

## Research Article



## Formulation and Evaluation of Theophylline Controlled Release Matrix Tablets by Using Natural Gums

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### ABSTRACT

Controlled release tablet will provide a long lasting and more reliable release of drug in GIT to develop a once daily formulation. They prolong the dosing intervals and increases patient compliance than the existing conventional dosage forms.<sup>1</sup> Theophylline is an oral bronchodilator medicine which is prescribed for people with breathing problems, such as asthma and chronic obstructive pulmonary disease (COPD). It is a BCS class I drug with high solubility and high permeability. The lowest levels of epinephrine and cortisol in the body around 10 PM to 4 AM and elevated histamine and other mediator levels that occur between midnight and 4 AM, play a major role in the worsening of asthma during the night.<sup>2</sup> By formulating a controlled release Theophylline matrix tablets we can control the release up to 12 hours, so that we can effectively control the asthma throughout the sleep. The objective of the present study is to prepare controlled release tablets of Theophylline with natural gums i.e., guar gum and xanthan gum, to evaluate pre and post compression parameters and to determine drug-excipient compatibility. Natural gums are used as they are safe, easily available and cost effective. By using combination of guar gum and xanthan gum controlled release was obtained with 1:0.5 drug and polymer ratio. The optimized formula was F<sub>7</sub>. The Hardness of the tablets ranged between 4.0 Kg/Cm<sup>2</sup> to 6.5 Kg/Cm<sup>2</sup>. The %friability of the prepared tablets was well within acceptable limits. There was no significant weight variation observed between average weight and individual weight. The %drug release after 24 hrs was found to be 97.28%. The compatibility study was also carried out using the FT-IR. The FT-IR graphs of drug alone and drugs and excipients were taken. There were no extra peaks found, so it was concluded that the excipients were compatible with drugs.

**Keywords:** Asthma, Chronic obstructive pulmonary disease, Controlled release tablet, Theophylline.

### INTRODUCTION

Controlled release tablets will maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged periods.<sup>3,4</sup> Matrix technologies are popular among the oral controlled drug delivery technologies because of their simplicity, manufacturing ease, high level of reproducibility, stability of the raw materials and dosage form and ease of scale-up.<sup>3,5</sup> Matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers.<sup>6</sup> Theophylline is a methylxanthine derivative and it is very effective in the chronic treatment of bronchial asthma and bronchospastic reaction. Its therapeutic concentration range is narrow from 10 to 20 mcg/ml while toxicity usually appears at concentration above 20 mcg/ml.<sup>7</sup> Since Theophylline is having narrow therapeutic index it can be used as a controlled release product so as to protect asthma patients from frequent attacks and to prevent from toxic side effects.<sup>3,8</sup> Theophylline is absorbed along the entire length of GIT (Gastro intestinal tract). The main aim of the study was to formulate therapeutic controlled release tablets using natural polymers like guar gum and xanthan gum and to evaluate the prepared tablets.

### MATERIALS AND METHODS

#### Materials

Theophylline is obtained as a gift sample from Dr. Reddy's laboratories, Hyderabad, India. PVP-k30 and Ethyl

cellulose were purchased from Merk India Talc, Magnesium stearate, lactose, Xanthan gum, guar gum, isopropyl alcohol were purchased from NSB pharmaceuticals, Guntur, India.

#### Methods

##### Formulation and preparation of Theophylline controlled release matrix tablets

Theophylline controlled release tablets were prepared by both direct compression and wet granulation techniques using natural polymers such as guar gum, xanthan gum. The formulae F<sub>1</sub> and F<sub>2</sub> were prepared by direct compression technique. Accurately weighed amounts of Theophylline and other excipients were blended in a geometric fashion using polybags blending method. Then sifted through sieve no 20, pre compression parameters were determined and the powder blend was directly compressed into tablets using 12mm round flat faced punches in a rotary tablet press (ELITE multi station tablet compression machine).

The formula F<sub>3</sub>, F<sub>4</sub>, F<sub>5</sub>, F<sub>6</sub> and F<sub>7</sub> were prepared by wet granulation technique. Accurately weighed quantities of Theophylline and other excipients except magnesium stearate and talc were mixed together in geometric fashion in mortar and pestle. Isopropyl alcohol in which PVP K-30 was previously dissolved was added drop wise to the above powder mixture and mixed well to form a coherent mass. Then the coherent mass was passed through sieve no-12 and the granules were dried at 50°C



for 15 minutes. Dried granules were passed through sieve no-20, magnesium stearate and talc were added and pre compression parameters were determined. Then the lubricated granules were compressed into tablets using

12mm round flat faced punches in a rotary tablet press (ELITE multi station tablet compression machine). The compositions of Theophylline controlled release tablets were given in table 1.

**Table 1:** Composition of Theophylline controlled release matrix tablets (mg/tablet)

Ingredients	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>
Theophylline	300	300	300	300	300	250	400
Guar gum	---	---	---	75	125	250	100
Xanthan gum	75	150	150	75	75	---	100
Lactose	225	150	150	150	100	100	---
Ethyl cellulose	---	---	---	---	---	5%	---
Magnesium stearate	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10
PVP K30	---	---	3%	3%	3%	---	10%
Isopropyl alcohol	---	---	q.s	q.s	q.s	q.s.	q.s
Total weight of the tablet	620	620	620	620	620	620	620

**Table 2:** Pre compression parameters of Theophylline controlled release matrix tablets

Parameter	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>
Angle of repose	35 <sup>0</sup> 07'	32 <sup>0</sup> 31'	31 <sup>0</sup> 47'	34 <sup>0</sup> 17'	33 <sup>0</sup> 21'	30 <sup>0</sup> 12'	32 <sup>0</sup> 03'
Bulk density	0.34	0.35	0.33	0.34	0.37	0.37	0.39
Tapped density	0.47	0.46	0.44	0.43	0.46	0.48	0.48
Carr's index	27.66	23.91	25	20.93	19.56	22.91	18.75
Hausner's ratio	1.38	1.31	1.33	1.26	1.24	1.29	1.23

The compressed tablets were dedusted and evaluated for various tablet properties viz., weight variation, hardness, friability, *in vitro* drug release studies, swelling index etc., and interpreted the results according to the US Pharmacopoeial standards.

### Pre-compression characteristics

#### Angle of repose

Angle of repose was determined using fixed funnel method. Accurately weighed quantity of powder blend was taken in a funnel. The height of the funnel was adjusted to 2cm from the working platform. The powder was allowed to flow freely through the funnel on to the surface of working platform. The height (h) and radius (r) of the powder cone was measured and angle of repose was calculated by following formula.<sup>9</sup>

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

#### Bulk density

Apparent bulk density was calculated by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is. Bulk density was determined by using following formula.<sup>10</sup>

$$\text{Bulk density} = \text{Mass/Volume}$$

#### Tapped density

Weighed sample of powder mixture was transferred to a graduated cylinder and was tapped for a fixed number of taps. The tapped density was determined by using the following formula.

Tapped density = Weight of powder taken/Tapped volume

#### Compressibility index

Based on the bulk density and the tapped density, the percentage compressibility of the powder mixture was determined by the following formula.<sup>11</sup>

Compressibility Index = [(Tapped density - Bulk density)/Tapped density] X100

#### Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula.

Hausner's ratio = Tapped density/Bulk density

#### Evaluation of Theophylline controlled release matrix tablets

##### Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm<sup>2</sup>. Test was done in triplicate.

##### Weight variation

Twenty tablets were selected randomly from the lot, weighed individually to check for weight variation and % deviation is calculated according to the following formula



Percent Deviation =

$$\frac{\text{Individual weight} - \text{Average weight} \times 100}{\text{Average weight}}$$

Average weight

### **Friability**

Friability of the tablets was determined using Roche friabilator. This device subjects 10 tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed tablets were placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) was calculated by the following formula.<sup>12</sup>

$$F = [(W_0 - W) / W_0] \times 100$$

Where,

$W_0$  is the weight of the tablets before the test and

$W$  is the weight of the tablet after the test

### **Drug Content**

Randomly 10 tablets were selected and average weight was determined. Then the tablets were triturated to get a fine powder. From the resulting triturate, a quantity of powder was weighed accurately that was equivalent to 100 mg of Theophylline. The powder was transferred into a 100 ml volumetric flask containing 50 ml of methanol, shaken for 15 minutes and volume was made up to 100 ml with same solvent. The volumetric flask was sonicated for 30 minutes using ultrasonic bath sonicator to extract the drug completely. Then the solution was filtered using whatman filter paper. A volume of this solution was taken into 10 ml volumetric flask and made up to the volume with water to obtain a solution that is equivalent to 10mcg/ml of Theophylline and the absorbance was measured using UV-Visible Spectrophotometer at 272nm.

### **In vitro disintegration time**

The disintegration test was carried out using tablet disintegration test apparatus (elite single unit disintegration apparatus) Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed 0.1N HCL was used as a disintegration medium and the temperature was maintained at  $37^\circ \pm 2^\circ\text{C}$ . Average of three determinations was taken.<sup>13</sup>

### **In vitro dissolution study**

The tablets were evaluated for *in vitro* drug release. It was carried out by using USP type II paddle [Electro lab dissolution tester (USP) TDT-08L] dissolution apparatus. The dissolution was carried out at 100 rpm and at a temperature of  $37 \pm 0.5^\circ\text{C}$ . 900 ml of dissolution medium was taken and the tablet was placed in it and dissolution was carried out. 5ml of sample was withdrawn at each interval of 15min, 30 min, 45 min, 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs, 10 hrs and 12 hrs. Sink conditions were maintained

by replacing the collected samples with same volume of fresh medium. 0.1 N HCl was used as dissolution medium for first 2 hrs and then the medium was changed to phosphate buffer pH 6.8. min, 1hr, 2hrs, 4hrs, 6hrs, 8hrs, 10hrs and 12hrs. After filtration and appropriate dilution, the samples were analyzed by UV spectrophotometer (ELICO SL 129 model) at 272 nm.<sup>1</sup>

### **Drug release kinetics**

To analyze the mechanism of drug release rate kinetics, the results of *in vitro* release profile were plotted in various kinetic models like zero order, first order, Higuchi model and Korsmeyer – Peppas.<sup>14</sup>

### **Drug excipient compatibility study**

Optimized dosage form was subjected to FTIR studies to investigate the drug excipient interactions.

## **RESULTS AND DISCUSSIONS**

### **Pre-compression characteristics**

Table 2 gives information about Evaluation of pre-compression parameters of various formulation blends of Theophylline controlled release matrix tablets. Bulk density, was found in the range of 0.34- 0.39 g/cm<sup>3</sup> and the tapped density between 0.43 – 0.48 g/cm<sup>3</sup> and compressibility index was in the range of 18.75 – 27.66 %. This indicates good flow ability of the powder blend. The good flow ability of the powder blend was also indicated by the angle of repose which is in the range of 30°12'– 35°07' which is below 40° indicating good flow ability.

### **Evaluation of Theophylline controlled release matrix tablets**

Among all the seven formulation only  $F_7$  has shown disintegration time of >30 min. The remaining six formulations were disintegrated in less than 10 min. so the final optimized formula was  $F_7$  and it was subjected to tablet evaluation parameters.

The shorter disintegration time of remaining six formulations was due to the presence of lactose because, Lactose, by its water-soluble and hydrophilic nature, facilitates gel formation and shortens the penetration time of the dissolution medium into the matrix. Moreover, this soluble substance acts as a channeling agent by rapidly dissolving and easily diffusing outward, therefore decreasing tortuosity and/or increasing the matrix porosity.<sup>15</sup>

Table 3 gives the information about evaluation of Theophylline controlled release matrix tablet of optimized formula  $F_7$ . The Hardness of the tablets ranged between 4.0 Kg/Cm<sup>2</sup> to 6.5 Kg/Cm<sup>2</sup>. The percent friability of the prepared tablets was well within acceptable limit. There was no significant weight variation observed between average weight and individual weight. The results showed in Table 3 indicated that the tablets possessed enough mechanical strength to maintain their integrity.

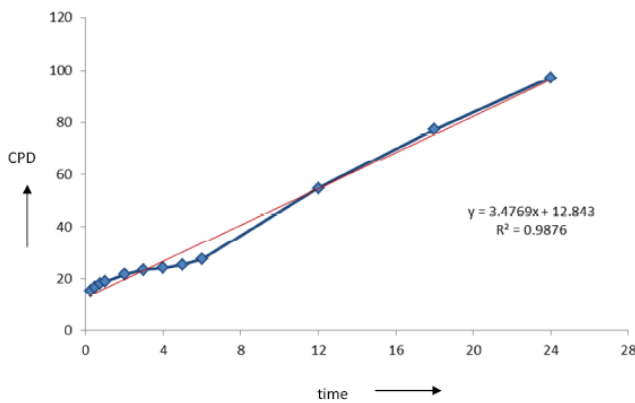


**Table 3:** evaluation of Theophylline controlled release matrix tablets of optimized formula F<sub>7</sub>

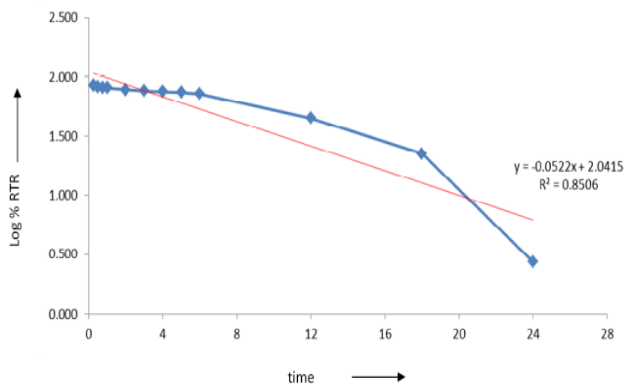
Parameter	Values
Hardness ± SD (n=3)	5.5±0.5 kg/cm <sup>2</sup>
Friability	0.27%
Weight variation (n=20) (average)	±0.375%
<i>In vitro</i> disintegration time	> 30 min

***In vitro* dissolution study**

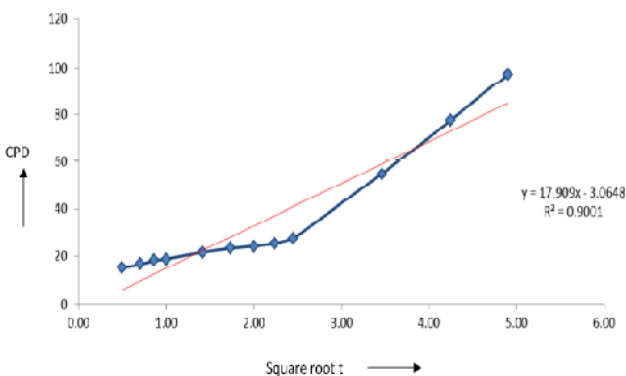
Figures 1-4 gives the information about the dissolution profile of Theophylline controlled release matrix tablets of optimized formula F<sub>7</sub>.



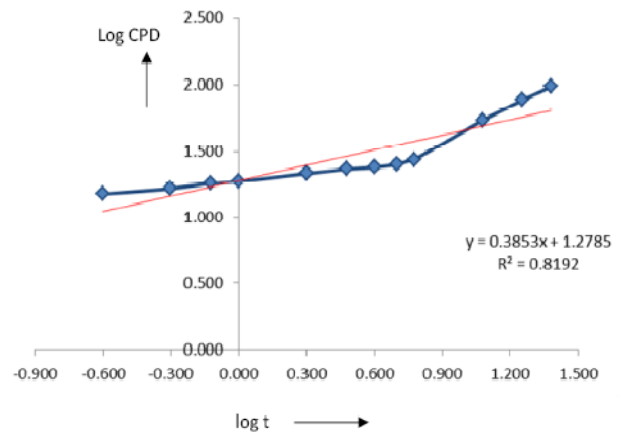
**Figure 1:** Zero order release model of Optimized formulation; CPD: cumulative %drug release



**Figure 2:** First order release model of Optimized formulation; RTR: remaining to release



**Figure 3:** Higuchi release model of Optimized formulation



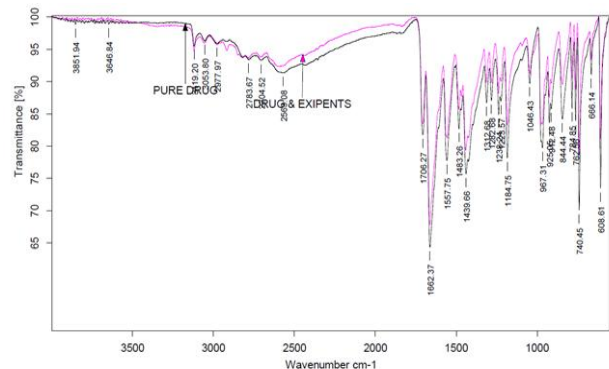
**Figure 4:** Korsmeyer and peppas release model of Optimized formulation

**Drug release kinetics**

In Zero order  $r^2$  value was 0.9876 and in first order  $r^2$  value was 0.8506 describing the drug release rate is independent of concentration of drug. The best linearity was found in Zero order (Figure 1,  $r^2 = 0.9876$ ) indicating the release of drug from matrix tablet followed zero order.

**Drug excipient compatibility study**

The compatibility study was also carried out using the FT-IR. The FT-IR graphs of drug alone and drugs and excipients were revealed the compatibility of drug and excipients as there were no extra peaks found in all cases. Therefore, it was concluded that the excipients were compatible with drugs (Figure 5).



**Figure 5:** Comparative study of FTIR data of pure drug and drug + excipients of formula F<sub>7</sub>

**CONCLUSION**

Theophylline controlled release matrix tablets were prepared by using natural gums and evaluated. Drug release studies were conducted with the optimized formula F<sub>7</sub> and the drug release was found to follow zero order. The FTIR studies confirmed that the drug and excipients were compatible.



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