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Original article

FORMULATION OF TRIMETAZIDINE MATRIX TABLET USING METHOCEL AND EFFECT OF DIFFERENT PARAMETERS ON DRUG RELEASE FROM MATRIX TABLET

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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 concentrations and their in vitro drug release was studied. Effects of hydrophobic and hydrophilic binders, lubricant concentration and effect of water insoluble diluents on in vitro drug release were studied. Effect of Methocel E was compared with the effect of Methocel K. The formulated products were also compared with marketed product. 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. Hydrophobic binders in F10 to F13 showed slow release of drug. Low concentration of PVP K25 showed fast release of drug. Water insoluble diluent DCP reduces release rate of drugs while there was no change in drug release rate after changing contents of lubricants in formulation. Mathematical treatment of the in vitro drug release 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 tablet surface which was reflected from Higuchi's model.

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

Methocel Kullanılarak Trimetazidin Matriks Tabletlerin Formülasyonu ve Matriks Tabletten İlaç Salımına Değişik Parametrelerin Etkisi

Trimetazidin dihidroklorür, hemen salım yapan dozaj formundan hızlıca absorbe olur ve diğer doz zamanında plazmada çok düşük konsantrasyona erişir. Plazmada sabit ilaç seviyesini sürdürmek için farklı Methocel E konsantrasyonları ile matriks tabletler hazırlanmış ve in vitro ilaç salımları incelenmiştir. Hidrofobik ve hidrofilik bağlayıcıların, lubrikan konsantrasyonunun ve suda çözünmeyen doldurucuların in vitro ilaç salımı üzerine olan etkisi değerlendirilmiştir. Methocel E'nin etkisi Methocel K ile karşılaştırılmıştır. Hazırlanan formülasyonlar piyasa preparatı ile de karşılaştırılmıştır. Düşük viskoziteli Methocel ile formüle edilen F1'den F3'e kadar olan matriks tabletler hızlı ilaç salımı göstermiştir. 12 saatlik bir ilaç salımı ile F6 formülasyonu en iyi formülasyon iken yüksek viskoziteli Methocel kulllanılarak hazırlanan F7'den F9'a kadar olan formülasyonlar 12 saatten daha uzun süren çok yavaş bir ilaç salımı göstermişlerdir. F10'dan F13'e kadar olan formülasyonlardaki hidrofobik bağlayıcılar yavaş ilaç salımı elde edilmesine neden olmuşlardır. PVPK25'in düşük konsantrasyonları hızlı ilaç salımı göstermişlerdir. Suda çözünmeyen bir doldurucu olan DCP salım hızını düşürürüken formülasyonlarda lubrikan içeriğinin değiştirilmesi in vitro ilaç salımında herhangi bir değişikliğe neden olmamıştır. İn vitro ilaç salımı için gerçekleştirilen matematiksel uygulamalar formülasyonların birinci derece kinetiğine göre ilaç saldığını önermektedir. Matriskden ilaç salımı iki mekanizmanın kombinasyonu şeklinde olmuştur; matriks tabletten difüzyon ve tablet yüzeyinden erozyon. Bu durum Higuchi kinetiğini göstermektedir.

Anahtar kelimeler. *Trimetazidin dihidroklorür, Matriks tablet, İn vitro, Methocel E, Higuchi Modeli*

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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 symptoms of angina are not adequately controlled by mono-therapy of nitrates, β-blockers or calcium channel blockers, these are used in combinations, but these drugs have adverse effects. In this case Trimetazidine Dihydrochloride (TMZ) 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).

Polymeric matrix tablets, offer a great potential as oral controlled drug delivery systems. Often hydroxylpropylmethylcellulose (Methocel) 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).

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).

EXPERIMENTAL

Material & Methods

Trimetazidine dihydrochloride was generously gifted by Synmedic Labs, Faridabad, Haryana. Methocel E100LV, E4M CR Premium, E10M CR Premium, K4M CR Premium were provided by Colorcon Asia Pvt. Ltd, Goa, India. Polyvinyl Pyrrolidone K 25 and Lactose were provided by HiMedia Laboratories Pvt. Ltd, Mumbai. Isopropyl Alcohol was provided by Merck Ltd, Mumbai. Magnisium stearate and talc were supplied by S.D. Chem. Ltd, Mumbai. Ethyl cellulose and Eudragit RS 100 were provided by Evonic Degussa India Pvt. Ltd. Mumbai. Dibutyl sebacic acid was provided by Sigma aldrich, Banglore. All other chemicals were of analytical grade used as received.

Selection of granulating fluid

Granules G1, G2, G3 and G4 were prepared by using water, Ethanol:Dichloromethane (DCM) (50:50), Isopropyl alcohol (IPA) and IPA:Water (9:1) respectively as granulating fluid (Table 1). All powders were separately weighed, screened through a size 20 mesh and granulated with PVP K25 in water, ethanol:dichloromethane (50:50), IPA, IPA:water (9:1) solution using approximately 100 ml fluid per 1000 g of powder. The wetted powder mass was then screened through a size 10 mesh and resultant granules were dried in an oven at 50 °C for five hours. The dry granules were rescreened through a size 10 mesh and the granule mass was recorded. The magnesium stearate and talc were weighed, sieved through a size 44 mesh and added to the granule blend and blending was continued. The blend was compressed into tablets on Rotary Press, tooled with one set of punches to a target weight of 250 mg and hardness about 4-5 kg/cm^2.

Table 1. Granules for selection of granulating agent

Ingredients	Quantity (mg)			
	G1	G2	G3	G4
TMZ	35	35	35	35
E4M	35	35	35	35
PVP	20	20	20	20
Mag. Stearate	3	3	3	3
Talc	3	3	3	3
Lactose	154	154	154	154
Water	q.s.	-	-	-
Ethanol:DCM (50:50)	-	q.s.	-	-
IPA	-	-	q.s.	-
IPA:Water (9:1)	-	-	-	q.s.

G1 to G4 were granules of Trimetazidine (TMZ) prepared by using different granulating liquids. G1 was prepared by using water, G2 by using ethanol:DCM (50:50), G3 by using IPA and G4 by using IPA:Water (9:1) as granulating fluid., E4M: Methocel E4M CR Premium, PVP: Polyvinyl pyrrolidone, DCM: Dichloromethane, IPA: Isopropyl alcohol.

Preparation of matrix tablets

Different tablet formulations F1 to F9 of TMZ were prepared by wet granulation technique (Table 2). 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. The 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 using 8 mm diameter, biconvex punches on a rotary press (Rimek, Ahmedabad).

Evaluation of granules

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by using bulk density apparatus (Shital Scientific Ind. Mumbai). After 300 taps, the tapped volume of packing was noted. LBD and TBD were calculated by equation 1 and 2 respectively. The compressibility index volume was determined by calculating Carr's Index by equation 3. The angle of repose of granules was determined by funnel method and calculated by equation 4.

$$LBD = \frac{Weight\ of\ powder}{Volume\ of\ packing} \qquad (1)$$

$$TBD = \frac{Weight\ of\ powder}{Tapped\ volume\ of\ powder} \qquad (2)$$

$$Carr's\ Index\ (\%) = \frac{(TBD - LBD)}{TBD} \qquad (3)$$

$$\theta = \tan^{-1}\left(\frac{h}{r}\right) \qquad (4)$$

Where, 'θ' is angle of repose, 'h' is height in cm of powder cone and 'r' is radius of base of powder cone 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 (5-7).

Table 2. Tablet formulations to prepare matrix tablets 250mg.

Ingredients	Quantities (mg)								
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
TMZ	35	35	35	35	35	35	35	35	35
E 100LV	35	52.5	70	-	-	-	-	-	-
E4M	-	-	-	35	52.5	70	-	-	-
E10M	-	-	-	-	-	-	35	52.5	70
PVP K30	20	20	20	20	20	20	20	20	20
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Lactose	154	136.5	119	154	136.5	119	154	136.5	119
IPA:water (9:1)	qs	qs	qs	qs	qs	qs	qs	qs	qs

Weight per tablet is 250 mg containing 35 mg of TMZ. Formulations were matrix tablets prepared by using different grades of Methocel. F1 to F3 contained Methocel E100LV (E100LV) 14%, 21% & 28% respectively, F4 to F6 contained Methocel E4M CR Premium (E4M) 14%, 21% & 28% respectively, F7 to F9 contained Methocel E10M CR Premium (E10M) 14%, 21% & 28% respectively. All formulation contained 8% of Polyvinyl Pyrrolidone (PVP K30), 3 mg of Magnesium stearate, 3 mg of talc, Lactose as diluent to adjust weight of tablet.

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 (8). The thickness and diameter was determined for 10 tablets by using a digital vernier caliper. Friability was determined by rotating 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 (9).

Drug Content

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 and dissolved in approximately 50 ml of phosphate buffer pH 6.8 and shaken for 15 m. 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 determined from a calibration curve prepared with standard TMZ in the same medium (10).

Scanning electron microscopy

The dried tablet samples were coated with gold using auto coating unit (e5200 coater, London, England) for 2 minutes and coating thickness of about 200 A° was obtained. Surface morphologies of tablets were characterized and 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 and 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 performed by using Type II USP dissolution test apparatus 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 to 12 h. Rotation speed of 50 rpm at temperature of 37±0.5 °C of dissolution medium (900 ml) was maintained throughout the experiment. 10 ml of sample was withdrawn at interval of 1 h and replaced with the same volume of pre-warmed (37±0.5°C) fresh dissolution medium. The withdrawn samples were filtered through 0.45 µm membrane filters 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 performed 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.

Effect of hydrophobic binders

Formulation showing up to 100 % release for 7 h in dissolution studies was selected to study effect of hydrophobic binders on release pattern. This formulation was further modified by incorporating different hydrophobic binding agents viz. Ethyl Cellulose and Eudragit RS 100 as shown in Table 3 (F10 to F13). Tablets were evaluated for drug content and release profile and compared with selected formulation.

Effect of concentration of PVP

Effect of concentration of PVP on drug release was studied by preparing F14 using half concentration of PVP K25 than optimized formulation as shown in Table 3. Tablets were evaluated for drug content and release profile and compared with optimized formulation.

Effect of Lubricant

The effect of lubricants and glidants on release profile of Methocel E4M matrix tablets was studied by decreasing the amount of lubricant by preparing formulation F15 (Table 3). Tablets were evaluated for drug content and release profile and compared with optimized formulation.

Effect of Insoluble filler

The effect of incorporation of insoluble filler was studied by preparing F16 using dibasic calcium phosphate (DCP) instead of soluble filler lactose (Table 3). Tablets were evaluated for drug content and release profile, and compared with optimized formulation.

Effect of Methocel K4M

To study the effect of Methocel K4M on drug release, formulations F17 & F18 were formulated by using Methocel K4M instead of Methocel E4M (Table 3). Tablets were evaluated for drug content and release profile and compared with optimized formulation.

Table 3. Modified formulations to prepare matrix tablets 250 mg.

Ingredients	Quantities (in mg)								
	F 10	F 11	F 12	F 13	F 14	F 15	F 16	F 17	F 18
TMZ	35	35	35	35	35	35	35	35	35
E4M / K4M*	35	35	35	35	70	70	70	35*	70*
PVP K30	-	-	-	-	12.5	20	20	20	20
EC	5	10	-	-	-	-	-	-	-
Eudragit RS100	-	-	10	20	-	-	-	-	-
Magnesium Stearate	3	3	3	3	3	1	3	3	3
Talc	3	3	3	3	3	1	3	3	3
Lactose	169	164	164	154	126.5	123	-	119	154
DCP	-	-	-	-	-	-	119	-	-
IPA::water (9:1)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Weight per tablet is 250 mg containing 35 mg of TMZ. Formulations F10 to F16 were matrix tablets prepared by using Methocel E4M CR Premium (E4M) 14% (F10 to F13) & 28% (F14 to F16) respectively. Formulation F17 & F18 were matrix tablets prepared by using Methocel K4M CR Premium (K4M*) 28%. Formulation F10 to F13 were prepared by using hydrophobic granulating agents, ethyl cellulose (EC) and Eudragit RS100. F10 & F11 was contained Ethyl cellulose (EC) 5 mg & 10 mg respectively. F12 & F13 was contained Eudragit RS100 10 mg & 20 mg respectively. Formulation F14 was contained 4% of Polyvinyl Pyrrolidone (PVP K30). Formulation F15 was contained reduced concentration of Magnesium stearate and talc. Formulation F16 contained Dibasic calcium phosphate (DCP) as diluent.

Stability studies

Stability study of optimized formulation was performed at 40 °C, 75 % RH for 3 months. Formulation was analyzed for its appearance, thickness, diameter, weight variation test, friability test, hardness test, drug content, *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 grade and concentration on *in vitro* profile was studied. Before formulating matrix tablet, granulating fluid was selected.

Granulating fluid was selected by preparing different granules viz. G1, G2, G3 & G4 by using water, Ethanol:DCM (50:50), IPA and IPA:Water (9:1) respectively as granulating fluid. The granules were evaluated for angle of repose, LBD, TBD, Hausner's ratio, bulkiness and void volume (Table 4). Utilization of water led to the large amount of lump formation and the obtained wet mass was difficult to pass through sieve to form the granules due to hydrophilic and gel forming nature of Methocel. Methocel was moderately soluble in mixtures of ethanol and DCM (50:50), the viscosity of Methocel solution using this mixture was less than that in the water. Ethanol and DCM were rapidly evaporated, forming granules without lump formation but containing more amount of fine. IPA exhibited a good Methocel wetting property and slower evaporation than ethanol, leads to granules without lump formation but contained large amount of fine. In order to increase binding property and decrease amount of fine, 10% (v/v) water was added to IPA. With this mixture Methocel would act as its own binder by forming a gel layer when come in contact with water. Granules obtained from this had good characteristics. Friability of tablets prepared from G1, G2, G3 and G4 was checked and it was found that friability of G4 was 0.28±0.12 % which was much less than G2 and G3. Thus it was concluded

that IPA:water (9:1) was best granulating liquid which was used further in preparation of formulations.

Table 4. Effect of granulating liquid on the granule properties.

Formulation	G1	G2	G3	G4
Angle of Repose	26°34′±0.67′	28°46′±0.68′	34°31′±0.45′	27°41′±0.51′
LBD (gm/ml)	0.28±0.01	0.37±0.02	0.41±0.02	0.31±0.01
TBD (gm/ml)	0.34±0.01	0.46±0.01	0.50±0.02	0.37±0.03
Bulkiness (ml/gm)	2.94±0.11	2.2±0.06	2.0±0.07	2.64±0.03
Carr's Compressibility Index	17±2.3	18±4.1	17±2.1	16±0.79
Hausner's ratio	1.20±0.084	1.20±0.06	1.4±0.35	1.20±0.011
Friability of tablet	0.18±0.042	0.84±0.071	0.90±0.074	0.28±0.12

G1 to G4 represent Granules prepared with different granulating fluids, LBD: loose bulk density, TBD: tapped bulk density, Friability of tablets prepared from these granules.

Table 5. Evaluation of granules used for formulation of matrix tablets of TMZ.

Formulation	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Angle of Repose	27°13′ ±0.32′	26°36′ ±0.31′	25°41′ ±0.59′	29°39′ ±0.29′	27°36′ ±0.41′	28°26′ ±0.42′	27°42′ ±0.49′	26°38′ ±0.37′	28°19′ ±0.34′
LBD (g/ml)	0.282 ±0.03	0.280 ±0.09	0.278 ±0.01	0.261 ±0.01	0.259 ±0.02	0.258 ±0.02	0.237 ±0.03	0.235 ±0.02	0.231 ±0.02
TBD (g/ml)	0.333 ±0.05	0.329 ±0.037	0.327 ±0.06	0.308 ±0.039	0.305 ±0.014	0.303 ±0.021	0.274 ±0.026	0.27 ±0.025	0.269 ±0.04
Bulkiness ml/g	3 ±0.071	3.03 ±0.037	3.05 ±0.111	3.24 ±0.125	3.27 ±0.091	3.30 ±0.031	3.44 ±0.048	3.70 ±0.051	3.71 ±0.06 1
Carr's compressibility index.	15.31 ±0.39	14.89 ±0.31	14.98 ±0.19	15.25 ±0.48	15.08 ±0.35	14.85 ±0.21	14.44 ±0.37	14.44 ±0.35	14.1 ±0.12
Hausner's Ratio	1.18 ±0.07	1.17 ±0.04	1.17 ±0.06	1.18 ±0.02	1.17 ±0.01	1.17 ±0.01	1.18 ±0.01	1.14 ±0.01	1.13 ±0.02

F1 to F9 represents matrix tablets of TMZ with different grades and concentrations of Methocel.

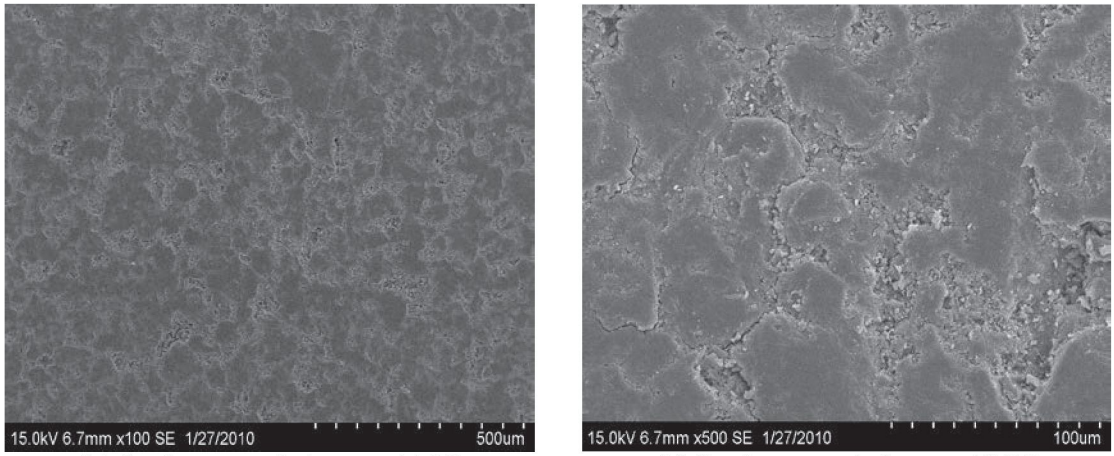
After selecting granulating liquid different matrix tablets of TMZ with different viscosity grade of Methocel and its different concentrations were prepared. Total nine formulations were prepared from F1 to F9 by wet granulation method. Granules are the key factor in tablet production as various physical 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 5). 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 decreased as viscosity and concentration of Methocel increased in formulation F1 to F9. It was 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 (11). The moisture content of all the formulations was found to be satisfactory.

The tablets were evaluated for hardness, friability, drug content, thickness, diameter and swelling characteristics. The results of hardness and friability of the prepared matrix tablets 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 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 3 hours in water. Swelling characteristics of formulations indicated that tablet surface area 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 & b). More increase in axial swelling might be due to compression force and gravitational force acting in axial direction of tablets (12).

(a) At 0 h (b) After 3 h.

Figure 1. Swelling characteristics of Formulation F6.



(a) Surface morphology at 100X (b) Surface morphology at 500X

Figure 2. SEM image of matrix tablet surface.

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

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 & F3) were the fastest releasing products and showed complete release of TMZ in only 4-6 h while the formulations with the higher viscosity grades (E4M and E10M) showed slower release rates. The release rate was also extended as concentration of Methocel increased. The release rate was faster with lower viscosity grade of E100LV, probably owing to less polymer entanglement, less gel strength and smaller effective molecular diffusional area as compared with higher viscosity grades of E4M and E10M. As the viscosity increased, gel layers provide a more tortuous, resistant barrier and longer diffusional path which resulted in slower release of TMZ from these matrices (13-14).

Kinetics of the release process of drug in all formulations as well as in the marketed preparation was described by various equations. Zero-order rate equation describes the system where release rate is independent of the concentration of the dissolved species (15). The first-order equation describes the release from the systems where dissolution rate is dependent on the concentration of the dissolving species (16). 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 (17). 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 (18). The applicability of all of these equations was tested. The kinetics data for all models is shown in Table 6. 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, showing that the release was an apparent first-order process. Exact mechanism was found out by fitting dissolution data of all formulations in Higuchi square root equation & 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) which indicated that the release process was diffusion-controlled. Thus amount of drug released was dependent on the matrix drug load (19). As concentration was reduced with time, the diffusional path increased resulting in drug release at a comparatively slower rate in later phase. To confirm the diffusion mechanism, the data was fitted to Korsmeyer-Peppas model. All formulations showed good linearity (r) ranging from 0.958 to 0.997 with slope (n) 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 (20). In the case of the Fickian release mechanism, the rate of drug release is much less than that of polymer relaxation i.e. erosion. So the drug release is chiefly dependent on the diffusion through the matrix. In the non-Fickian 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 (21). The n values for formulations F1 to F3 ranged from 0.725 to 0.627, indicating that the release mechanism was non-Fickian or anomalous ($0.45 < n < 0.89$). The n values for formulations F4 to F6 ranged from 0.485 to 0.431 and for formulations F7 to F9 from 0.417 to 0.403. 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 as well as diffusion. As viscosity and concentration of Methocel increased effect of diffusion on drug release increased and effect of erosion decreased.

The result of dissolution studies of formulation F4 composed of Methocel E4M 1:1 shown release rate of 34.99 % of TMZ at end of 1 hour and 99.48 % at end of 7 hours. This formulation was further modified by incorporating different hydrophobic granulating agents Ethyl Cellulose 2 % and 4 % (F10 and F11), and Eudragit RS100 4 % and 8 % (F12 and F13). The dissolution studies of these tablets indicated that F10, F11, F12 and F13 released 29.15 %, 19.92 %, 30.6 %, and 26.24 % at end of 1hour and 90.80 %, 78.36 %, 95.66 % and 89.96 % at end of 12 h respectively (Fig. 4). It indicated that incorporation of hydrophobic granulating agents along with Methocel better retard release rate of TMZ compared to hydrophilic granulating agent, PVP (22-23).

Table 6. Kinetic model fitting of release profile for formulation F1 to F9.

Formulations		F1	F2	F3	F4	F5	F6	F7	F8	F9	MP
Zero order	r	0.961	0.938	0.967	0.987	0.932	0.922	0.921	0.898	0.899	0.931
First order	r	0.984	0.989	0.993	0.986	0.992	0.998	0.989	0.998	0.992	0.995
Higuchi's	r	0.975	0.976	0.984	0.991	0.992	0.998	0.993	0.989	0.997	0.995
Korsmeyer-Peppas	n	0.725	0.685	0.627	0.485	0.475	0.431	0.417	0.408	0.403	0.399
	r	0.958	0.967	0.984	0.992	0.991	0.997	0.989	0.992	0.997	0.992

F1 to F9 represents various formulations of TMZ, MP: marketed product (Esvedon CR 35mg), r: correlation coefficient, n: diffusional exponent based on korsmeyer-peppas equation.

Release pattern of F14 which had 4 % of PVP K25 was fast and formulation released 99.16 % of drug within 10 h. When concentration of PVP K25 was 8 % as in F6 the release rate was in controlled manner and 98.58 % drug was released within 12 h (Fig. 5). It was indicated that increase in concentration of PVP K25 will better retard release of TMZ (24-25).

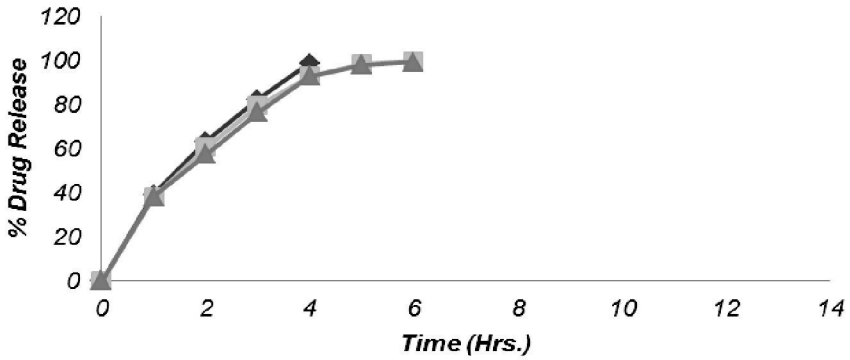
The effect of lubricant and glidant on release profile of Methocel E4M matrix tablet was studied by preparing formulation F15. There was no significant difference in the release profile when mixture of lubricants was incorporated in 3 % as in case of F6 and 1 % as in case of F15 (Fig. 6). It may be due to high gel strength of Methocel that neutralize hydrophobic effect of lubricants (26). This is not the case for conventional immediate release dosage forms, which have been shown to be susceptible to the hydrophobic effects of magnesium stearate and talc, lengthening drug disintegration and dissolution time.

The effect of changing soluble filler lactose with insoluble filler DCP, on TMZ release was studied by formulating F16 and comparing with F6, both containing Methocel E4M level at 28 %. the release profiles showed a decrease of about 5–7 % (after 6 h) as the filler was changed from lactose to DCP (Fig. 7). It also retards the initial burst release. Due to low solubility, DCP can contribute less than lactose to the osmotic pressure and thus reducing water transport into the gel. In addition, due to the high concentration of particulate DCP in the gel it is likely that the effective diffusion of the dissolution medium is lower in the DCP tablets than lactose tablets. This is a conceivable scenario as DCP theoretically renders low volume for water transport in the gel (27). Addition of soluble fillers enhances the dissolution of soluble drugs by decreasing the tortuosity of the diffusion path of the drug while insoluble fillers like DCP get entrapped in the matrix (28).

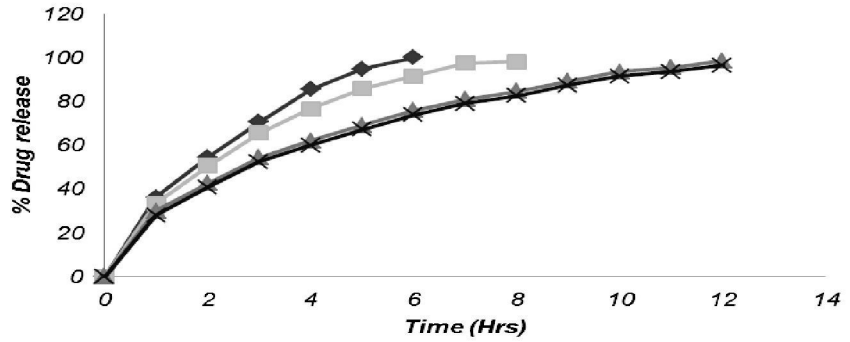
Effect of Methocel K4M on drug release was studied by formulating F17 & F18 and compared with F6 containing Methocel E4M. The matrices consist of the same weight percentages of the drug and Methocel E4M / Methocel K4M, compressed under the similar pressure, with the same die geometry. Furthermore, the same dissolution medium was used throughout the investigation. It was observed that the order of release rate from different grades of Methocel depends dramatically on the drug: polymer ratio. At drug:polymer ratio1:1 Methocel K4M (F18) has a lower drug release rate than Methocel E4M (F6). However, at

higher drug:polymer ratio of 1:2 Methocel K4M (F17) has equal retardant property as Methocel E4M (Fig. 8).

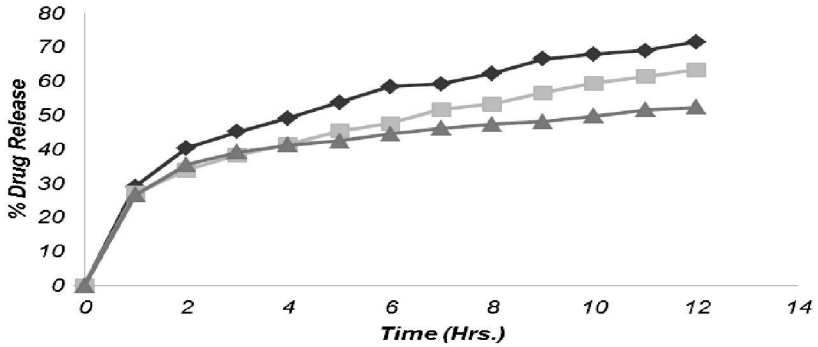
Stability studies were conducted for F6 at 40°C and 75% RH. After 3 months the samples were analyzed for Appearance, Thickness, Diameter, Weight Variation Test, Friability Test, Hardness Test, Drug content and *in vitro* Dissolution Analysis. There were no significant changes observed in the Appearance, Thickness, Diameter, Weight Variation Test, Friability Test, Hardness Test, Drug content and *in vitro* Dissolution Analysis (Fig. 4) of TMZ Matrix Tablet.



(a) F1 (–♦–), F2 (–■–) F3 (–▲–)

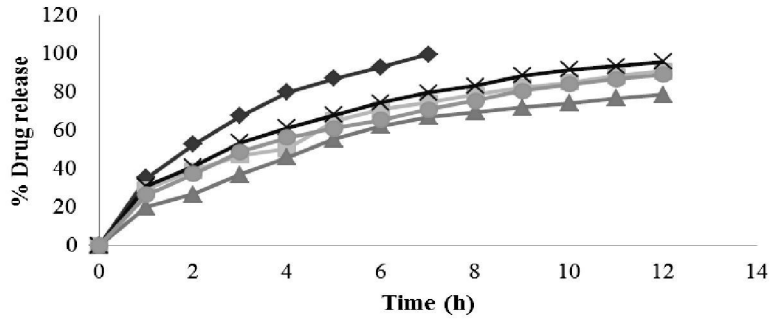


(b) *F4 (–♦–), F5 (–■–), F6 (–▲–), marketed product (–X–)*



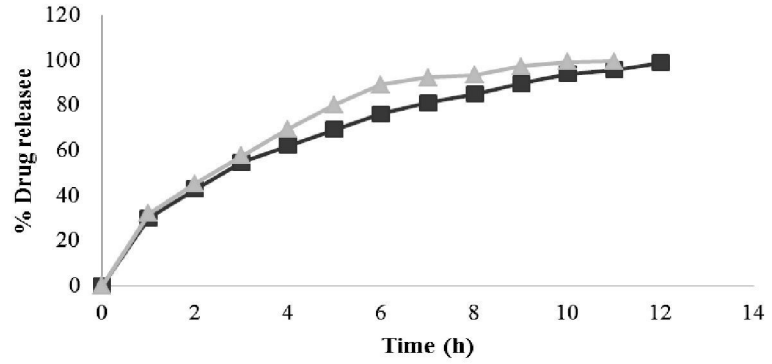
(c) *F7 (–♦–), F8 (–■–) F9 (–▲–)*

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



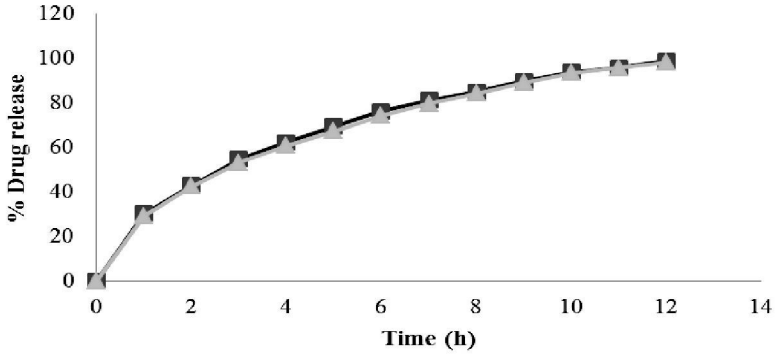
F4 (–♦–), F10 (–■–), F11 (–▲–), F12 (–x–), F13 (–●–)

Figure 4. Comparative evaluation of *In vitro* Drug release of F4, F10, F11, F12 and F13.



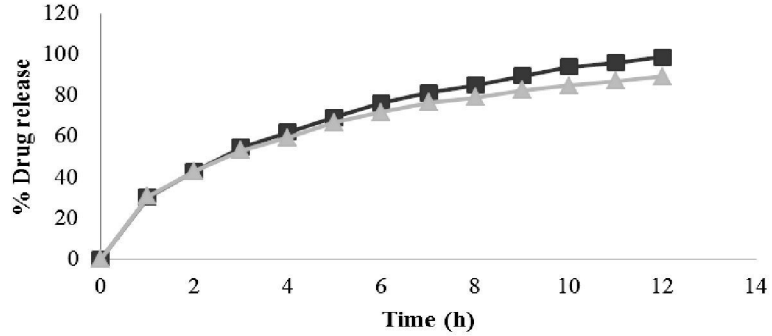
F6 (–■–), F14 (–▲–)

Figure 5. Comparative evaluation of *In vitro* Drug release of F6 and F14.



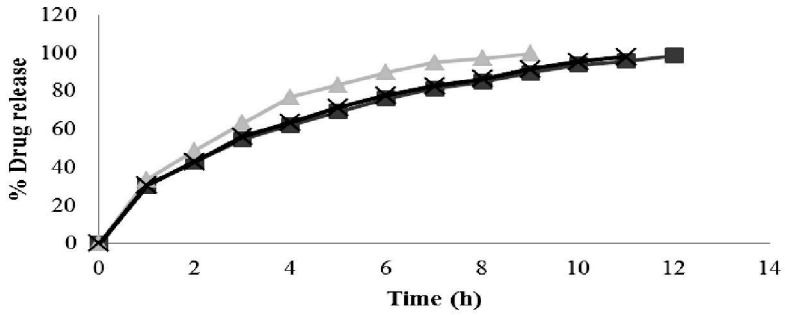
F6 (–■–), F15 (–▲–)

Figure 6. Comparative evaluation of *In vitro* Drug release of F6 and F15.



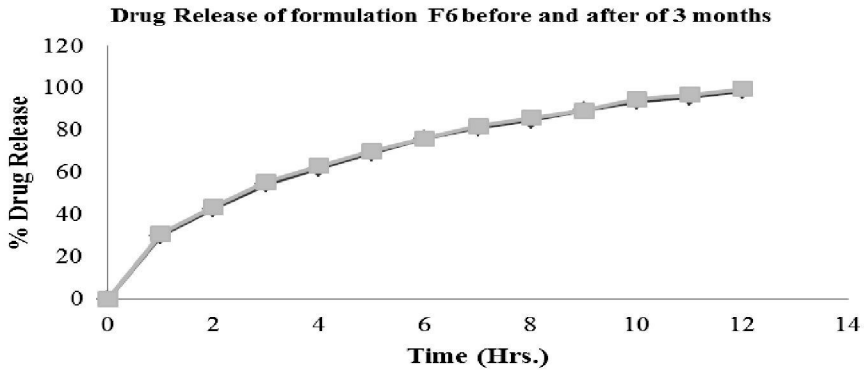
F6 (–■–), F16 (–▲–)

Figure 7. Comparative evaluation of *In vitro* Drug release of F6 and F16.



F6 (–■–), F17 (–▲–), F18 (- x-)

Figure 8. Comparative evaluation of *In vitro* Drug release of F6, F17 and F18.



Before (–♦–)), After (–■–)

Figure 9. Stability study.

CONCLUSION

IPA:water (9:1) was selected as good granulating fluid. Granules prepared from water were not of uniform size and contain no fine granules as Methocel E form highly viscous and entangled gel layers around particles with water generating larger granules. The granules produced using the mixtures of Dichloromethane:ethanol (50:50) contained more fines due to insolubility of lactose in mixture and rapid evaporation. Use of IPA also produced fine granules but less than Dichloromethane:ethanol (50:50) granules as it has more wettability. Addition of 10% water in IPA produced granules of good characteristics because lactose was soluble in water and Methocel form gel layer in contact with water of granulating liquid. Release rate from matrix tablets prepared by using lower viscosity grades and low concentration of Methocel was fast probably owing to less polymer entanglement, less gel strength and also due to the smaller effective molecular diffusional area at lower viscosity as compared with higher viscosity grades of Methocel. The percentage swelling increased with increase in polymer viscosity and concentration as higher viscosity grades of Methocel have higher and faster water absorption capacities and swell more rapidly increasing the diffusional path length and the diffusion coefficient. Incorporation of Eudragit and EC controlled the drug release in a better manner which could be attributed to the decreased penetration of the solvent molecules in the presence of hydrophobic polymer decreasing diffusion of the drug from the matrix. Hydrophilic binder PVP with Methocel showed efficient release rate retarding property. Rate of drug release tended to decrease with increasing content of either Methocel or PVP. Drug release rate was not affected by changing amount of lubricant and glidant, may be due to strong hydrophilic nature of Methocel and PVP. Substitution of soluble lactose with insoluble DCP affects the drug release rate. The presence of insoluble filler like DCP changes the release profile due to a change in the rate of swelling at the tablet surface. Methocel K4M was considered as better drug release retardant than Methocel E4M. At low concentration level Methocel K4M was better retardant but after increasing content of Methocel both polymers showed equal retardant property. A matrix tablet prepared with Methocel E4M and a granulating agent of a hydrophobic polymer is a better system for sustained release dosage form of a highly water-soluble drug like TMZ.

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