Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2009, 1 (2) 93-101
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071

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

T. Raja sekharan*, S. Palanichamy, S. Shanmuganathan, A. Karthikeyan, S. R. Senthilkumar, A. Thanga thirupathi

Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, Anaikuttam, Sivakasi, Tamilnadu, India

---

Abstract

Controlled release matrix tablets of theophylline were prepared with hydrophilic polymer xanthan gum and evaluated. Controlled release matrix tablets of theophylline were prepared by wet granulation technique by varying polymer ratios (1:1 and 1:2) and hardness (5, 6 and 7 kg/cm^2). Tablets were prepared by wet granulation technique. The granules are subjected for preformulation studies. Compressed tablets were evaluated for hardness, uniformity of weight, friability, drug content, thickness and diameter. All the formulation showed compliance with pharmacopoeial standards. IR spectroscopy revealed that there was no interaction between the drug and the polymer used in the formulation. *In vitro* dissolution studies were performed using Disso 2000 (paddle type). Among all formulations F6 showed controlled 73.18 $\pm$ 1.55 % after 10 hr. The kinetic treatment showed that the drug release followed higuchi model. F-6 formulation was subjected to stability studies at three different temperatures for 6months period. It was found to be stable. From this study it was proved that the release of theophylline from matrix tablets was influenced by both polymer ratio and hardness.

Key words: Theophylline, xanthan gum, controlled release, matrix tablets

---

Introduction

Theophylline a methylxanthine, relaxes bronchial muscle, although its precise mode of action is still debated [1]. Theophylline and its more soluble etylenediamine salt, aminophylline, were the bronchodilators of choice in the United States for the management of asthma. Although this primary role has now been taken by the β_2-adrenoceptor agonist, theophylline continues to have an important place in the therapy of asthma because it appears to have an important place in the therapy of asthma because it appears to have anti-inflammatory as well as bronchodilator activity [2]. The main advantages of these formulations for oral use are

improved absorption and fewer gastrointestinal adverse effects. The latter can also be reduced by using slow release formulations and these formulations have also been shown to produce a plasma concentration/time profile with adequate therapeutic concentration for upto 12 hr after a dose, despite the short $t_{1/2}$ of theophylline [3]. Theophylline in controlled release formulation is administered in the evening to achieve an elevated theophylline level overnight when the risk of asthma is found to be maximum [4]. With the conventional formulations of theophylline, the maintenance of therapeutic concentration over the dosing interval will require administration atleast every 6 hrs and even shorter intervals for smokers and children. The controlled release formulations were designed to obviate these problems [5]. Hydrophilic polymers are becoming very popular in formulating oral controlled-release tablets. As the dissolution medium or biological fluid penetrates the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology. Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. Xanthan gum is a natural, biosynthetic, edible gum and an extracellular polysaccharide produced by the bacterium Xanthomonas campestris [6]. Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range [7]. In this study theophylline was investigated in the form of controlled release formulations using xanthan gum with two different ratios (1:1 and 1:2) and three different hardness (5, 6 and 7 kg/cm^2). *In vitro* release study was done in pH 7.4 and the percentage of drug release was estimated at 277 nm using UV double beam spectrophotometer.

Materials and Methods

Theophylline was procured from Amratlal and co. Chennai. Xanthan gum and magnesium stearate was obtained from Loba chemi. Pvt; Ltd, Mumbai. Lactose monohydrate was obtained from Paxmy speciality chemi. Chennai. Polyvinyl pyrolidone and isopropyl alcohol was purchased from S.d.fine-chem.Pvt; Ltd, Mumbai. All other chemical used were of analytical grade.

Formulation of theophylline controlled release matrix tablets

Tablets of all the formulations were prepared by wet granulation method (Table 1). Formulations were prepared by mixing theophylline and xanthan gum uniformly. Lactose was added to the drug and polymer mixture and blended thoroughly for 5 min. Polyvinyl pyrolidone K30 (PVP K30) was dissolved in sufficient quantity of isopropyl alcohol (IPA). PVP K30 in IPA was added to the drug, polymer and lactose mixture and mixes it thoroughly to form a coherent mass. It was sieved manually through sieve # 16. to form granules. Then the granules were collected and dried at 40 $\pm$ 2°C for 2 h. The dried granules were passed through sieve # 16. The granules were then subjected to the preformulation test. After preformulation studies, the granules were mixed with magnesium stearate. 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.

Table 1 Theophylline controlled release tablets formulation

Composition (For one tablet) (mg)	Theophylline: Xanthan gum (1:1)	Theophylline: Xanthan gum (1:2)
Theophylline	100	100
Xanthan gum	100	200
Lactose monohydrate	280	180
Polyvinyl pyrolidone K30 (PVP K30)	10	10
Magnesium stearate	10	10
Iso propyl alcohol (IPA)	q.s	q.s

Evaluation of granules

The angle of repose [8] of the granules was determined by fixed funnel method to assess the flow property of the granules. Loose bulk density [8, 9] (LBD) were measured using the formula LBD = Weight of the powder/ volume of the powder. Tapped bulk density [8, 10] (TBD) were measured using the formula TBD = Weight of the powder/ tapped volume of the powder. Reciprocal of bulk density is known as bulkiness [11]. Bulkiness = 1/ bulk density. Compressibility index [8] of the granules was determined by using the formula CI (%) = Tapped density – Bulk density × 100/ Tapped density. Hausner ratio [8] was determined by using the formula HR = Tapped density/ Bulk density.

Evaluation of formulated tablets

Hardness [12] of the tablets was performed using Monsanto hardness tester. Uniformity of weight [13] was performed as per specification. Friability test [13] was performed using Roche friabilator. Drug content [13] was estimated using UV double beam spectrophotometer. Thickness and diameter were measured using a vernier caliper.

FTIR Studies

It was used to study the interaction between the drug, polymer and the excipients. FT-IR studies were obtained by KBR disk method using computer-mediated Fourier transformed infrared spectroscopy (FT-IR) (Shimadzu). The spectra of matrix tablet formulation F-6 was compared with those of pure theophylline and xanthan gum [14]. The drug, polymer and excipients must be compatible with one another to produce the product stable and efficacious.

In vitro dissolution studies

In vitro drug release of the samples was carried out using disso-2000 dissolution apparatus (paddle type). The dissolution medium, 900 ml pH 7.4, was placed into the dissolution flask maintaining the temperature of 37 $\pm$ 0.5° and rpm of 50. One theophylline tablet was placed in the dissolution apparatus. The apparatus was allowed to run for 10 h. Samples measuring 10 ml were withdrawn every 30 min intervals upto 10 h using 10 ml pipette. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with pH 7.4 and analyzed at 277 nm using pH 7.4 as blank.

Kinetic Studies

The theophylline release data from all the formulations were fitted in various kinetic models like zero order, first order, higuchi, hixon – crowell and Koresmeyer Peppas [15].

Stability studies

Stability studies were aimed at determining the result of aging and storage under various conditions on the formulated controlled release tablets. It was carried out to evaluate the stability of F6 formulations after storing at different temperatures for a period of 6 months. The prepared tablets were kept at three different temperatures 4 ± 2°C, 28 ± 2°C and 45 ± 2°C for 6 months [16]. Every two months intervals the tablets were evaluated for all physical parameter. The percentage of theophylline content and *in vitro* drug release studies were determined by double beam UV double beam spectrophotometer.

Results and Discussion

The present study was carried out to formulate and evaluate the theophylline controlled release matrix tablets. A wet granulation method was employed to produce theophylline controlled release tablets. Lactose was selected as filler in the formulations, as tablets containing lactose are reported to show good friability and low weight variation with no sign of sticking, binding and capping. PVP K30 is an excellent and versatile all purpose binder. It is recommended to granulate soluble powder with alcoholic solution of PVP K30. Magnesium stearate was incorporated as a glidant and antiadherent.

Physico-chemical characteristics of theophylline matrix granules

The granules of different formulations were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and hausner ratio. The results are shown in table 2. The granules shows good flow properties with the angle of repose ranging from 30° – 35°. The bulk density was found to be in the range of 0.3125 gm/cm^3 to 0.3947 gm/cm^3. The tapped density was found to be in the range of 0.3658 gm/cm^3 to 0.4545 gm/cm^3. The bulkiness was found to be in the range of 2.5 to 3.2 cm^3/gm. The compressibility index and hausner ratio was found to be in the range of 13-15 and 1.15-1.17. Above all the results shows that the granules having good flow properties.

Table 2 Evaluation of Theophylline Granules with Xanthan gum

Parameters*	Theophylline : Guar Gum					
	5 kg/cm^2		6 kg/cm^2		7 kg/cm^2	
	1 : 1 (F1)	1 : 2 (F2)	1 : 1 (F3)	1 : 2 (F4)	1 : 1 (F5)	1 : 2 (F6)
Angle of repose (θ)	30.83 ± 0.5204	32.68 ± 0.5840	31.98 ± 0.8492	31.76 ± 0.9792	32.81 ± 0.6131	32.01 ± 0.5313
Bulk density (gm/cc)	0.3107 ± 0.008	0.3049 ± 0.004	0.3164 ± 0.009	0.3087 ± 0.005	0.3149 ± 0.013	0.3127 ± 0.010
Tapped density (gm/cc)	0.3651 ± 0.007	0.3548 ± 0.011	0.3600 ± 0.007	0.3624 ± 0.007	0.3626 ± 0.012	0.3653 ± 0.012

Bulkiness (cc/gm)	3.22 ± 0.08	3.28 ± 0.04	3.12 ± 0.08	3.24 ± 0.05	3.18 ± 0.13	3.18 ± 0.10
Compressibility index (%)	14.89 ± 1.14	14.00 ± 3.36	12.14 ± 2.43	14.79 ± 2.40	12.04 ± 3.92	13.81 ± 2.71
Hausner ratio	1.17 ± 0.02	1.16 ± 0.05	1.17 ± 0.03	1.17 ± 0.03	1.16 ± 0.06	1.17 ± 0.04

*Mean ± standard deviation of five determinations

Physico-chemical characteristics of theophylline matrix tablets

The formulated tablets were evaluated for their physical characters. The results are tabulated in table 3. The thickness and diameter was found to be in the range of 4.1 ± 0.00 to 4.2 ± 0.04 and 12.5 ± 0.03 to 12.6 ± 0.04. The hardness of the tablets was checked with Monsanto hardness tester. The hardness of all the formulated tablets was found to be 4.96 ± 0.34 to 7.03 ± 0.24. The uniformity of weight indicates that all the tablets were with low standard deviation values. In the friability test, the loss of weight was in the range of 0.11 ± 0.05 to 0.38 ± 0.05 it is below 1% it indicates that the formulated tablet passes the test. The percentage drug content of all formulations was found to be in the range of 95.8 ± 0.41 to 97.4 ± 0.22.

Table 3 Evaluation of Tablets

Parameter	Theophylline : HPMC K100M					
	5 kg/cm^2		6 kg/cm^2		7 kg/cm^2	
	1:1 (F1)	1:2 (F2)	1:1 (F3)	1:2 (F4)	1:1 (F5)	1:2 (F6)
Hardness [a] (kg/cm^2)	5.02 ± 0.21	4.96 ± 0.34	6.03 ± 0.13	6.01 ± 0.19	7.03 ± 0.24	6.98 ± 0.37
Uniformity of weight [b] (mg)	498.8 ± 5.2	500.5 ± 5.7	500.1± 3.5	499.2 ± 6.2	499.5 ± 6.6	500.6 ± 7.6
Friability [c] (%)	0.29 ± 0.04	0.24 ± 0.03	0.20 ± 0.07	0.38 ± 0.05	0.20 ± 0.06	0.11 ± 0.05
Drug content [c] (%)	95.8 ± 0.41	96.8 ± 0.60	97.0 ± 0.33	97.4 ± 0.22	96.0 ± 0.14	97.0 ± 0.29
Thickness [c] (mm)	4.2 ± 0.00	4.2 ± 0.04	4.1 ± 0.03	4.1 ± 0.05	4.1 ± 0.02	4.1 ± 0.00
Diameter [c] (mm)	12.6 ± 0.01	12.5 ± 0.03	12.5 ± 0.05	12.6 ± 0.04	12.6 ± 0.02	12.6 ± 0.03

a = 5; b = 20; c = 10

FT-IR studies

FT-IR study revealed that there was no shift in the peaks of theophylline and xanthan gum in matrix tablets compared to pure theophylline and xanthan gum. It was found that there was no interference to the drug with excipients and polymer used in the present study.

In vitro release studies

Matrix tablets of all the formulations were subjected to study *in vitro* release study for 10 h. F1 formulation shows 99.0 ± 0.59 after 8 h, F2 formulation shows 84.6 ± 1.69, F3 formulation shows 99.9 ± 0.51 after 8.5 h, F4 formulation shows 75.6 ± 1.53, F5 formulation

shows 99.9 ± 0.61 and F6 formulation shows 73.8 ± 1.55 after 10 h. Among all the formulation F6 formulation shows prolonged drug release when compared to other formulations. It was shown in figure 1. It indicates that the polymer ratio and hardness plays a vital role in the drug release. As the polymer ratio and hardness increased the drug release rate was decreased. Hardness makes polymer and drug particles more intact. Maintenance of suitable hardness is an important factor of controlled release pattern of matrix tablets.

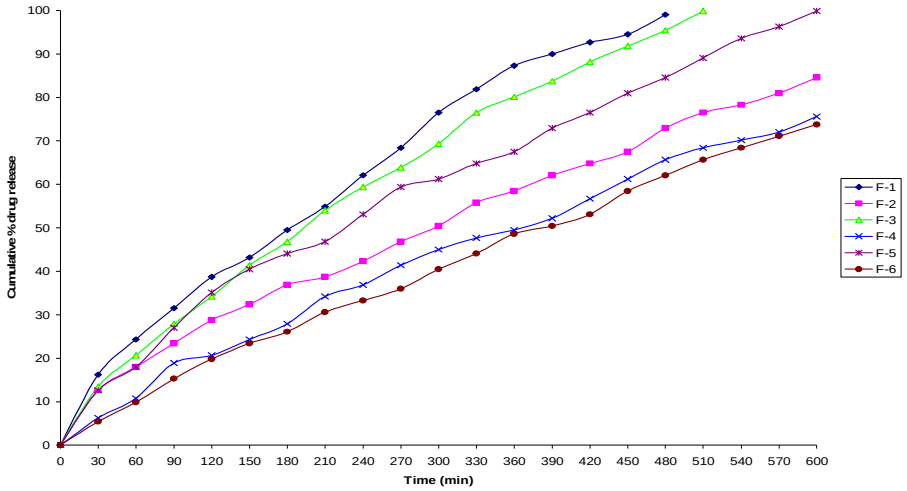


Figure 1: Comparison of *in vitro* release study of F-1 to F-6 formulations

Mechanism of drug release

Drug release mechanism from the matrix tablets of formulation F1 – F6 follows higuchi model (Table 4). The release exponent n was between 0.6812 to 0.7387 ($0.5 < n < 0.89$), which appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion and may indicate that the drug release is controlled by more than one process. Thus, it was proposed that these formulations delivered their active compound by coupled diffusion and erosion. Reddy et al observed similar results with a matrix tablet of nicorandil with an n value of 0.71 [17] and Fassihi and Ritschel with a matrix tablet of theophylline with an n value of 0.7 [18]. Both these groups of researchers also considered the corresponding n values to indicate an anomalous release mechanism.

Stability studies

F-6 formulation was selected for the stability studies. At the time of stability studies, F-6 formulation was observed for changes in physical appearance and evaluated for the physico-chemical parameters and subjected to *in vitro* drug release studies for every 2 months intervals upto 6 months at three different temperatures. The results are presented in the table 5. The results showed that there was no significant change in the physical appearance, physico-chemical properties and *in vitro* drug release of the tablets at the end of the storage period. The *in vitro* release graph was shown in the figure 2, 3 and 4. Hence, F6 formulated tablets withstand for a period of 6 months at different temperature without any change.

Table 4 Drug release kinetics of all six formulations

Formulation code	Correlation co-effecient	Zero order	First order	Higuchi	Hixcon crowell	Koresmeyer Peppas	
						n value	r^2 value
F-1	r^2	0.9785	0.8582	0.9767	0.9669	0.7380	0.9969
F-2	r^2	0.9845	0.9731	0.9788	0.9912	0.6812	0.9980
F-3	r^2	0.9821	0.9846	0.9776	0.9227	0.7387	0.9995
F-4	r^2	0.9896	0.9857	0.9664	0.9950	0.7069	0.9867
F-5	r^2	0.9789	0.7637	0.9825	0.9084	0.7147	0.9984
F-6	r^2	0.9960	0.9802	0.9559	0.9928	0.7099	0.9797

Table 5 Stability study for the formulation F-6 at three different temperatures

Parameter*		$4^0 \pm 2^0$ C			$28^0 \pm 2^0$ C			$45^0 \pm 2^0$ C		
	0 day	2 months	4 months	6 months	2 months	4 months	6 months	2 months	4 months	6 months
Physical changes	-	No changes	No changes	No changes	No changes	No changes	No changes	No changes	No changes	No changes
Hardness [a] (kg/cm^2)	6.98 ± 0.37	6.97 ± 0.45	6.95 ± 0.36	7.04 ± 0.30	7.01 ± 0.45	7.05 ± 0.36	6.95 ± 0.31	7.03 ± 0.46	6.94 ± 0.28	6.99 ± 0.52
Uniformity of weight [b] (mg)	500.6 ± 7.6	504.3 ± 3.6	501.9 ± 4.5	505.4 ± 4.2	495.8 ± 3.0	500.8 ± 7.2	499.3 ± 6.3	501.7 ± 5.8	498.2 ± 7.2	501.3 ± 3.0
Friability [c] (%)	0.11 ± 0.05	0.15 ± 0.07	0.18 ± 0.03	0.32 ± 0.14	0.10 ± 0.01	0.25 ± 0.10	0.22 ± 0.09	0.10 ± 0.02	0.25 ± 0.09	0.22 ± 0.06
Drug content [c] (%)	97.0 ± 0.29	98.2 ± 0.12	98.0 ± 0.16	97.8 ± 0.22	98.6 ± 0.15	98.4 ± 0.26	98.0 ± 0.18	98.2 ± 0.15	97.8 ± 0.26	96.4 ± 0.18
Thickness [c] (mm)	4.1 ± 0.00	4.1 ± 0.03	4.1 ± 0.02	4.1 ± 0.03	4.1 ± 0.02	4.1 ± 0.03	4.1 ± 0.04	4.1 ± 0.02	4.1 ± 0.03	4.1 ± 0.04
Diameter [c] (mm)	12.6 ± 0.03	12.6 ± 0.04	12.6 ± 0.02	12.6 ± 0.01	12.6 ± 0.03	12.6 ± 0.04	12.6 ± 0.02	12.6 ± 0.03	12.6 ± 0.04	12.6 ± 0.02
Dissolution after 10 hr (%)	73.8	73.8	73.8	72.9	73.8	73.8	72.9	73.8	72.9	72.9

Note: a = 5; b = 20; c = 10

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

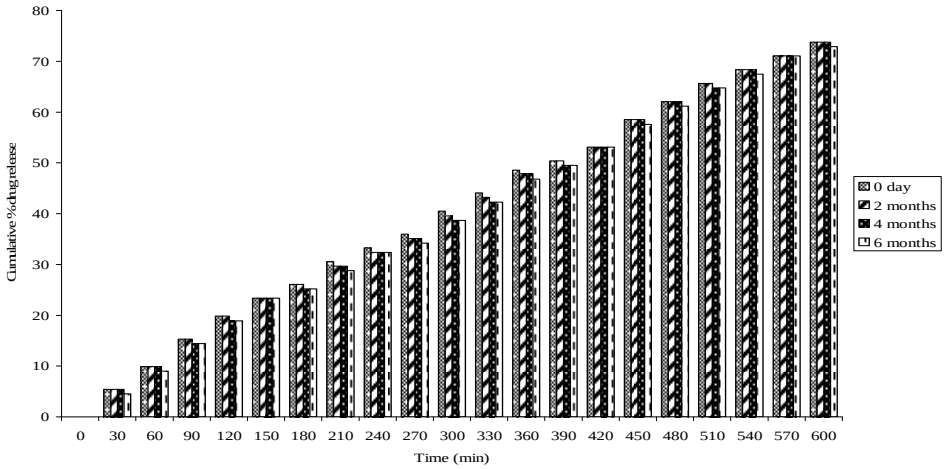


Figure 3: Stability study of F-6 formulation at $28^0 \pm 2^0$ C for a period of 6 months

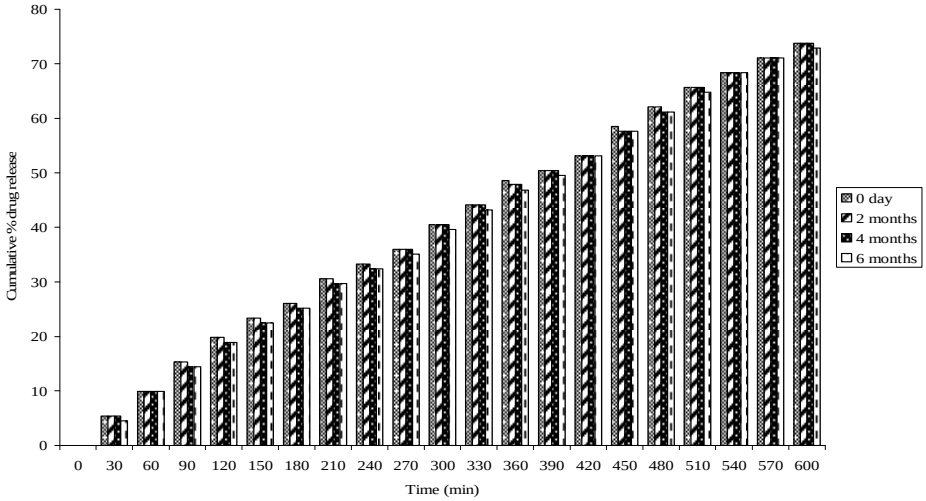
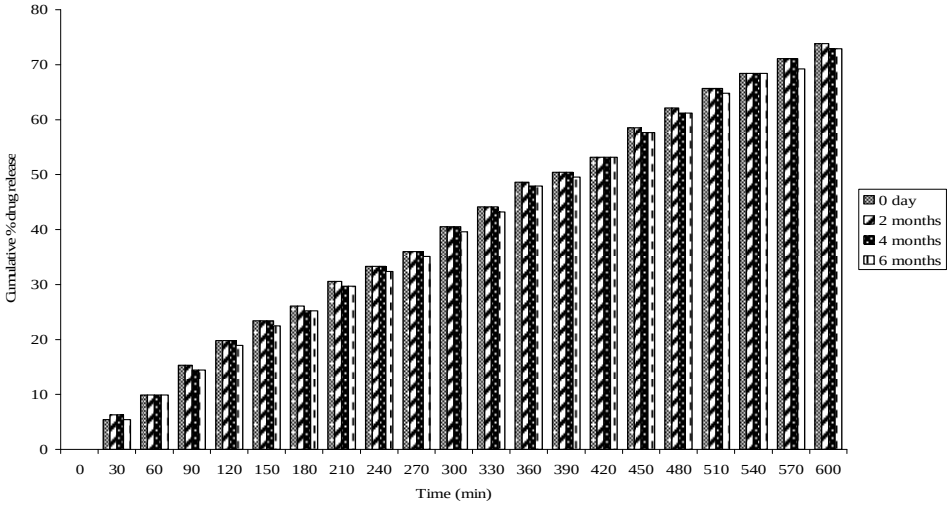


Figure 4: Stability study of F-6 formulation at $45^0 \pm 2^0$ C for a period of 6 months



Acknowledgements

The authors are grateful to the correspondent Mr. S. Sriram Ashok, Sankaralingam Bhuvaneswari College of pharmacy, Sivakasi for his support during the present research work.

References

[1] PN Bennett; MJ Brown. Clinical pharmacology. 10th ed., Churchill livingstone Elsevier, New York, **2008**; pp. 503.
[2] Charles R. Craig, Robert E. Stitzel. Modern pharmacology with clinical applications. 5th ed., Little brown and company, New York, **1997**; pp. 494.
[3] DG Grahame-Smith, JK Aronson. Oxford textbook of clinical pharmacology and drug therapy. 2nd ed., Oxford university press, New York, **1995**; pp. 715.
[4] HN Shivakumar, Sarasija Suresh, BG Desai. *Indian J Pharm Sci*, **2007,** 69 (1), 73 – 79.
[5] Swaminathan Subramanian, Rajiv Dhand, SK Garg, PL Sharma. *Indian J Pharmacology*, **1987**, 19, 74-84.
[6] Jaleh Varshosaz, Naser Tavakoli, Fatemeh Kheirolahi. *AAPS PharmSciTech* **2006**, 7 (1), E1-E7.
[7] Raymond C Rowe, Paul J Sheskey, Sian C Owen. The Handbook of Pharmaceutical Excipients, Pharmaceutical Press and American Pharmacists Association, **2006**, 599-601.
[8] United States of Pharmacopeia-National Formulary. USP 30 – NF 25. The Unit States Pharmacopeial Convention, Rockville, MD, **2007**, Volume 1, 644, 242, 645, 731 and 634.
[9] Herbert A. Liberman, Leon Lachman, Joseph B. Schwartz. Pharmaceutical dosage forms: Tablets volume-2, 2nd ed., Marcel dekker, New York, **2005**, pp. 165-167.
[10] D Shah, Y Shah, M Rampradhan. *Drug Dev Ind Pharm*, **1977**, 23, 567 – 574.
[11] Patrick J. Sinko. Martin's Physical pharmacy and pharmaceutical sciences, 5th ed., Lippincott Williams and Wilkins, New York, **2006**, pp. 557.
[12] E Rudnic and J Schwartz. B. Oral solid dosage forms In: Remington's Pharmaceutical Sciences, Ed. Gennaro, A. R. 18thed., Mack Publishing Company. Easton, Pennsylvania, USA, **1990**, pp. 1633-1665.
[13] Pharmacopoeia of India, Ministry of health and family welfare. Govt. of India controller of publications, New Delhi, **2007**; 663,183 and 662.
[14] CH.N Pathra, MK Bhanoji Rao, KS Yadav, K Prakash. *Indian J Pharm Sci* **2004**, 66 (5), 636 – 641.
[15] Hamid A. Merchant, Harris M. Shoaib, Jaweria Tazeen, Rabia I. Yousuf. *AAPS PharmSciTech*, **2006**, 7 (3), E1 – E6.
[16] PG Yeole, Galgatte, IB Babla, D Nkhat. *Indian J Pharm Sci*, **2006**, 68 (2), 185-189.
[17] KR Reddy, S Mutalik, S Reddy. *AAPS PharmSciTech*, **2003**, 4: E61.
[18] RA Fassihi, WA Ritschel. *J Pharm Sci*, **1993**, 82, 750-754.