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Formulation and Evaluation of Theophylline Controlled Release Matrix Tablets using Guar gum

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ABSTRACT

Theophylline controlled release matrix tablets were prepared with guar gum in two ratios and with three different hardness of 5, 6 and 7kg/cm^2. Theophylline controlled release granules were prepared and evaluated for the angle of repose, bulk density, tapped density, compressibility index and hausners ratio. All the formulation showed good flow properties. The compressed tablets were evaluated for the hardness, uniformity of weight, friability, drug content and invitro dissolution studies. All the formulations showed compliance with pharmacopial standards. There was no interaction between drug, polymer and other excipients. It was confirmed by FTIR studies. Among all the formulations F6 (i.e. polymer ratio1:2 and hardness 7kg/cm^2) showed prolong release when compare to other formulations. The drug release kinetics showed zero order. The optimum formulation (F6) was stable when it was stored at $4^0 \pm 2^0$ C, $28^0 \pm 2^0$ C and at $45^0 \pm 2^0$ C for 6 months.

KEYWORDS: Controlled release, Guar gum, Matrix tablets, Theophylline.

INTRODUCTION

Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged periods[1]. Matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers[2]. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because

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of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form and ease of scale-up and process validation[3]. 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 g/ml while toxicity usually appears at concentration above 20 g/ml[4]. Since theophylline 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[5]. The main aim of the study was to formulate therapeutic controlled release tablets using natural polymer like guar gum with two different ratios (1:1 and 1:2) and also varying the hardness of the tablets (5, 6 and 7 kg/cm^2 respectively).

Materials

Theophylline was procured from (Amratlal and co. Chennai). Guar gum and magnesium stearate were obtained from (Loba chemi. Pvt; Ltd, Mumbai). Lactose monohydrate was received from (Paxmy speciality chemi. Chennai). Polyvinyl pyrolidone and isoprophyl alcohol were obtained from (S.d.fine-chem.Pvt; Ltd, Mumbai). All other chemicals used were of analytical grade.

Methods

Preparation of controlled release matrix tablets

Table 1. Composition of Theophylline CR matrix tablets (mg/tablet)

Ingredients (mg)	Theophylline: Guar Gum (1:1)	Theophylline: Guar Gum (1:2)
Theophylline	100	100
Guar gum	100	200
Lactose monohydrate	296	196
Polyvinyl pyrolidone K30 (PVP K30)	2	2
Magnesium stearate	2	2
Iso propyl alcohol (IPA)	q.s	q.s

(1:1) and (1:2) are drug : polymer ratio

Matrix tablets were prepared by wet granulation technique. Theophylline controlled release tablets were prepared with guar gum and other additives that are listed in the table-1. Theophylline, guar gum and lactose were mixed together. Isopropyl alcohol in which PVP K-30 was previously dissolved was added to the above powder mixture and mixed well to form a coherent mass. Then the coherent mass

was passed through sieve no-16 and the granules were dried at 40° ± 2°C for 2 hours. Dried granules were passed through sieve no-20. After the granules were evaluated, magnesium stearate was added to the granules. Then the lubricated granules were compressed into tablets weighing 500mg using 12mm round flat faced punches in a rotary tablet press (Rimek mini press-1, Model RSB-4, Karnavathi Engineering, Ahmedabad) to a hardness of 5, 6 and 7 kg/cm^2. The compressed tablets were dedusted and evaluated for various tablet properties.

Evaluation of granules

The granules were evaluated for angle of repose[6,7], bulk density[8], tapped density[8], compressibility index and hausner ratio[9] for micromeritic properties.

Evaluation of tablets

To design tablets and tablet production quality test, the formulated tablets were evaluated for thickness and diameter (using a vernier caliper), hardness test (using Monsanto hardness tester)[10] and friability (using Roche friabilator)[11]. For weight variation test[12], 20 tablets of each formulation were selected at random and weighed individually. The individual weights were compared with average weight for determination of weight variation. The results were expressed in table-3. For content uniformity test[13], ten tablets were powdered in a mortar. The powder equivalent to 100mg of theophylline was weighed and transferred to 100ml volumetric flask. It was dissolved in pH 7.4. From this appropriate dilution were made and the absorbance was analyzed at 277nm using UV double beam spectrophotometer.

FT-IR studies

It was used to study the interactions between the drug and polymer. The drug and polymer must be compatible with one another to produce a stable product. Drug and polymer interactions were studied by using FTIR (Shimadzu, Japan model – 8400S) as per the method described by Pathra et.al[14]. IR spectral analysis of pure theophylline, guar gum and theophylline with guar gum (1:2) were carried out. The peak and patterns produced by the pure drug were compared with combination of pure drug and polymer.

In-vitro release studies

In-vitro drug release study was carried out using disso 2000 apparatus (basket type). Dissolution medium 900 ml of pH 7.4 was placed into the dissolution flask maintaining the temperature at 37^{o}C ± 0.5^{o}C and rpm of 50 for 10hrs. Samples measuring 10ml were with drawn every 30min intervals, replace same quantity of fresh dissolution medium. Collected samples were suitably diluted with pH 7.4 and analyzed at 277 nm using pH 7.4 as blank in UV-double beam spectrophotometer.

Drug release kinetics

To analyze the mechanism of drug release rate kinetics, the results of invitro release profile were plotted in various kinetic models like zero order, first order, higuchi model and korsmeyer – peppas[15].

Stability studies

The optimised formulation F6 was taken for the stability study. The tablets were packed in amber-

colored bottle and kept at $4^0 \pm 2^0$ C, $28^0 \pm 2^0$ C (RH 60 ± 5%) and $45^0 \pm 2^0$ C (RH 75 ± 5%) for a period of 6 months. The tablets were observed physically for any colour change. Tablets were taken at 2, 4 and 6th months intervals and evaluated for drug content and *invitro* release study[2].

Results and Discussion

The granules of all the formulations were evaluated for angle of repose, bulk density, tapped density, and compressibility index and hausner ratio. The angle of repose was found to be 31°02' ± 0.66 – 32°55' ± 0.69. It indicates that granules have a good flow property. The bulk density and tapped density was found to be in the range of 0.3538 ± 0.00 - 0.3947 ± 0.01 gm/cc and 0.3990 ± 0.01 - 0.4439 ± 0.01 gm/cc respectively. The compressibility and hausner ratio was found to be 9.89 ±1.66 to 14.21 ± 1.27 and 1.11 ± 0.02 to 1.17 ± 0.02 indicating good flow character of the granules (table-2). All the results are within the prescribed limits[10].

Table 2. Evaluation of theophylline matrix granules

Parameters*	Theophylline : Guar Gum					
	5 kg/cm^2		6 kg/cm^2		7 kg/cm^2	
	1 : 1 (F-1)	1 : 2 (F-2)	1 : 1 (F-3)	1 : 2 (F-4)	1 : 1 (F-5)	1 : 2 (F-6)
Angle of repose (θ)	31°02'± 0.66	32°51'± 0.74	31°61' ± 0.67	32°55'± 0.62	32°55' ± 0.69	32°14'± 0.77
Bulk density (gm/cc)	0.3886 ± 0.01	0.3714 ± 0.01	0.3808 ± 0.01	0.3538 ± 0.00	0.3642 ± 0.01	0.3947 ± 0.01
Tapped density (gm/cc)	0.4336 ± 0.01	0.4122 ± 0.01	0.4439 ± 0.01	0.3990 ± 0.01	0.4146 ± 0.01	0.4412 ± 0.01
Compressibility index (%)	10.36 ± 1.74	9.89 ± 1.66	14.21 ± 1.27	11.31 ± 1.86	12.11 ± 2.85	13.04 ± 3.51
Hausner ratio	1.12 ± 0.04	1.11 ± 0.02	1.17 ± 0.02	1.13 ± 0.02	1.14 ± 0.04	1.15 ± 0.04

***** All values are expressed as mean ± SD, n=5

The hardness of the tablets for all the formulations was in the range of 5-7 kg/cm^2. The uniformity weight of 20 tablets of all the formulations was within 5% deviation. The friability of all the formulation was less than 1%. Drug content of all the formulations were found to be in the range of 96 to 99 % (table-3). All the results are within the prescribed limits[10].

The FT-IR studies showed that N-H stretching, C-H stretching, C-O stretching, C-H bending, O-H deformation, C-H out of plane bending of pure theophylline and theophylline with guar gum (1:2 ratio) were almost in the same region of wave number ranging from 3529 cm^{-1} to 609.53 cm^{-1}. It showed that there was no significant interaction between the drug and polymer and they are

compatible with each other.

Table 3. Evaluation of theophylline controlled release matrix tablets

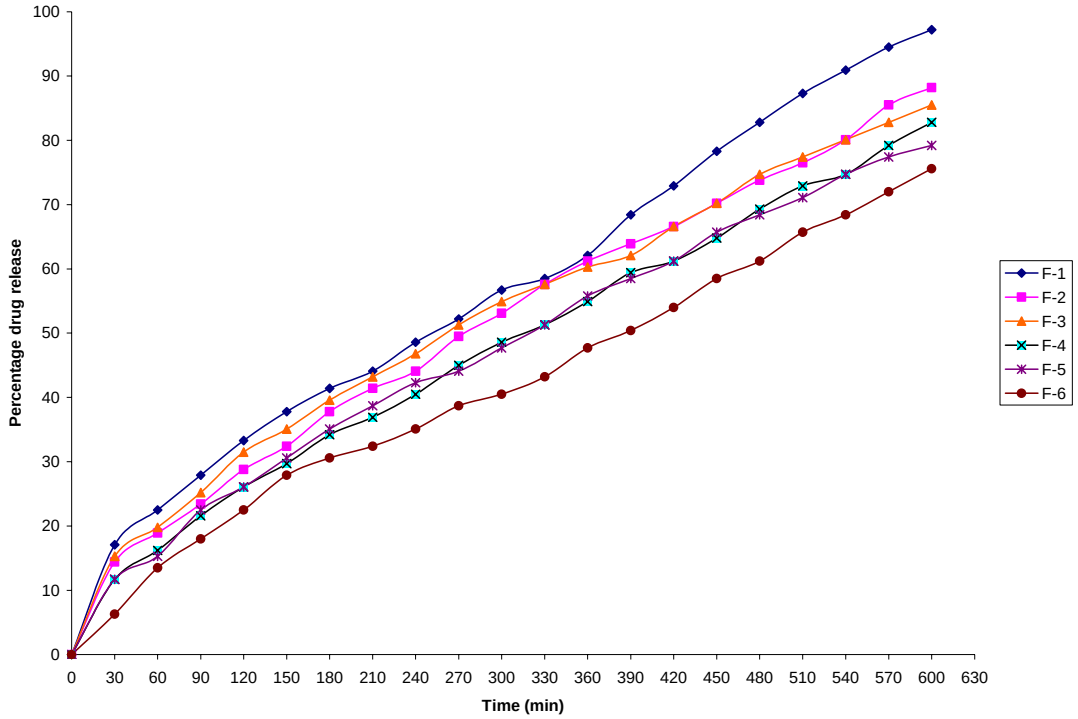
Parameters*	Theophylline : Guar gum					
	5 Kg/Cm^2		6 Kg/Cm^2		7 Kg/Cm^2	
	1 : 1 (F-1)	1 : 2 (F-2)	1 : 1 (F-3)	1 : 2 (F-4)	1 : 1 (F-5)	1 : 2 (F-6)
Hardness (kg/cm^2)	5.01 ± 0.23	5.03 ± 0.18	5.97 ± 0.12	6.02 ± 0.16	7.03 ± 0.34	7.01 ± 0.25
Uniformity of weight (mg)	499.9 ± 6.2	501.6 ± 5.5	500.2 ± 3.9	498.4 ± 4.4	498.7 ± 3.7	500.2 ± 7.2
Friability (%)	0.25 ± 0.05	0.23 ± 0.07	0.30 ± 0.09	0.28 ± 0.04	0.15 ± 0.07	0.19 ± 0.06
Drug content (%)	96.8 ± 0.20	97.4 ± 0.40	97.6 ± 0.35	97.4 ± 0.24	96.6 ± 0.28	98.8 ± 0.38
Thickness (mm)	4.2 ± 0.01	4.2 ± 0.03	4.1 ± 0.04	4.2 ± 0.00	4.1 ± 0.03	4.1 ± 0.02
Diameter (mm)	12.6 ± 0.00	12.5 ± 0.02	12.5 ± 0.03	12.6 ± 0.01	12.6 ± 0.04	12.6 ± 0.03

***** All values are expressed as mean ± SD, n=5

The results of the invitro release study for all the formulations are shown in figure-1.

At the end of 10th hours the cumulative percentage drug release for the formulations F1-F6 was found to be 97.2 ± 0.77; 88.2 ± 0.96; 85.5 ± 1.25; 82.8 ± 0.49; 79.2 ± 0.77 and 75.6 ± 1.66 respectively. Among the six formulations, F6 showed prolonged drug release. An increase in the compression force increases the hardness and the apparent density of the tablet, thereby reducing the matrix porosity in the tablet. The release rate decreases with increase in compression force[16]. The drug release was found to be faster at lower compression force than at higher ones because of the relatively larger matrix porosity of the tablet, which allowed greater penetration of dissolution fluid into the matrix, thus enhancing polymer disentanglement and drug dissolution[17]. The controlled drug release may also be due to increased proportion of polymer[18].

Figure 1. Comparison of *invitro* drug release study of theophylline controlled release formulations F-1 to F-6



The release rate kinetic data for all formulations is shown in table-4. When the data were plotted according to zero order, the formulations showed a high linearity with regression co-efficient values (R^2) between 0.9748 – 0.9895. It showed that the drug release follows zero order[19]. Diffusion is related to transport of drug from the matrix tablets into the dissolution medium depends upon the concentration. This is explained by Higuchi's equation. When the data were plotted according to Higuchi's equations, the regression co-efficient values (R^2) were between 0.9630 – 0.9879.By using korsmeyer model, the mechanism of drug release was determined. If n = < 0.45, it is fickian diffusion and if n= 0.45 – 0.89, it is non-fickian diffusion transport[19]. The results of all the formulations showed that the n values are between 0.6739 – 0.6901. It proved that all formulations followed non-fickian transport mechanism[19] both diffusion and erosion[20].

Stability study for the optimized formulation F-6 showed that there was no significant colour change in all the tablets after 6 months. Drug content was estimated and invitro drug release was carried out after 2, 4 and 6 months. The percentage of drug content was between 96.8 to 98.8% upto 6 months (table-5) in all the three temperatures. Dissolution studies showed that there was no much deviation in the percentage of drug release (figure-2,3and4). It showed that F-6 formulation was stable at different temperatures upto 6 months.

Table 4. Drug release kinetics of theophylline controlled release matrix tablet formulations

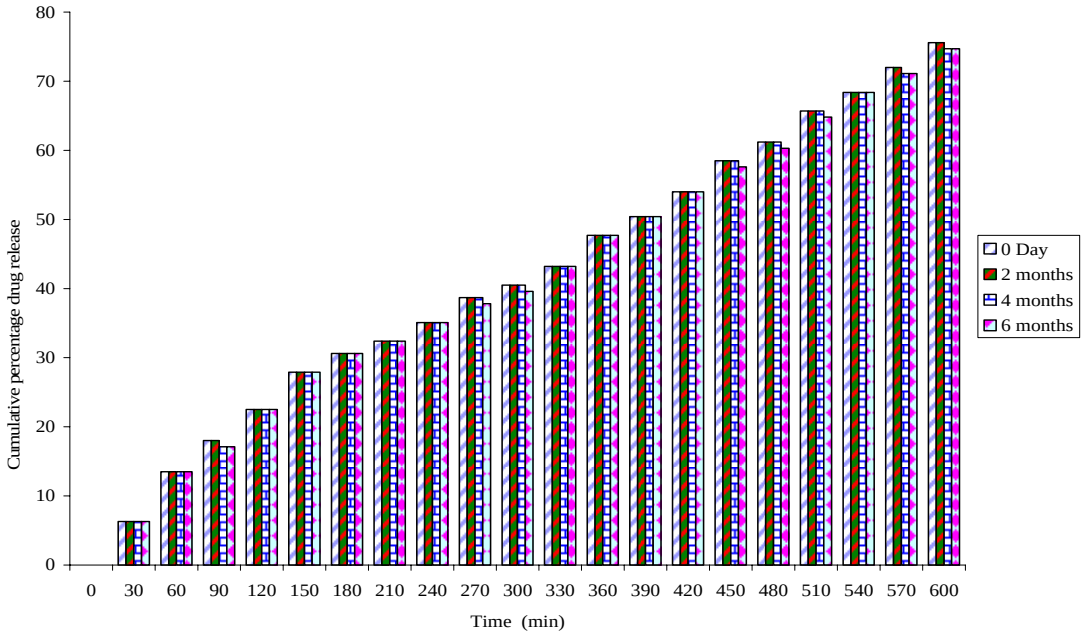
Formulation Code	Correlation Co-efficient (r^2) value				Korsmeyers - Peppas	
	Zero order	First order	Higuchi	Hixon crowell	Slope (n)	Correlation Co-efficient (r^2) value
F-1	0.9854	0.8523	0.9683	0.9423	0.6846	0.9901
F-2	0.9846	0.9552	0.9789	0.9853	0.6816	0.9958
F-3	0.9748	0.9760	0.9879	0.9919	0.6739	0.9938
F-4	0.9889	0.9693	0.9739	0.9892	0.6802	0.9984
F-5	0.9831	0.9851	0.9808	0.9952	0.6784	0.9985
F-6	0.9895	0.9698	0.9630	0.9855	0.6901	0.9910

Table 5. Stability study for the optimized formulation F-6 drug content estimation

Time in months	Percentage drug content		
	$4^0 \pm 2^0$ C	$27^0 \pm 2^0$ C	$45^0 \pm 2^0$ C
0 day	98.8 ± 0.38	98.8 ± 0.38	98.8 ± 0.38
2	98.8 ± 0.60	98.8 ± 0.83	97.6 ± 0.41
4	97.6 ± 0.33	97.6 ± 0.76	97.4 ± 0.29
6	97.4 ± 0.51	97.0 ± 0.93	96.8 ± 0.22

* All values are expressed as mean ± SD, n=5

Figure 2. Stability study of F-6 formulation at $4^0 \pm 2^0$ C for a period of 6 months



Figure

3. Stability study of F-6 formulation at $28^0 \pm 2^0$ C for a period of 6 months

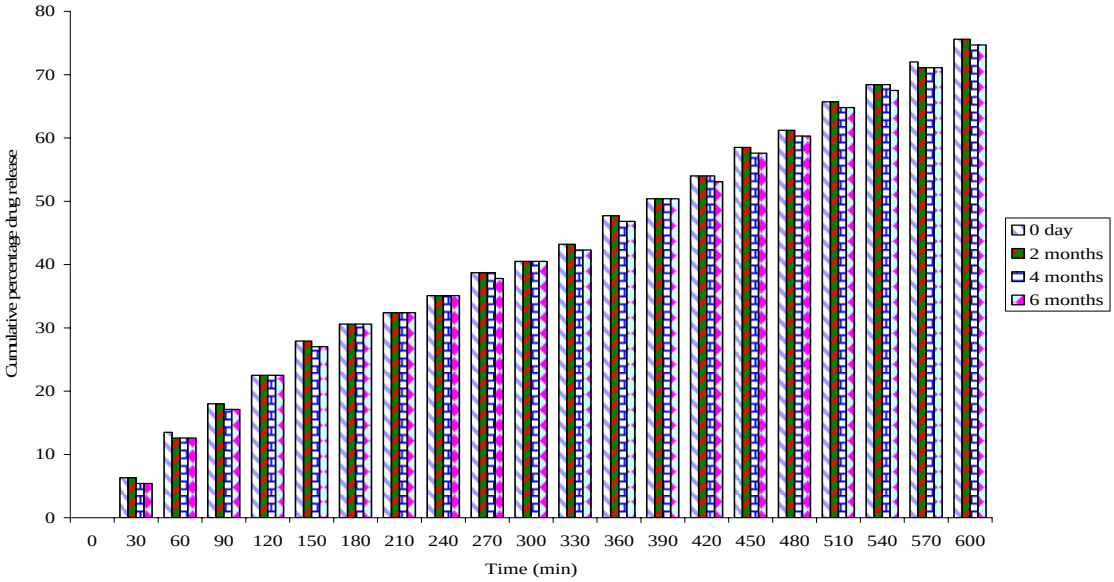
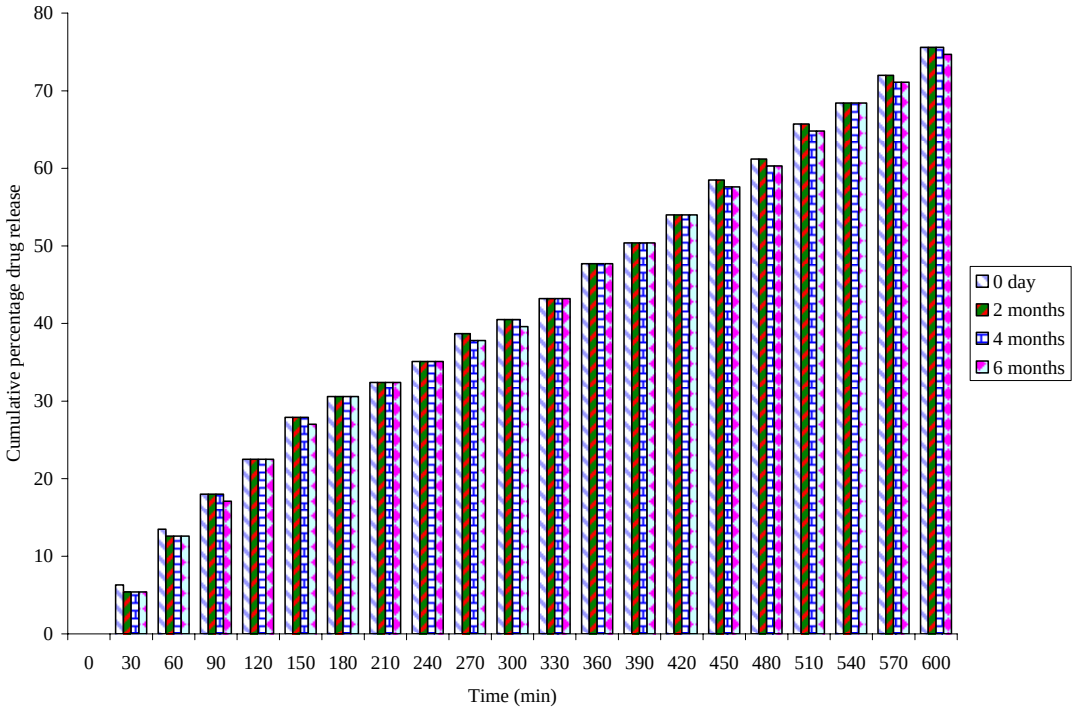


Figure 4. Stability study of F-6 formulation at $45^0 \pm 2^0$ C for a period of 6 months



Conclusion

Results of the present study confirmed that the polymer ratio and hardness plays a major role in drug release. As the polymer ratio and hardness of the tablets increased the drug release was prolonged.

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