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RESEARCH PAPER

KINETIC STUDY ON EXTENDED RELEASE OF THEOPHYLLINE CAPLET WITH DIFFERENT BRANDS HYPROMELLOSE MATRIX

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The aim of the present investigation was to prepare and evaluate kinetics of extended release formulations of theophylline using Methocel K4M CR Premium/MK and Metolose 90SH-4000SR/M9. All formulated tablets with various concentrations (%4.0; 4.25; 4.5; 4.75; 5.0) of hypermellose were prepared by wet granulation method and found to be complied with the official requirements. The results showed the zero order kinetics and similarity (f2>50) with the marketed brand product were indicated by the formulations containing MK 4.75% - MK 5.0% and M9 5%. It was concluded that the higher the hypromellose concentration the slower the release of drug.

Key words: Theophylline, Hypromellose, Extended release kinetics, Independent parameters.

INTRODUCTION

For very small dosage administration of drugs resulting in restrictive absorption, the usage of controlled release is better suited (Bhardwaj *et al* 2000). Theophylline, which has short half-life, belongs to narrow therapeutic index Drug (Bayomi *et al* 2001). To this character, extended release formulation should be prepared to achieve adequate blood levels and maintained with a minimal fluctuations. Meanwhile, administration of such dosage form often reduce patient disobedience, resulting in attaining effective therapy.

Although many researchers reported multiparticulate and other sustained release formulations (Dahiya *et al* 2008; Dahiya and Tyagi, 2008; Dahiya and Gupta, 2011; Basarkar *et al* 2013; Tyagi and Kori, 2013; Verma *et al* 2014; Nagpal *et al* 2014; Dahiya and Onker, 2015), matrix tablet has also been found as one of the most significant extended release pharmaceutical formulation. Extended release formulations generally formulated as coated tablet, consist of complex and expensive steps. Hydroxypropyl Methyl Celullose (HPMC) or Hypromellose with special substitution site have been commonly used in simple controlled release formulations (Ishikawa *et al* 2000; Saiful *et al* 2010; Sultana and Khosru, 2012; Abdassah *et al* 2015). This is based on highly adsorbable hydrogelling capacity in the matrix as viscosity barrier for drug release (Shin-Etsu, 2005). In this study, we used hypromellose from different origin and having similar grade : Methocel K4M-CR Premium (Dow), Metolose 90SH-4000SR (Shin-Etsu) for comparing drug release kinetic profiles and theophylline retarded caplet (market derived) as standard quality evaluation.

This paper depicts the kinetic release profile of theophylline extended release formula from different origin hypromellose matrices, labscale manufacturing and testing the release behavior of these products using dependent methods (mathematical model) and independent

methods [similarity factor (f2), difference factor (f1)]. The purpose of this work was to produce theophylline extended release caplets using difference hypromellose matrix and to evaluate the release kinetic profile.

MATERIALS AND METHODS

The following materials were obtained from commercial sources: Theophylline anhydrous (ex Jilin Shulan, China), Metolose 90SH-4000SR (ex ShinEtsu, Japan), Methocel K4M-CR Premium (ex Dow Chemical, USA), Lactose-SD (ex Grande, USA), Talcum (ex Haicen, China) and Magnesium stearate (ex Faci, Indonesia), marketed theophylline retard caplets, artificial gastric fluid pH 1.2 and artificial intestinal fluid pH 6.0 without enzymes (attempt to match USP XXX NF XXV) and reagents (Merck, appropriate analysis grade).

Preparation of theophylline extended release caplet

All caplets were prepared by wet granulation method. The compositions of Theophylline ER matrix caplets are given in the **Table 1**. Theophylline and Lactose SD were mixed together. Hypromellose was dissolved in a portion of water to make a 10% binder solution. Which then added to the mixed powder, mixed well to form a coherent mass. This mass was then passed through no. 10 sieving mesh and resultant granules were dried in the oven at 50±5°C for 24 h. The dried granules were further passed through no. 16 sieving mesh.

The dried granules were then characterized, mixed with lubricant (magnesium stearate and talcum) and then som-pressed to form 400 mg caplets using single punch tablet machine (Korsch, Tipe EK 0).

Table 1. Composition of Theophylline ER matrix caplets (mg/tablet)

Composition	Formulation				
	F1 (4%)	F2 (4.25%)	F3 (4.5%)	F4 (4.75%)	F5 (5%)
Theophylline (mg)	300	300	300	300	300
Lactose SD (mg)	78	77	76	75	74
Hypromellose* (mg)	16	17	18	19	20
Mg. Stearate (mg)	4	4	4	4	4
Talcum (mg)	2	2	2	2	2
Total weight (mg)	400	400	400	400	400

*Hypromellose : Metolose 90SH-4000SR (M9) and Methocel K4M-CR Premium (MK)

Evaluation of granules

The granules were evaluated for loss on drying, flowability, compressability (Carr's index), and angle of repose.

Evaluation of caplets

The prepared caplets were evaluated for content uniformity, weight uniformity, size uniformity, hardness, friability, and *in vitro* drug release.

In vitro drug release study

In vitro drug release profile was carried out as per USP XXX NF XXV using Sotax AG CH-4008 BASEL, Tipe AT-6 apparatus (paddle type). The dissolution studies were performed using 900 ml of artificial gastric fluid pH 1.2 at 37±0.5°C and 50 rpm. Each 10 ml sample was drawn at 5, 10, 15, 30, 45, 60 min, replaced with the artificial intestinal fluid pH 6.0 without enzymes. Ten ml samples at 90, 120, 150, 180, 240, 300, 360, 420, 480 minute were withdrawn and replaced with same quantity of fresh dissolution medium each time. Collected samples were suitably diluted with dissolution medium and analyzed at 269 nm, using fresh dissolution medium as blank in UV-double beam spectrophotometer.

Drug release kinetic profile

One way ANOVA tool was used to analyze the concentration variation of hypromellose to caplets release data. If there are any effect which influenced the dissolution mechanism, it would be studied by plotting dissolution profiles in various kinetic models *i.e.* zero order, first order and higuchi model. (dependent methods). To know which of the formulation possessed the most similar release behaviour to the marketed products, the difference factors (f_1) and similarity factors (f_2) are recommended which are computed by independent methods.

RESULTS AND DISCUSSION

Granules properties

The granules of all formulations exhibited good quality as summarized in **Table 2a,b**. All granules were found suitable to the compression requirement (Aulton, 2002).

Table 2a. Properties of theophylline matrix granules (F1-F3)

Parameters	F1		F2		F3		Req.
	M9	MK	M9	MK	M9	MK	
Loss on drying (%)	0.55	0.50	0.77	0.66	0.64	1.02	< 2
Angle of repose (°)	19.13±0.95	14.21±0.54	19.98±0.41	14.17±0.48	19.43±0.63	12.66±1.45	< 25
Flowability (g/detik)	14.78±0.42	18,98±0.66	14.02±0.28	19.86±0.53	14.67±1.01	20.06±0.96	> 10
Carr index (%)	13.82±2.01	12.67±0.61	14.67±2.18	14.64±2.74	13.44±1.36	14.13±2.55	5-18

Table 2b. Properties of theophylline matrix granules (F4-F5)

Parameters	F4		F5		Req.
	M9	MK	M9	MK	
Loss on drying (%)	0.47	0.84	0.37	0.60	< 2
Angle of repose (°)	18.97±0.75	14.90±0.46	18.16±0.40	13.51±0.09	< 25
Flowability (g/detik)	15.04±0.80	19.68±0.64	15.92±0.3	18.31±1.50	> 10
Carr index (%)	12.15±1.15	16.92±2.21	9.90±1.35	12.29±1.80	5-18

Caplets properties

Results of evaluation suggested that all caplet formulations were complied to the official friability specifications, as summarized in the **Table 3a,b**. This means all formulations did not affect theophylline release in the caplets form.

The contents uniformity of the drug in the caplets was complied to the USP XXX and NF XXV.

The content uniformity for the marketed product has also been fulfilled to the specification (100.63±1.70%).

Table 3a. Properties of theophylline caplets (F1-F3)

Parameters	F1		F2		F3		Req.
	M9	MK	M9	MK	M9	MK	
Length (mm)	16.94± 0.01	16.7±0.008	16.92±0.01	16.96±0.014	16.99±0.01	16.97±0.007	-
Width (mm)	6.46± 0.01	6.50±0.005	6.44±0.01	6.50±0.016	6.51±0.003	6.50±0.007	-
Thickness (mm)	3.70± 0.02	3.78±0.15	3.70±0.02	3.78±0.070	3.75±0.02	3.93±0.045	-
Weight (mg)	407.03±2.06	406±2.58	408.34±5.61	409.41±4.19	406.74±4.42	414.4±4.68	-
Hardness (N)	125.88±13.21	114.4±17.4	128.75±7.84	130.55±20.8	130.75±10.79	131±18.6	-
Friability (%)	0.401±0.003	0.52±0.06	0.396±0.050	0.37±0.05	0.374±0.030	0.50±0.15	< 1%
Contents (%)	99.67±1.45	103.13±3.15	98.66±1.23	101.35±2.3378	100.75±0.55	96.96±0.4972	90-110

***In vitro* drug release profiles**

Release patterns of different hypromellose origin and the marketed theophylline retard (as working standard), was conformed to the USP XXX NF XXV. The results suggested that all formulations met official specifications (**Table 4a,b)**. One way ANOVA also showed that difference in hypromellose concentrations provided different drug release profiles. With higher hypromellose concentration, more extended drug release was achieved. The release patterns of each formulations of the same origin (**Figure 1A, 1B**), looked alike but when analyzed with the release kinetics and independent parameters (**Table 5, 6**), they were found to exhibit different kinetic order and independent parameters compared to that of the marketed theophylline preparation.

Table 3b. Properties of theophylline caplets (F4-F5)

Parameters	F4		F5		Req.
	M9	MK	M9	MK	
Length (mm)	16.99±0.01	16.97±0.006	17.00±0.01	16.97±0.023	-
Width (mm)	6.51±0.01	6.50±0.005	6.52±0.01	6.49±0.030	-
Thickness (mm)	3.71±0.04	3.86±0.059	3.92±0.05	3.74±0.088	-
Weight (mg)	402.54±5.05	408.61±4.32	403.2±4.41	405.16±2.79	-
Hardness (N)	143.25±10.95	126.58±22.4	143.75±8.68	126.00±20.1	-
Friability (%)	0.352±0.022	0.37±0.08	0.350±0.019	0.37±0.03	< 1%
Contents (%)	100.10±1.73	97.65±2.2746	98.43±1.30	102.29±2.2026	90-110

Table 4a. Percentages of drug release from different hypromellose and marketed product (F1-F3)

Time (min)	% Drug release (mean±SD)							USP Req.
	F1		F2		F3		Theo. Std.	(%)
	M9	MK	M9	MK	M9	MK		
60	34.03 ±1.4	31.56 ±1.27	31.45 ±0.77	27.26 ±1.92	25.86 ±0.36	25.86 ±0.74	22.61±3.62	3-15
120	42.36 ±2.36	41.72 ±3.03	40.57 ±2.55	34.90 ±1.88	34.46 ±5.29	33.44 ±3.52	26.95±5.37	20-40
240	83.20 ±4.27	78.05 ±1.87	81.10 ±3.37	71.94 ±0.35	71.14 ±4.68	67.77 ±7.45	50.05±6.7	50-75
360	97.02 ±2.26	87.96 ±2.77	93.10 ±0,14	88.92 ±1.41	82.95 ±1.52	84.45 ±4.52	70.11±11.56	65-100
480	97.65 ±0.28	93.37 ±2.09	95.40 ±1.75	91.66 ±2.69	89.89 ±0.09	90.43 +0.99	85.11±6.82	>80

Table 4b. Percentages of drug release from different hypromellose and marketed product (F4-F5)

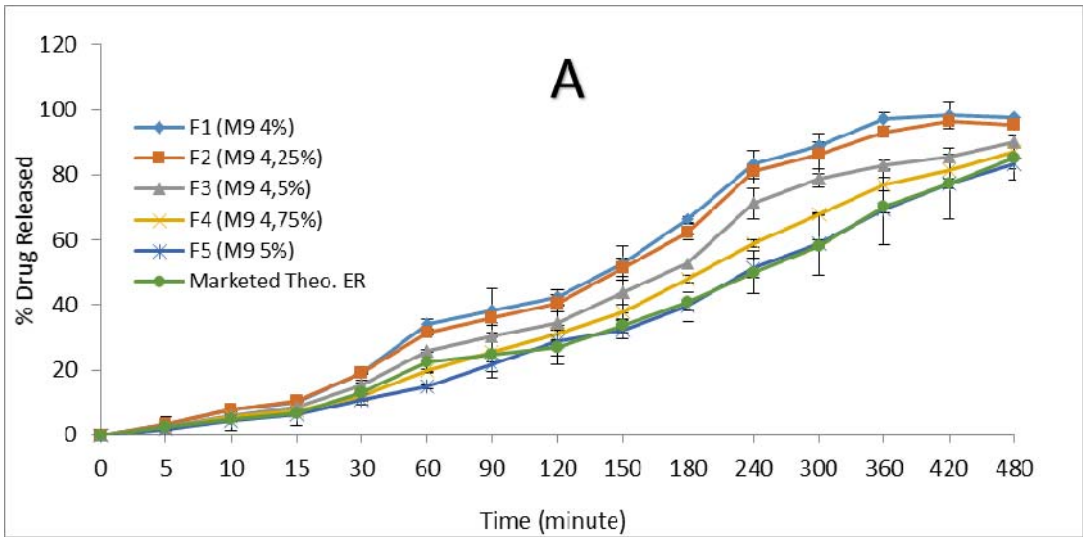
Time (min)	% Drug release (mean±SD)					USP Req.
	F4		F5		Theo. Std.	(%)
	M9	MK	M9	MK		
60	19.73±0.30	20.88±0.20	14.79±0.59	14.97±0.88	22.61±3.62	3-15
120	31.25±2.57	25.62±0.33	28.71±4.22	24.29±1.59	26.95±5.37	20-40
240	58.81±1.07	53.85±4.69	51.22±2.97	51.25±3.98	50.05±6.7	50-75
360	77.05±2.05	71.27±2.15	69.25±0.88	71.39±2.55	70.11±11.56	65-100
480	87.21±1.95	85.57±2.69	83.46±1.81	84.68±1.67	85.11±6.82	>80

Table 5. Kinetic parameters of different hypromellose and marketed product

Formulation	Regression Correlation (r^2)					
	0th Order		1st Order		Higuchi	
	M9	MK	M9	MK	M9	MK
F1	0.9151	0.9164	0.9574	0.9833	0.9785	0.9805
F2	0.9224	0.9432	0.9708	0.9734	0.9792	0.9708
F3	0.9419	0.9497	0.9896	0.9855	0.9786	0.9754
F4	0.9730	0.9797	0.9912	0.9688	0.9796	0.9683
F5	0.9894	0.9864	0.9821	0.9745	0.9693	0.9618
Theo. Std.	0.9855	0.9855	0.9711	0.9711	0.9725	0.9725

Table 6. Independent parameters of different formulations and marketed product

F : Theo. Std	*Similarity factor* (f_2)		*Difference factor* (f_1)	
	M9	MK	M9	MK
F1	36.18 ± 2..32	40.60 ± 2.26	43.07 ± 2.46	34.86 ± 2.07
F2	38.55 ± 1.89	45.37 ± 1.04	38.44 ± 2.07	25.90 ± 0.76
F3	49.29 ± 3.67	49.83 ± 5.87	21.48 ± 2.79	20.16 ± 4.69
F4	64.94 ± 1.98	79.62 ± 2.67	10.38 ± 1.68	4.61 ± 2.36
F5	78.53 ± 2.97	74.86 ± 2.38	4.48 ± 2.78	5.56 ± 2.09



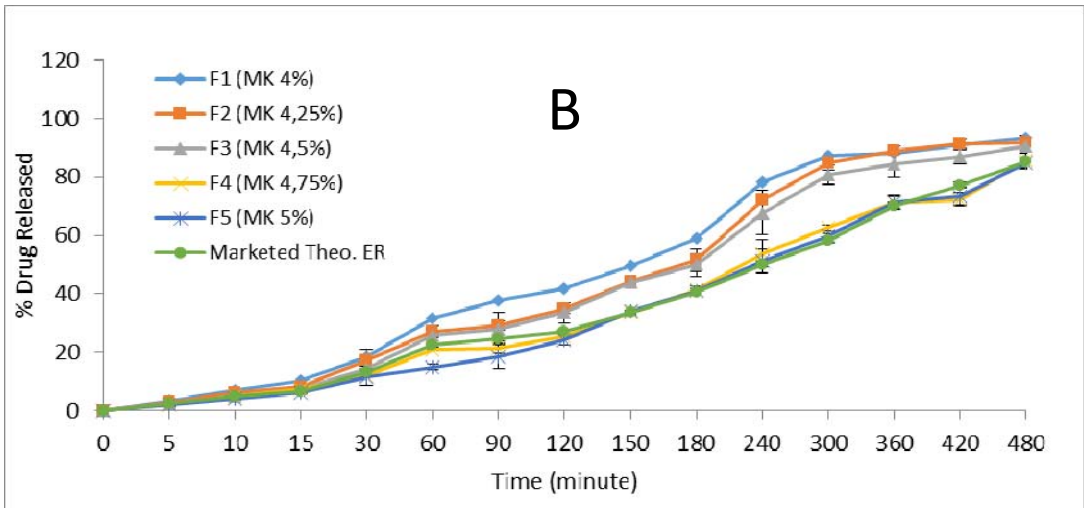


Fig. 1. In Vitro Release Profile of Theo. ER based on (A) Metolose 90SH-4000SR and (B) Methocel K4M CR Premium

Kinetic release analysis

Significant difference on theophylline content from both hypromellose origin was not found with One-way ANOVA (α = 0.05). However, results of Games-Howell Test showed that there was significant difference between M9 and MK.

When all release data were plotted using kinetic equation models (zero order, first order and higuchi model), it was indicated that data obtained from the kinetic release analysis of caplets F4 and F5 were closed to that of marketed theopylline product as indicated by regression coefficient (**Table 5**). These data have been relatively closed to the resume with independent methods which are compiled in **Table 6**. There had the similarity and difference factors on its equality which was achieved with F4 and F5.

Conclusion

Theophylline as extended release formulation with different hypromellose origin, may thus be

recommended as an oral delivery system to extend drug release for more than 8 h. Although all of the formulation provided extended release of theophylline, caplets prepared with hypromellose at 4.75-5% concentration was found to be the closest to the marketed product with respect to order of drug release and similarity factor.

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