±0.1	±0.2	±0.1	±0.2	±0.1	±0.1	±0.2
	Before Swelling	87.92	90.43	89.01	92.94	87.92	87.92	87.54	91.56	85.40
Surface Area (mm^2)		±1.3	±1.4	±1.2	±1.5	±1.2	±1.6	±1.5	±1.3	±1.7
	After Swelling	133.2	136.6	138.9	171.2	176.1	179.4	235.6	241.3	248.9
		±2.1	±2.3	±2.1	±2.3	±2.1	±2.1	±0.9	±0.8	±0.9
	Before Swelling	252	247	255	251	256	248	257	251	256
Weight (mg)		±2.3	±2.6	±2.8	±2.1	±2.9	±2.2	±2.5	±2.8	±1.9
	After Swelling	467	475	503	591	621	625	756	769	799
		±2.5	±2.4	±2.8	±2.1	±2.6	±2.4	±2.1	±2.6	±1.9
Tensile Strength (N/mm^2)		0.1	0.124	0.135	0.078	0.097	0.113	0.128	0.133	0.144
		±0.01	±0.01	±0.08	±0.01	±0.01	±0.01	±0.01	±0.10	±0.01

The release rate was also extended as concentration of Methocel was increased. The release rate was faster with lower viscosity grade of E100LV, probably owing to less polymer entanglement, less gel strength and also to the larger effective molecular diffusional area at lower viscosity as compared with higher viscosity grades of E4M and E10M. As the viscosity increased, gel layers provided a more tortuous, resistant barrier and longer diffusional path which resulted in slower release of TMZ from these matrices[14, 15].

In order to describe the kinetics of the release process of drug in all formulations as well as in the marketed preparation, various equations were used. Zero-order rate equation describes the system where release rate is independent of the concentration of the dissolved species[16]. The first-order equation describes the release from the systems where dissolution rate is dependent on the concentration of the dissolving species[17]. The Higuchi square root equation describes the release from system where solid drug is dispersed in insoluble matrix and the rate of drug release is related to the rate of diffusion[18]. The Korsmeyer-peppas equation is used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved[19].

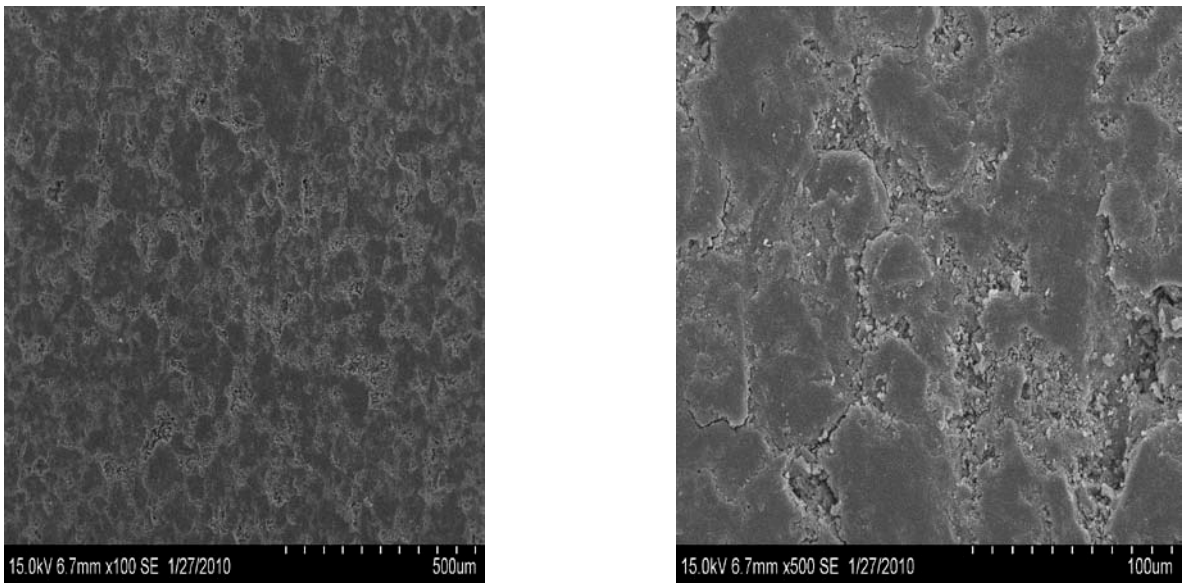
(a) **(b)**

Fig. 1: Swelling characteristics of Formulation F6- (a) at 0 h (b) After 3 h

The applicability of all of these equations was tested. The kinetics data for all models is shown in Table 4. Drug release process was not zero-order in nature. The dissolution data of all formulations when fitted in accordance with first order equation, a linear relationship was obtained with 'r' (correlation coefficient) value close to unity and higher than value of 'r' obtained from the zero-order equation for all formulations, showing that the release was an apparent first-order process[20]. To find out exact mechanism, dissolution data of all formulations were fitted in Higuchi square root equation and Korsmeyer-Peppas equation. All the formulations in this study were best expressed by Higuchi's classical diffusion equation, as the plots showed high linearity (r: 0.975 to 0.998). The linearity of the plot indicated that the release process was diffusion-controlled. Thus amount of drug released was dependent on the matrix drug load[21].

As concentration reduced on drug release, the diffusional path increased resulting in comparatively slower drug release rate in later phase. To confirm the diffusion mechanism, the data was fitted to Korsmeyer-Peppas model. All formulations showed good linearity (r: 0.958 to0.997), with slope (n) values ranging from 0.375 to 0.725. In Korsmeyer-Peppas model, 'n' is the diffusional exponent indicative of mechanism of drug release. A value of n = 0.45 indicates Fickian or case I release; 0.45 < n < 0.89 indicates non-Fickian or anomalous release; n = 0.89 indicates case II release; and n > 0.89 indicates super case II release[22]. In the case of the Fickian release mechanism, the rate of drug release is much less than that of polymer relaxation (erosion). So the drug release is chiefly dependent on the diffusion through the matrix. In the non-Fickian (anomalous) case, the rate of drug release is due to the combined effect of drug diffusion and polymer relaxation. Case II release generally refers to the polymer relaxation[5,23]. The n values for formulations F1 to F3 ranged from 0.627 to 0.725, indicating that the release mechanism was non-Fickian or anomalous release (0.45 < n < 0.89). The n values for formulations F4 to F6 ranged from 0.431 to 0.485 and for formulations F7 to F9 from 0.403 to 0.417. Based on the n values, it was observed that at lower viscosity of Methocel i.e. F1 to F3, drug release from matrices were controlled by polymer relaxation (erosion) as well as diffusion. As viscosity and concentration of Methocel was increased effect of diffusion on drug release was also increased and effect of erosion was decreased. Stability studies were conducted for F6 under at 40° C/75 % RH. After 3 months the samples were analyzed for Appearance, Thickness, Diameter, Weight Variation Test, Friability Test, Hardness Test and Drug content *in vitro* Dissolution Analysis. There were no significant changes observed in the Appearance, Thickness, Diameter, Weight Variation Test, Friability Test, Hardness Test, Drug content [Table 5] and *in vitro* Dissolution Analysis [Fig. 4] of Trimetazidine Dihydrochloride Matrix Tablet.

From these results it can be concluded that Methocel control the drug release from matrix. Percent of total matrix material and viscosity of Methocel significantly influenced the release rate of TMZ. F6 gave satisfactory results to release TMZ matrix tablet up to 12 h.

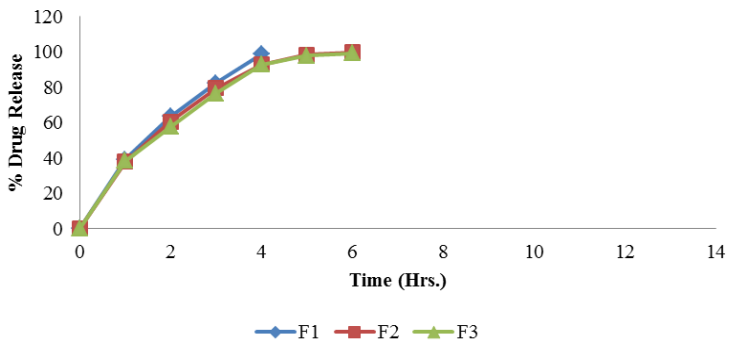


(a) **(b)**

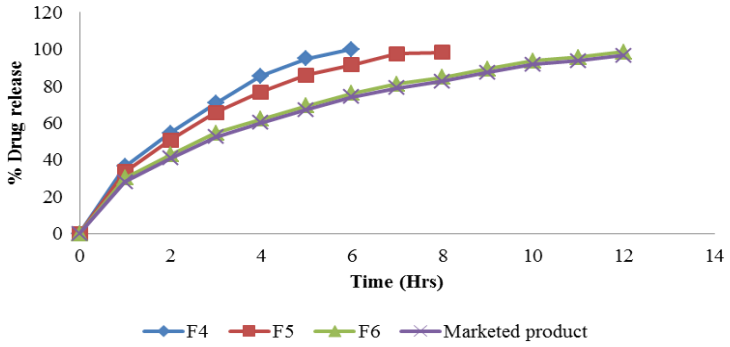
Fig. 2: SEM image of matrix tablet surface (a) at 100X and (b) 500X

Table 4: Kinetic model fitting of release profile for formulation F1 to F9

Formulations		F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order r		0.9612	0.9385	0.9679	0.9872	0.9321	0.9221	0.9216	0.8982	0.8999
First order r		0.9844	0.9893	0.9934	0.9865	0.9923	0.9981	0.9899	0.9989	0.9926
Higuchi's r		0.9755	0.9768	0.9841	0.9918	0.9925	0.9983	0.9933	0.9897	0.9973
Korsmeyer-	n	0.7251	0.6854	0.6273	0.4859	0.4757	0.4316	0.4171	0.4083	0.4031
Peppas	R	0.9589	0.9671	0.9845	0.9927	0.9910	0.9979	0.9892	0 .9921	0.9973



(a)



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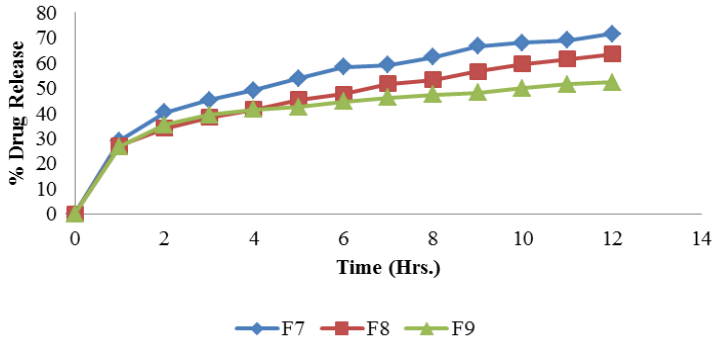

(c)

Fig. 3: *In vitro* Drug release of different formulation. (a) F1 to F3, (b) F4 to F6, (c) F7 to F9

Table 5: Stability study of F6 under accelerated condition as per ICH guidelines

Particulars	Result
Thickness	3.5 mm
Diameter	8.1 mm
Weight before swelling	252 mg
Weight after swelling	623 mg
Surface area before swelling	89.09 mm^2
Surface area After swelling	178.69 mm^2
Hardness	5.1 kg/cm^2
Friability %	0.15 %
Drug content	99.6 %

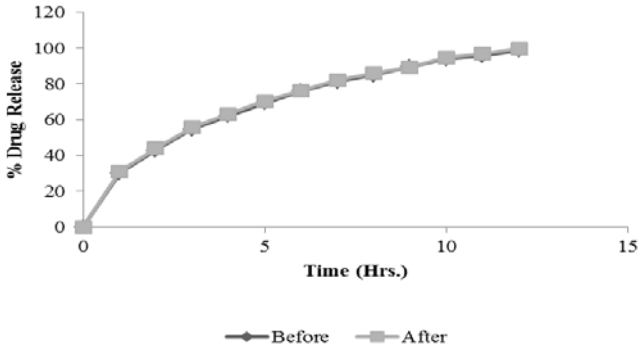

Fig. 4: Drug release data of formulation F6 before and after stability study.

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