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Research Article

FORMULATION DEVELOPMENT AND PROCESS OPTIMIZATION OF THEOPHYLLINE SUSTAINED RELEASE MATRIX TABLET.

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ABSTRACT

The purpose of this research work to prepare a sustained release matrix tablet of Theophylline. Different grades of hydroxypropyl methyl cellulose were evaluated for gel forming properties. Differential Scanning Calorimeter (DSC) study shows that drug and other excipients are compatible with each other. The effects of polymers concentration on drug release profile were investigated. A 3^2 full factorial design was applied to systemically optimize the drug release profile. The amounts of HPMC K-4M (X_1) and HPMC K-100M (X_2) were selected as independent variables. Cumulative % release of drug for 1st hour and 8th hour were selected as dependent variables. The results of the full factorial design indicated that a low amount of HPMC K-100M and a high amount of HPMC K-4M favors sustained release of Theophylline from matrix tablet. Accelerated stability study was also performed for three months indicated that optimized formulation was stable. Finally, process optimization was carried out to optimize the process parameters like kneading time, mixing time, thickness of the tablet and lubrication time.

Keywords: Sustained release, Theophylline, Matrix tablet, Kneading time.

INTRODUCTION

Sustained release preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristic of the conventional intermittent dosage regimen[1]. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action[2].

Theophylline is structurally classified as a methylxanthine. THP is a non-specific adenosine antagonist, antagonizing A_1, A_2, and A_3 receptors almost equally, which explains many of its cardiac effects and some of its anti-asthmatic effects. Bioavailability is 100%. It is excreted unchanged in the urine (up to 10%). It is metabolized extensively in the liver (up to 90%). The protein binding is 40%.The success of THP controlled release as a bronchodilator to treat bronchitis is due to its prolonged release rate[3,4]. THP, a bronchodilator, relaxes and opens the air passages to the lungs, making it easier to breathe. This drug is used mainly in solid oral dosage forms, particularly slow release forms, and has a narrow therapeutic index, requiring regular monitoring of serum THP concentrations to avoid adverse effects[5, 6].

Among the various types of cellulose ether derivatives, HPMC polymers are popular in controlled release matrices due to their compatibility with numerous drugs[7, 8]. HPMC

offers the advantage that, although wet massing may be used to conventionally granulate the material direct compression of the drug blended drug with HPMC is easily accomplished[9,10]. The adjustment of the polymer concentration and the viscosity grade and the addition of different types and levels of excipients in the HPMC matrix can modify the drug release rate[7,10,11].

The objectives of the present work were to prepare sustained release matrix tablets of THP by wet granulation method and to study the effect of variables such as:

(i) Effect of concentration of hydrophilic polymers (hydroxypropylcellulose) on the drug release profile on tablets and (ii) effect of different process variables such as kneading time, mixing time, thickness of tablets and lubrication time on release behavior of tablets.

EXPERIMENATAL METHODOLOGY

Materials

THP and hydroxypropyl methylcellulose K-4M (HPMC K-4M) were received as a gift samples from Lincoln Pharmaceuticals Ltd., Ahmedabad, India. Microcrystalline cellulose, polyvinyl pyrrolidone K-90 (PVP K-90) and magnesium stearate were generous gift samples from Shital Chemicals Ltd., India. All other chemical and reagent were of analytical grade and used as received.

Methods

1) Drug-excipients interaction studies

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of solid dosage form[12]. Differential Scanning Calorimeter (DSC) allows the fast Evaluation of possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipients and final tablet were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C.

Full factorial design

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amounts of HPMC K-4M (X_1) and HPMC K-4M (X_2) were selected as independent variables. Percentage release of drug for 1^{st} hour (Q_1) and 8^{th} hour (Q_8) were selected as dependent variables.

Preparation of tablets

The tablets were prepared by wet granulation technique. Drug and polymers were passed through 60 # sieve and then dry blend of drug were granulated with PVP K-90 as a binder which was dissolved in isopropyl alcohol. The mass was dried at 50°C and sized through 22 # sieve. Finally, magnesium stearate were mixed as glidant, and then tablet blend was compressed on Rotary tablet compression machine (CMB4 -35 stations) using 16/32 mm, SC break line/plain.

Table 1 : Formulation of preliminary trial

Ingredients	Batch code						
	P_1	P_2	P_3	P_4	P_5	P_6	P_7
THP	400	400	400	400	400	400	400
HPMC K-4M	25	-	50	-	55	40	50
HPMC K-100M	-	25	-	50	40	40	30
PVP K-90	16	16	16	16	16	16	16
MCC (Avicel)	149	149	124	124	94	104	104
Magnesium sterate	10	10	10	10	10	10	10
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Wt. (mg)	600	600	600	600	600	600	600

Evaluation of tablet blends

Angle of repose

The fixed funnel and free-standing cone methods employ a funnel that is secured with its tip at given height, H, which was kept 2 cm, above graph paper that is placed on a flat horizontal surface. With R, being the radius of base of conical pile, angle of repose can be determined using following equation[13]:

$$\Phi = \tan^{-1}\frac{H}{R} \qquad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Bulk density and tapped density

Density is a term obtained by dividing weight of powder by volume of powder. It is given as g/cm^3. Bulk density (ρ_B) is determined by the bulk volume and the weight of dry powder in a graduated cylinder. Bulk volume of powder is sum of tapped volume plus void volume. Void volume is eliminated by tapping the graduated cylinder on flat horizontal surface from constant height and by constant force for 4000 times. This tapped volume gives the tapped density (ρ_T)[13]. The equations are as following:

$$\rho_B = \frac{W}{V_B} \qquad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

$$\rho_T = \frac{W}{V_T} \qquad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Where W is the weight of dry blend, V_B is the bulk or untapped volume, V_T is the tapped volume.

Compressibility index

Compressibility index gives the important property of granules. It is also known as Carr's index[13]. It can be calculated by following equation:

$$Compressibility\ Index = \frac{\rho_T - \rho_B}{\rho_T} X100 \ . \ (4)$$

Evaluation of tablets

Prepared tablets were evaluated for certain physical properties like uniformity of weight, hardness, friability and dissolution study etc.

Uniformity of weight

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg by using Sartorious balance (BT 124 S). Weight control is based on a sample of 20 tablets[14].

Dimensions

The dimensions (diameter and thickness) were then determined to within ± 0.01 mm by using digital vernier calipers[14].

Hardness

The hardness of the tablets was determined by diametric compression using a Hardness

testing apparatus (Monsanto Type). A tablet hardness of about 4-5 kg is considered adequate for mechanical stability. Determinations were made in triplicate[14].

Friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 400 tablets are dedusted in a drum for a fixed time (4000 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %[14].

$$\% \, Friability = \frac{W_0 - W}{W_0} X100 \quad \ldots\ldots\ldots\ldots\ldots (5)$$

***In-vitro* dissolution study**

The release rate of THP SR matrix tablet was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer (pH=6.8), at 37 ± 0.5°C and 100 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 4, and 8 hour. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a 0.45 um membrane filter. Absorbance of these solutions was measured at 271 nm using a UV – 1800; M/s Shimadzu UV/V is double beam spectrophotometer.

Accelerated stability studies

Optimized formulation were packed in blister and stored in ICH certified stability chambers maintained at 40°C and 75% RH for three months. The tablets were withdrawn periodically and evaluated for drug content and release studies.

Process optimization

To study the effect of process parameters on release behavior of THP sustained release tablets, various parameters were selected for study (Table 2). Formulation of F_7 batch is selected for the reference study to study these process parameters.

Table 2 : Process parameters for formulation of F_7

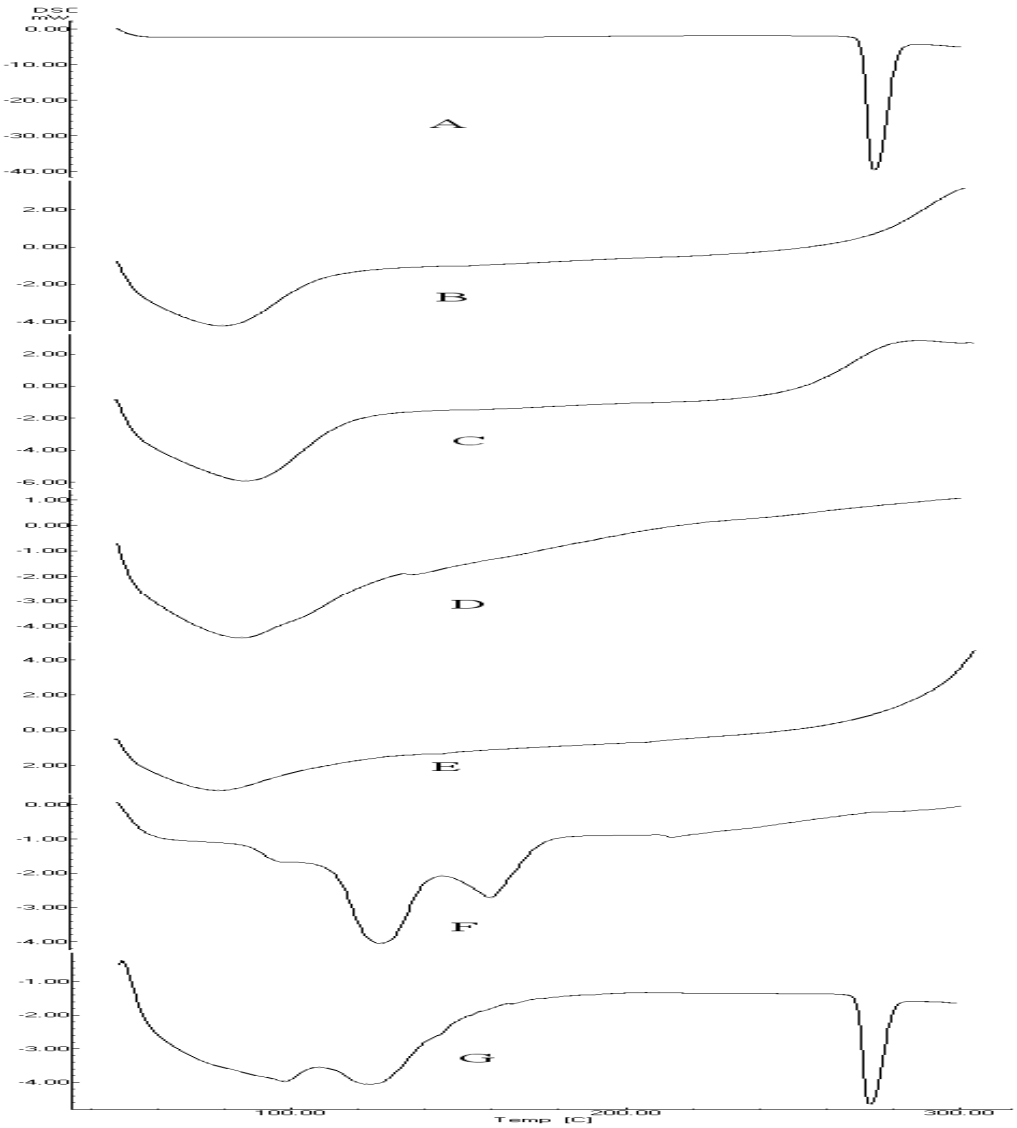
Process parameters	Procedure
Kneading time	To know the effect of kneading time taken for the granulation, three trials were taken with the kneading time of 3, 5 and 10 min, in the RMG (10L)[15, 16].
Mixing time	To know the effect of mixing time taken for the granulation, three trials were taken with the kneading time of 5, 10 and 20 min, in the Octagonal Blender[17, 18].
Thickness	To know the effect of tablet thickness, three trials were taken with the thickness of 3.7, 3.8 and 3.9 mm by calipers[19].
Lubrication time	To see the effect of lubrication time, three trials were taken with the lubrication time of 2, 5 and 7 min, in the Octagonal blender[18].

RESULT AND DISCUSSION

differential scanning calorimetry (DSC) analysis

DSC curves obtained for pure THP, HPMC K-4M, HPMC K-100M, PVP K-90, Avicel, Mg. stearate and their physical mixtures are shown in Fig. 1. Pure powdered THP showed a melting endotherm at 276.52°C. DSC scan of HPMC K-4M showed single broad endotherm at 109.93°C due to melting whereas during scanning of HPMC K-100M, a broad endotherm ranging from 89.56°C was observed. DSC thermo grams of physical mixture of drug and excipients showed the melting peak of the drug at 274.52°C and broad endothermic peak at 122.58°C due to melting of HPMC. Physical mixture of all above ingredients showed their identical peaks at defined temperature range. Presence of all peaks indicates that all ingredients are compatible with each other and THP forms matrix with HPMC K-4M and HPMC K-100M.

Fig. 1 : DSC Spectra of THP (A), HPMC K-4M (B), HPMC K-100M (C), PVP K 90(D), Avicel (E), magnesium stearate (F) & physical mixture of THP with formulation excipients (G)



Full factorial design

Table 3 : Effect on dependent variable 3^2 full factorial design layouts for sustained release tablet of THP

Batch No	Variables levels in coded form		% Drug release (Q_1)	% Drug release (Q_8)
	X_1	X_2		
F1	-1	-1	28.12	90.21
F2	-1	0	27.45	76.9
F3	-1	+1	23.54	72.88
F4	0	-1	20.55	71.8
F5	0	0	18.8	69.42
F6	0	+1	18.76	67.55
F7	+1	-1	14.01	66.5
F8	+1	0	13.22	57.69
F9	+1	+1	13.17	53.44

Translation of coded levels in actual units

Variables level	**Low (-1)**	**Medium (0)**	**High (+1)**
Concentration of HPMC K-4 M (X_1)	5.0 %	7.5 %	12.0 %
Concentration of HPMC K-100 M (X_2)	5.0 %	7.5 %	12.0 %

Note: All the batches contained the constant amount of drug as 400 mg, rest process parameters were kept constant and optimum.

Table 4 : Summary of results of regression analysis for sustained release matrix tablet matrix of THP

Coefficient	B0	B1	B2	B11	B22	B12	Multiple R^2
Q_1	19.45	-6.451	-1.201	0.548	-0.131	0.935	0.9951
Q_8	67.99	-10.39	-5.77	0.0133	2.393	1.067	0.974

Factorial equation for Q_1

Concerning Q_1, the results of multiple linear regression analysis showed that both the coefficients b_1 and b_2 bear a negative sign. It is possible that at higher polymers concentration, THP is trapped in smaller polymer cells and it is structured by its close proximity to the polymer molecules. So, increasing the amount of the polymer in the formulations increased the time it took for the drug to leave the formulation and retard release of drug into the medium.

$$\mathbf{Q_1 = 19.45 - 6.451\ X_1 - 1.201X_2 + 0.935\ X_1X_2 + 0.548X_1^2 - 0.131X_2^2} \quad \text{…….. (6)}$$

$$\mathbf{(R^2 = 0.9951)}$$

The Q_1 for all the batches F_1 to F_9 varied from 28.12 % to 13.17 % (Table 3) showed good correlation coefficient as **0.9951**. Results of the equation (6) indicated that both the concentration of the X_1 and X_2 were responsible for the Q_1.

Factorial equation for Q_8

The amount of drug released after 8 hrs is also important parameters for prominent drug

release from sustained release matrix formulation. The Q_8 for all the batches F_1 to F_9 varied from 90.21% to 53.44 % (Table 3). Therefore, increasing the concentration of either HPMC K-4M or HPMC K-100M is expected to decrease the drug release. Such delay in drug release may be because of the release rate is conditioned by the concentration of the polymer. The fitted equation relating the response Q_8 (Y) to the transformed factor is shown in following equation,

$$\mathbf{Q_8 = 67.99 - 10.39X_1 - 5.77X_2 + 1.067 X_1X_2 + 0.0133 X_1^2 + 2.393 X_2^2} \quad \text{……..} (7)$$

$\mathbf{(R^2 = 0.974)}$

From the results of the equation (7) it was concluded that the effect of the concentration of HPMC K4M (X_1) was very high and in minus sign while the effect of the concentration of HPMC K100M (X_2) was also in minus sign but it was lesser than X_1.

Evaluation of prepared blend of THP

Table 5 : Physical characteristics of prepared blend of THP

Batch code	Bulk density (gm/cc)	Tap density (gm/cc)	Carr's index (%)	Angle of repose (Φ)
F_1	0.45	0.58	22.41	30.25
F_2	0.40	0.52	23.07	28.79
F_3	0.44	0.55	20.00	28.56
F_4	0.41	0.53	21.15	29.00
F_5	0.46	0.59	22.03	30.19
F_6	0.47	0.56	16.07	29.67
F_7	0.39	0.49	20.40	28.37
F_8	0.45	0.59	23.72	30.62
F_9	0.43	0.54	20.37	28.57

Evaluation of prepare tablet of THP

Table 6 : Evaluation parameters of THP SR matrix tablet

Batch code	Hardness kg/cm^2 (n=10)	Thickness mm(n=10)	%Friability (n=10)	Weight Variation (n=20)
F_1	7.10 ± 0.60	3.65 ± 0.05	0.52	601±2.81
F_2	7.67 ± 1.00	3.70 ± 0.12	0.46	599±2.65
F_3	7.90± 0.50	3.75± 0.07	0.40	602±2.00
F_4	6.99 ± 1.20	3.60 ± 0.17	0.63	600±3.50
F_5	8.00 ± 0.89	3.75 ± 0.09	0.42	603±2.00
F_6	8.53 ± 0.55	3.85 ± 0.04	0.28	599±2.74
F_7	8.20 ± 0.98	3.80 ± 0.10	0.34	600±1.15
F_8	8.00 ± 1.20	3.75 ± 0.15	0.37	604±2.54
F_9	8.13 ± 1.50	3.78 ± 0.18	0.30	600±2.23

***In-vitro* dissolution studies**

Dissolution profiles of THP Sustained Release Matrix tablets of preliminary trials and factorial batches are shown in Fig. 2 and Fig. 3 respectively. From the release profile we can see that batches F_1 to F_6 shows release of drug more than 15 % at 1st hour. Whereas, batches F_7 to F_9 shows that release of drug at 1st hours between 5-15 %. But batches F_8 & F_9 shows that release of drug at 8th hour is less than 60 %. Whereas, batch F_7 shows release of drug at 8th hour more than 60 %.

Fig. 2 : Release profiles of preliminary batches P_1 to P_7

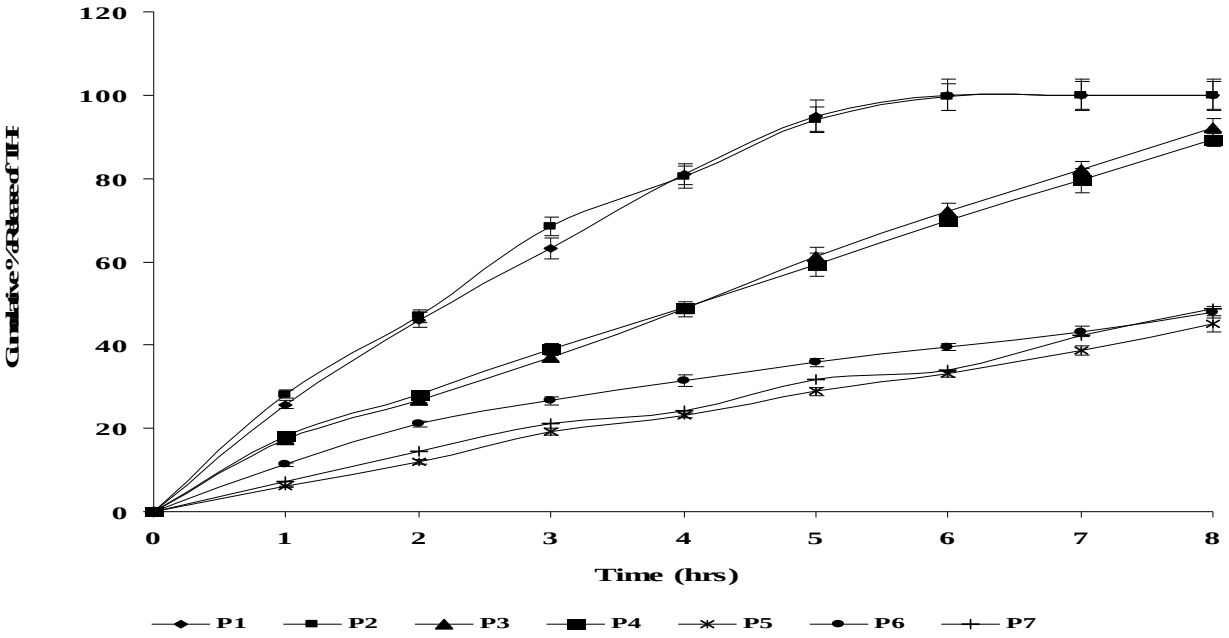
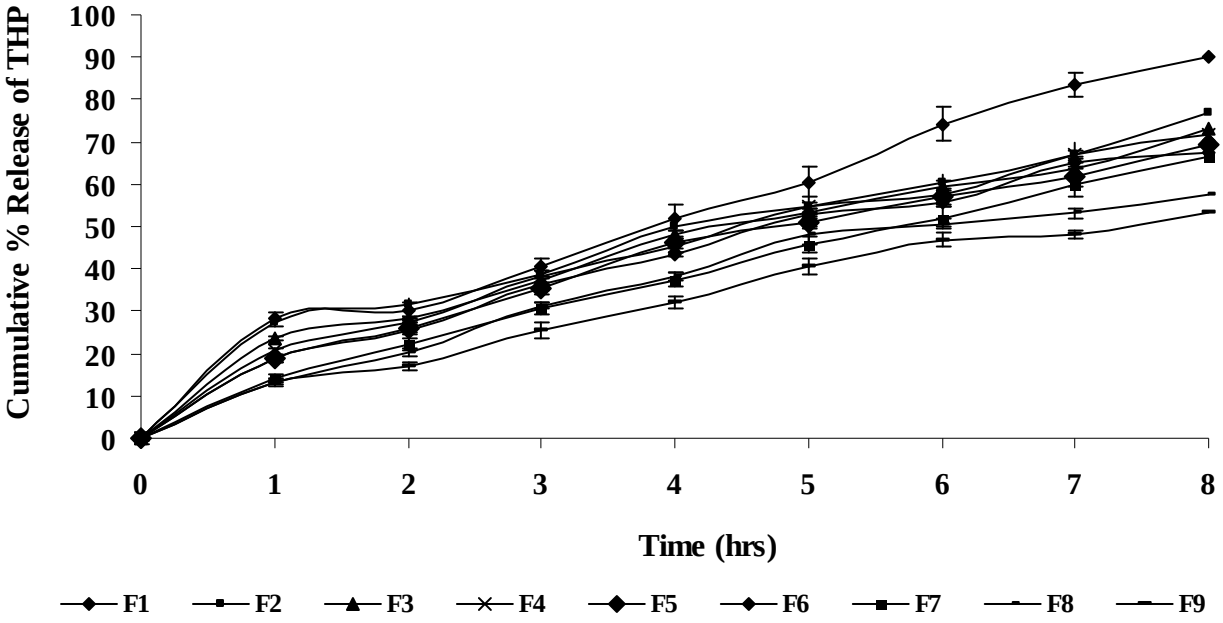


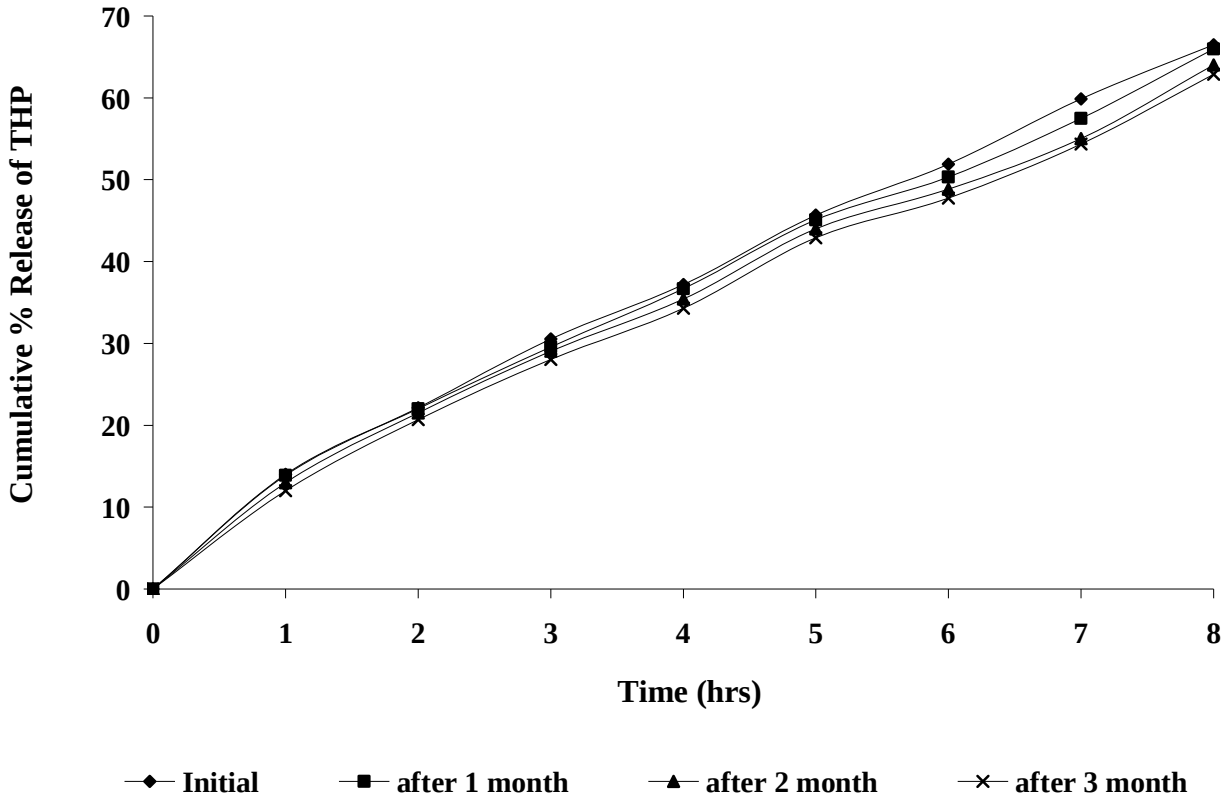
Fig. 3 : *In-vitro* dissolution profiles release of batches F_1 to F_9



Accelerated stability study of best batch (F_7)

Sample withdraws at the interval of one month for three months t showed no change in *in-vitro* drug release profile (Fig. 4). % Assay shows 99.79 (initial), 98.34 (after 1 month), 97.29 (after 2 month) and 97.00 (after 3 month). Results of the stability study shoe no remarkable change in the release profile of the THP Sustained Release Matrix tablet after the stability.

Fig. 4 : Drug release profile of THP SR matrix tablet before and after stability study of best batch F_7



Process optimization

Formulation of optimized batch F_7 has been taken for the study of process parameters. The results showed that all optimized parameters were precise and they showed good results cumulatively. On comparing the results with selected batch F_7, the physical parameters, micromeritic properties and *in-vitro* drug release study was done. So, we can conclude that there were no significant differences of kneading time (Fig. 5) and lubrication time (Fig. 6) on the release behavior of drug. But, in case of mixing time (Fig. 7) and thickness of tablets (Fig. 8) there were significant different in release of drug.

Fig. 5 : Comparative dissolution profiles of three batches having different kneading time

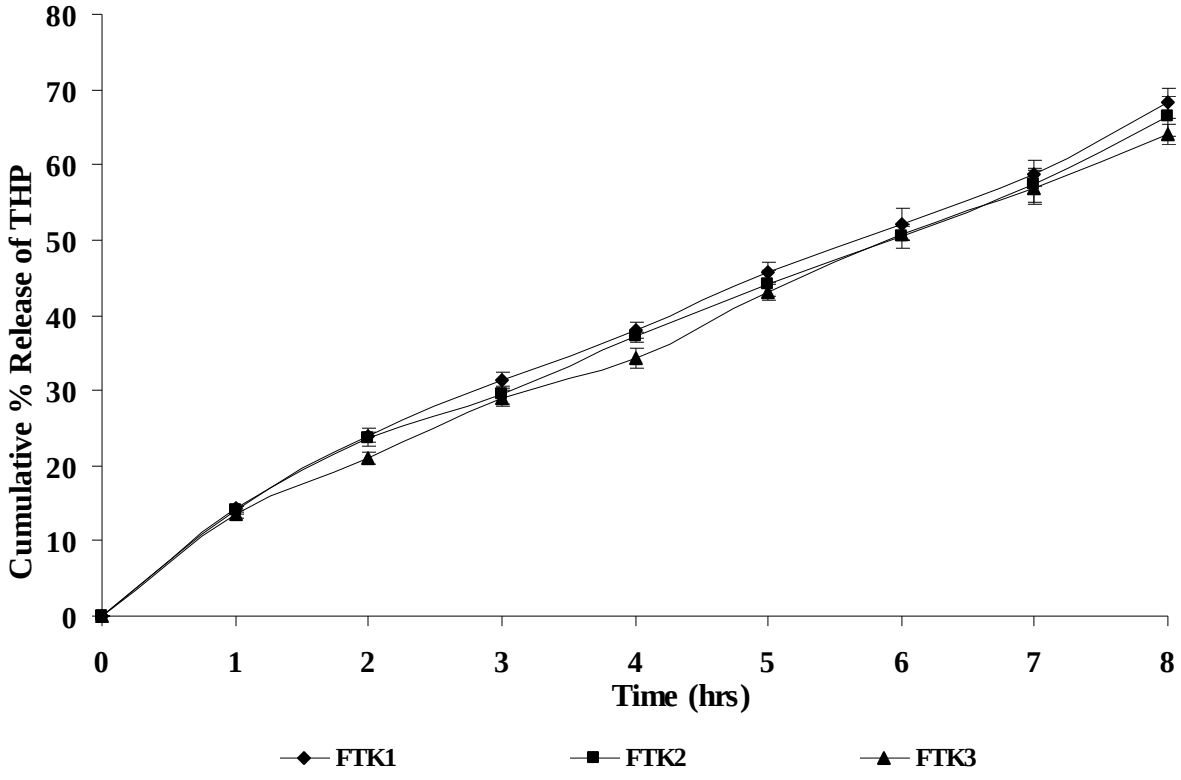


Fig. 6 : Comparative dissolution profiles of three batches having different mixing time

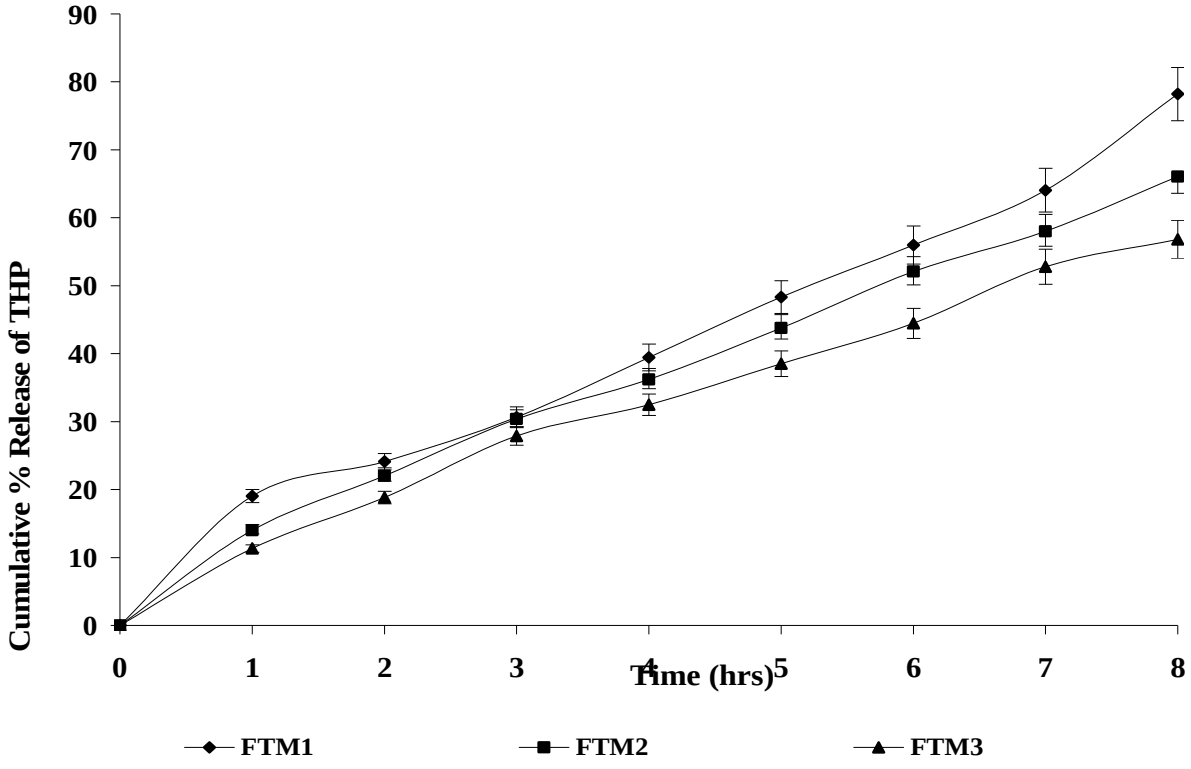


Fig. 7 : Comparative dissolution profiles of three batches having different thickness

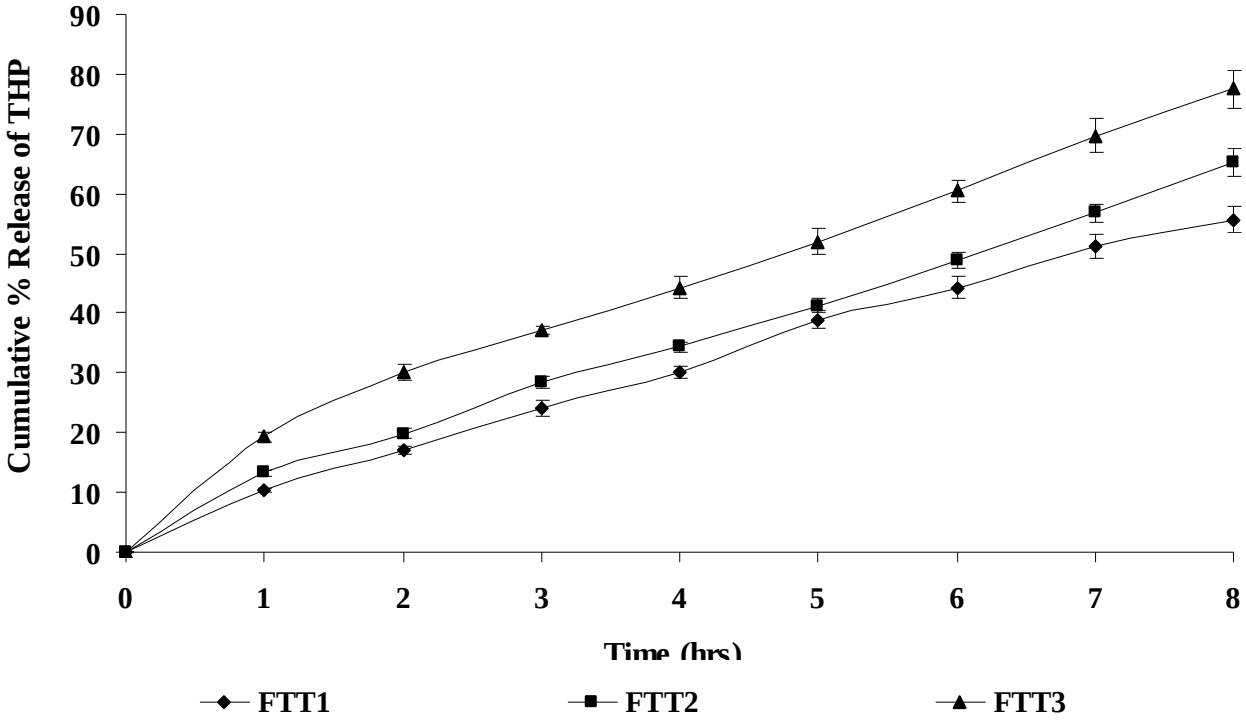
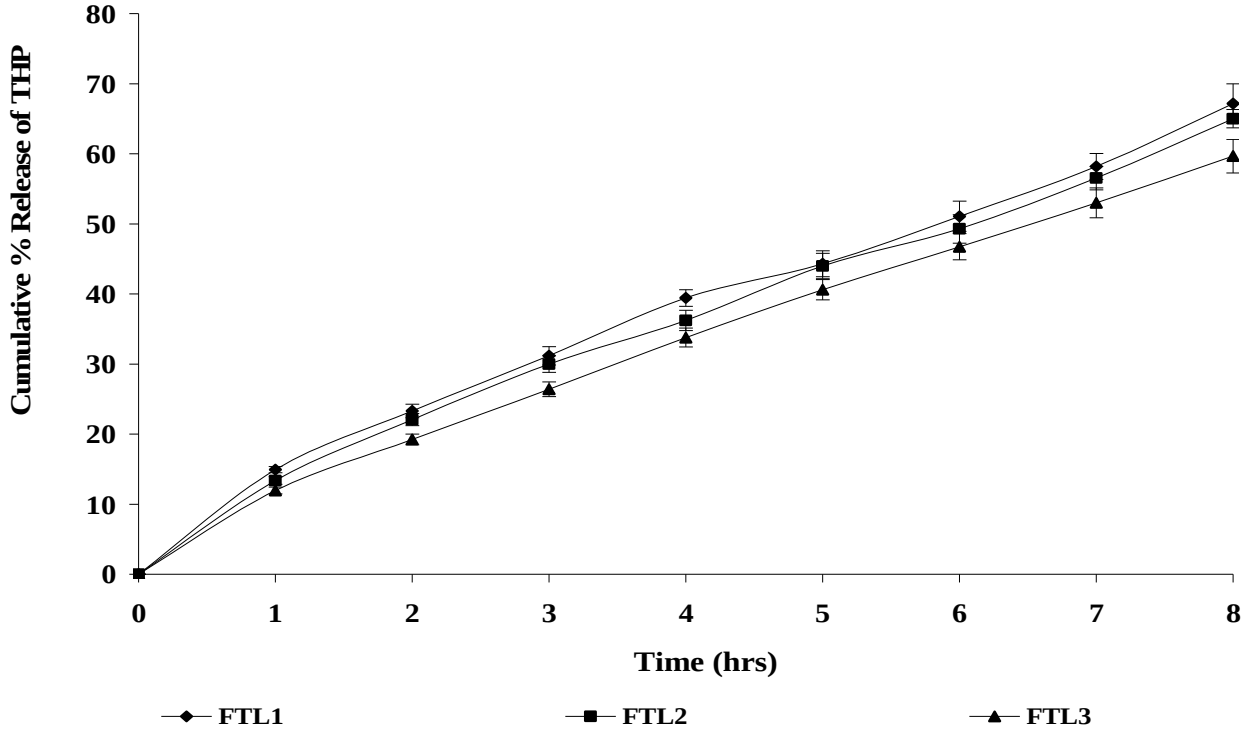


Fig. 8 : Comparative dissolution profiles of three batches having different lubrication time



CONCLUSION

From DSC study, we can show that there is no change in drug's melting peak (274.52°C) after the preparation of tablet. In formulation THP Sustained Release Matrix Tablet, a 3^2 full factorial design was employed for preparation of tablets possessing optimized characteristics (batches F_1 to F_9). The amount of HPMC K-4M(X_1) and HPMC K-100M (X_2) were selected as independent variables. Cumulative % drug release selected as dependent variable (response; Y). Based on result of multiple linear regression analysis, it was concluded that dissolution of tablet could be retarded for 8^{th} hour when X_2 is kept at high level. So, role of polymer concentration is very important in this formulation. So, we can conclude that drug and other excipients are compatible which each other. Stability study of batch F_7 after three month showed no change in in-vitro drug release profile. There were no significant differences in the case of process parameters like kneading time and lubrication time on the release behavior of drug. But in case of mixing time and thickness of tablets there were significant different in release of drug. It was concluded that by adopting a systematic formulation approach, an optimum point could be reached in the shortest time with minimum efforts.

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