Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2011, 3 (6):1-7
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0974-248X
USA CODEN: DPLEB4

Formulation and evaluation of theophylline sustained release matrix tablet

G. Rajalakshmi*, R. Balachandar and N. Damodharan

Department of Pharmaceutics, SRM College of Pharmacy, Kattankulathur, India

---

ABSTRACT

In the present study sustained release matrix tablets of Theophylline were prepared by direct compression method using different grades and ratios of hydroxy propyl methyl cellulose in presence of ethyl cellulose to examine their influence on tablet properties and drug release profile. Theophylline is used to treat chronic obstructive pulmonary disease (COPD) and asthma. The drug has a narrow therapeutic index and short half life (8 hours) which requires regular monitoring of serum theophylline concentration. Sustained delivery of the drug could reduce the adverse effects such as sinus tachycardia, nausea, tremor, indigestion etc. and improve the patient compliance. The formulated tablets were evaluated by measurement of hardness, friability, content uniformity, weight variation and drug release pattern. All the tablets met the pharmacopoeial requirements for physical tests. It was found that high viscosity grade hydroxy propyl methyl cellulose with ethyl cellulose shows a good retardation effect over drug release. Mathematical analysis of release kinetics indicates a near approximate fickian release character for most of the designed formulations. Invitro release studies showed that formulations containing hydroxy propyl methyl cellulose grade K15M sustain the drug release than formulations with hydroxyprpyl methyl cellulose 5cps.

Keywords: Therapeutic index, Direct compression, Sinus tachycardia, Fickian release.

INTRODUCTION

For any drug therapy to be successful, the drug must reach the target site or tissue or must reach the systemic circulation in optimum concentration which should be maintained for desired time. Therapeutic response of the drug also depends upon the pharmacokinetics of the drug in an individual patient and frequency of dosing. Many acute and chronic diseases require frequent dosing to maintain their concentration in systemic circulation. But with frequent dosing many problems like patient non compliance to the prescribed dose regimen, drug accumulation leading

to toxicity, etc. These problems can be solved by developing a new dosage form which prolongs the release of the drug from the dosage form with similar therapeutic response as that of conventional dosage forms and longer of action.

Conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments, creams and suppositories. These dosage forms can be considered to release their active ingredients into an absorption pool immediately [1]. The absorption pool represents a solution of a drug at the site of absorption, and the terms Kr, Ka, and Ke are first order rate constants for drug release, absorption and overall elimination respectively. Immediate release from a conventional dosage forms implies that Kr>>Ka or that observation of drug across a biological membrane, such as the intestinal epithelium, is the rate limiting step in delivery of the drug to its target site or area. For non immediate release dosage form, Kr<<<Ka, that is, release of drug from the dosage form is the rate limiting step. Non immediate release delivery systems may be divided conveniently into Delayed release, Sustained release, Site specific release and Receptor release.

A sustained release dosage forms allows a twofold or greater reduction in frequency of administration of the drug in comparison with frequency required by a conventional dosage forms [2]. The oral sustained release drug delivery system releases the drug content in a controlled manner producing a desirable blood serum level, reducing drug toxicity and improving patient compliance by prolonging dosing intervals [3-7]. Theophylline, a xanthine derivative is used as bronchodilators for moderate to severe reversible bronchospasm. It is also used in treating asthma and COPD [8]. The drug is well absorbed from GIT with 90-100% bioavailability. The drug has a narrow therapeutic index and short half life (8 hrs in adults). Because of the relatively short plasma half life of theophylline, there is a necessity for sustained release preparation. Many sustained release works have been reported earlier. Sustained release matrixes of Theophylline with ethyl cellulose [9], release of drug from Kollidon SR [10] have been studied. Preparation of drug embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for sustained release dosage form.

In the present study, different grades of hydroxy propyl methyl cellulose (hydroxy propyl methyl cellulose 5cps, hydroxy propyl methyl cellulose K 15M) were used in presence of ethyl cellulose. The influence of these polymers on the release rate kinetics were studied is this work.

MATERIALS AND METHODS

Theophylline was procured from Sigma, USA. Ethyl cellulose and Hydroxy propyl methyl cellulose (5cps, K15) were purchased from S.D Fine Chemicals, Mumbai. Magnesium stearate, poly vinyl pyrollidone K 30, Microcrystalline Cellulose were from Loba chemicals Pvt ltd,Mumbai. All other ingredients used were of analytical grad**e.**

Preparation of tablets:
Tablet ingredients of different formulation were weighed, milled and mixed thoroughly After mixing with 1% magnesium stearate, tablets containing 700mg theophylline were prepared by direct compression method using Cadmach tablet punching machine with 16/32deep concave

punch The compositions of the tablets formulations are given in Table 1and 2.

Table: 1 Formulation of Theophylline SR tablets using HPMC K15M

Contents	F_{1A} (mg)	F_{1B}(mg)	F_{IC}(mg)	F_{ID}(mg)	F_{IE}(mg)
Theophylline	200	200	200	200	200
HPMC K15M	400	360	320	280	240
Ethyl cellulose	-	40	80	120	160
PVP K30	24	24	24	24	24
MCC	70	70	70	70	70
Magnesium Stearate	6	6	6	6	6
Total	700	700	700	700	700

Table: 2 Formulation of Theophylline SR tablets using HPMC 5cps

Contents	F_{IIA} (mg)	F_{IIB}(mg)	F_{IIC}(mg)	F_{IID}(mg)	F_{IIE}(mg)
Theophylline	200	200	200	200	200
HPMC K15M	400	360	320	280	240
Ethyl cellulose	-	40	80	120	160
PVP K30	24	24	24	24	24
MCC	70	70	70	70	70
Magnesium Stearate	6	6	6	6	6
Total	700	700	700	700	700

Physical evaluation of Tablets:

Weight variation:

20 tablets from each formulation were weighed using an electronic balance and mean and relative study deviations of weight were determined based on an official method [11].

Hardness and friability: [11]

The diametrical crushing strength test was performed on 10 tablets from each formulations using Monsanto hardness tester. For each formulation, the friability of 20 tablets was determined using a Roche friabilator. 20 tablets from each formulation were weighed and tested at speed of 24 rpm for 4 min. After removing of dusts, tablets were reweighed and friability % was evaluated using the following equation,

$$\% F = \frac{W_1 - W_2}{W_1} X\ 100$$

W_1 = Initial weight of tablet W_2 = Final weight of tablet

Drug content:

From each batch, 20 tablets were taken and finely powdered. A portion equal to 700mg of Theophylline was accurately weighed, suitably dissolved and diluted using 0.1M HCl. The absorbance was measured spectrophotometrically using UV spectrophotometer (Schimadzu UV 1700 Pharmaspec) at 271nm.

Dissolution studies:

Invitro release rate studies were carried out using USP dissolution apparatus, Type II paddle (

Labindia DS 8000) speed of 100 rpm with 900ml of simulated intestinal fluid without pepsin (0.1 N HCl, pH 1.2) for 1 hour initially. The medium was replaced then with 900ml simulated intestinal fluid without pancreatin (pH 6.8 phosphate buffer) under sink condition. At predetermined time intervals, a 5ml of sample was withdrawn and replaced with fresh dissolution media for 5hours. After centrifugation and appropriate dilution, sample was analyzed by UV spectrophotometric method at 271nm for both media cumulative % of drug release was calculated.

Kinetic models:

Dissolution data were fitted to Zero order $w = w_0 - k_o t$, First order $Lnw = \ln w_o - k_1 t$, Hixson Crowell's cube root of time, $W^{1/3} = W_o^{1/3} - k_x t$ Higuchi square root of time $w = w_o - k_H t^{1/2}$ kinetic models, where W is the amount of drug released at time t and W_o is the initial amount of drug. Fitting was performed by employing PCP disso ver. 2.0 by linear regression method to determine the most probable release kinetic by using standard error of estimates. [12]

To estimate the drug release mechanism, dissolution data were also analyzed by Krosmeyer – Peppas model $M_t/M_\infty = Kt^n$, where $M_t/M\infty$ = amount of drug released at time t, K is a constant incorporating structural characteristic of the dosage form and n is the release exponent. When $n<0.5$ the drug diffuses through the polymeric matrix by a Fickian (case I) diffusion mechanism. For $0.5<n<1$, an anomalous non fickian mechanism occurs .n=1 indicates Zero order (case II) $n>1$ indicates non fickian super case II release mechanism [13].

RESULTS AND DISCUSSION

Physical evaluation of tablets:

Matrix tablets of Theophylline were prepared by DC method and subjected to differences evaluation tests. All the formulations having uniform weight, hardness and friability with Hardness of tablet was found to be satisfactory as per pharmacopoeial tolerance limit.IR studies indicated good compatibility between drug polymer and excipients. All tablet formulations were subjected to various evaluation parameters and the results obtained were within the range (Table 3). The weight variation test indicates that all the tablets were uniform with low standard deviation values. The hardness of tablets was between 6-8 kg/cm^2. The loss in total weight in friability test was in the range of 1%. The % drug content for different tablets varied from 99.5 – 101.3% indicating uniformity of drug content was carried out in 0.1N HCl and PO_4 buffer pH 6.8.

The Invitro release studies are given in table 3 and 4. The studies revealed that there was san average drug release of 31.09% in formation I and 88.5% for formulation II. From this it was clear that formulation II comprising Hydroxy propyl methyl cellulose 5cps released almost 90% of drug in first 6hrs whereas formulation I released only 31% which was effective in releasing drug over prolonged period of time in sustained manner for more than 6hrs and further study was warranted. The release profile is given in in figure 1 and 2.An inverse relationship was observed between concentration of polymer and release rate of Theophylline from matrix tablets kinetics models with Zero order and Higuchi are more suitable for controlled release formulations, while first order model is more appropriate for conventional tablets. The best fit with higher correlation ($r^2 > 0.98$) was found with first order equation for the majority of formulations. This fact was expected considering the diffusion was preferential mechanism for drug release from this kind of

matrices. On the other hand, theophylline although being a slight soluble drug, released from HPMC K 15 M matrices by diffusion and not by erosion, considering that matrices maintained their original shape from start to end of dissolution tests. The results are shown in table 5

Table: 3 Physical Evaluation of Tablets

Formulation Code	Weight variation %	Hardness (kg/cm)	Friability %	Drug Content %
F_{IA}	3.48	7	0.28	99.8
F_{1B}	4.55	7	0.22	100.8
F_{1C}	5.0	6	0.12	99.5
F_{1D}	4.9	7	0.37	101.3
F_{1E}	3.73	6	0.11	99.9
F_{1IA}	5.26	8	0.15	101.2
F_{1IB}	5.17	7.5	0.47	99.5
F_{1IC}	4.36	6	0.36	99.7
F_{1ID}	3.19	6	0.23	99.8
F_{1IE}	6.84	7	0.55	99.6

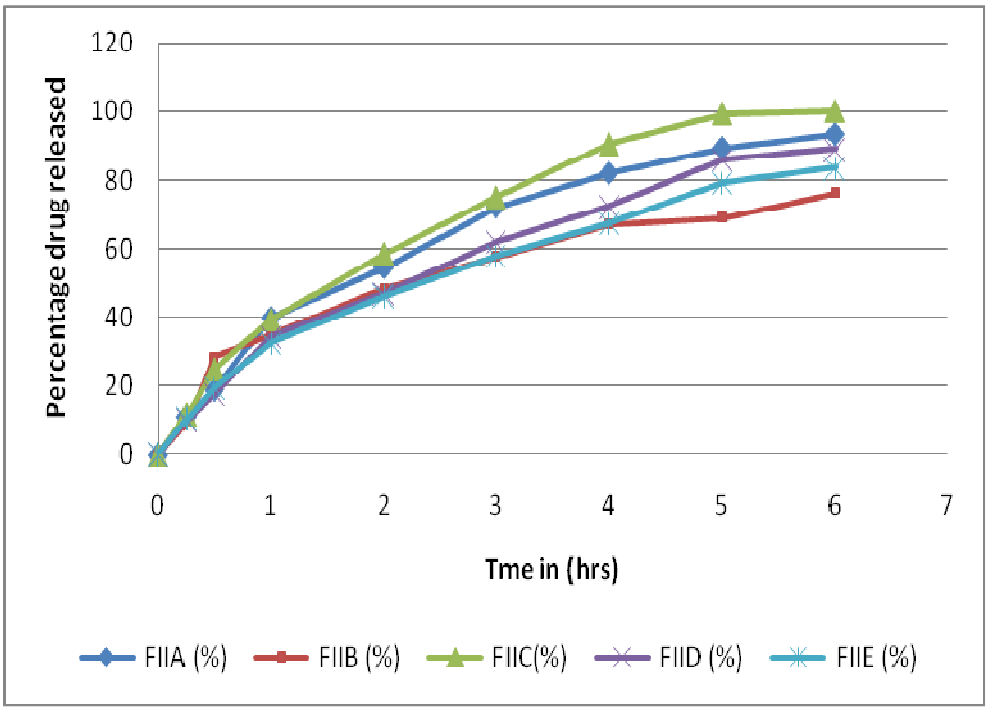

Fig: 1 Invitro release profile of Theophylline sustained release tablets using HPMC K 15M

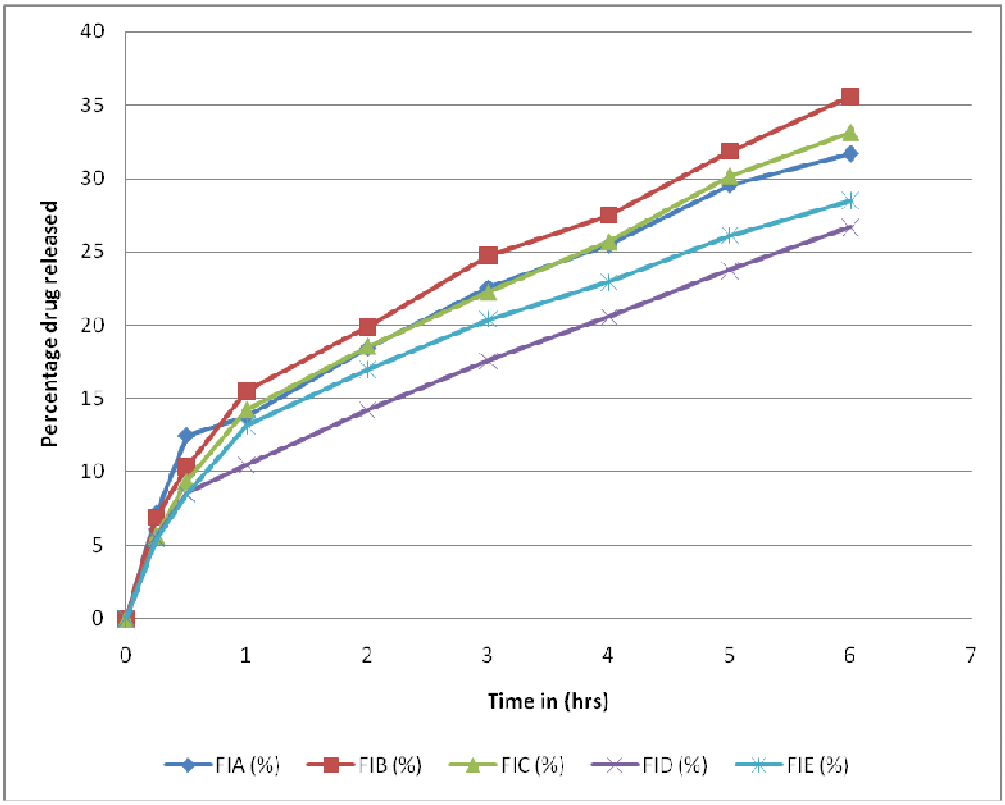

Fig: 2 Invitro release profile of Theophylline sustained release tablets using HPMC 5 cps

Table: 3 Percentage cumulative drug release of Theophylline

Time in (Hrs)	F_{IA} (%)	F_{IB} (%)	F_{IC} (%)	F_{ID} (%)	F_{IE} (%)
0	0	0	0	0	0
0.25	7.19	6.92	5.66	5.55	5.45
0.5	12.48	10.32	9.37	8.55	8.49
1	13.79	15.54	14.2	10.45	13.19
2	18.42	19.89	18.53	14.21	17.01
3	22.55	24.69	22.22	17.59	20.39
4	25.48	27.47	25.65	20.56	22.94
5	29.54	31.84	30.125	23.74	26.15
6	31.68	35.57	33.1	26.66	28.49

Table: 4 Percentage cumulative drug release of Theophylline

Time in (Hrs)	F_{IIA} (%)	F_{IIB} (%)	F_{IIC} (%)	F_{IID} (%)	F_{IIE} (%)
0	0	0	0	0	0
0.25	11.11	9.26	11.75	10.07	10.48
0.5	18.96	28.50	24.98	17.64	19.42
1	40.00	34.90	39.45	34.35	32.47
2	54.6	48.35	58.65	47.06	46.22
3	72.34	57.75	75.10	61.98	57.84
4	82.15	67.20	90.60	72.29	67.44
5	89.56	69.06	99.45	86.00	79.28
6	93.48	76.15	100.20	89.06	83.63

Table: 5 Formulation Coefficient (r) of Kinetic model of drug for different formulations

FORMULATIONS	ZERO ORDER (r)	FIRST ORDER (r)	HIGUCHI (r)
F_{IA}	0.9839	0.9899	0.9952
F_{IB}	0.9844	0.9913	0.9985
F_{IC}	0.9835	0.9906	0.9982
F_{ID}	0.9935	0.9964	0.9974
F_{IE}	0.9760	0.9836	0.9982
F_{IIA}	0.9604	0.9982	0.9929
F_{IIB}	0.9473	0.9867	0.9896
F_{IIC}	0.9665	0.9825	0.9942
F_{IID}	0.9796	0.9982	0.9947
F_{IIE}	0.9803	0.9963	0.9971

CONCLUSION

The sustained release formulations of theophylline were studied in this work. From the study it was concluded that high viscosity grade HPMC with ethyl cellulose shows a good retardation effect over drug release. The mathematical models were applied to release data suggest that all the formulations showed a diffusion controlled (Fickian) drug release throughout the period.

REFERENCES

[1] Robinson JR and Lee VHL, **1987**., 'Controlled Drug Delivery- Fundamentals and Applications', 2nd edition, Marcel Dekker, INC, New York, 09.
[2] D M Brahmankar and Sunil B Jaiswal, Biopharmaceutics and Pharmacokinetics a Treatise, 336-341
[3] B Sreenivasa Rao, L Prasana Raju , L Srinivas , A Seshasayana , K Himasanker , BS Sirisha and KV Ramanamurthy *Indian J. Pharm. Sci, 60*, **2004**,202-207.
[4] BS Nath, Venkatesh and Hiremath, *Indian J. Pharm Sci 62*, **2000**, 33-36.
[5] E Efentakis , M Vlachous and NH Choulis, Drug. Dev, *Ind. Pharm*, **1997**, *23*, 107-112.
[6] F Veiga,T Salsa and MEPina , *Drug. Dev. Ind. Pharm*, **1997**, *23*, 547-551.
[7] Goodman and Gilman's The pharmacological basis of therapeutics 9th edition, **1996**, pp 672-673.
[8] KD Tripathi, Essentials of Medical Pharmacology, 6th edition, Jaypee brother's medical publishers (P) limited, pp 217-222.
[9] D Nagaswamy Venkatesh , S Sangeetha, M.K.Samantha,S.Sankar and B.Suresh, *Int. J. of pharmaceutical sciences and Nanotechnology*, April-June **2008**. *1*, 60-63.
[10] M.D.Selim Raza, Mohiuddine Abdul Quqdir and Syed Shabbir haider, *Pak. J .of pharmaceutical sciences*. Jan **2002**, *15*, *(1)* 63-70.
[11] Leon Lachman, Herbert a liberman, joseph L.Kanig in "theory and practice of industrial pharmacy" 2nd edition, varghese publication. **1985**, pp 341.
[12] P Costa, *Int. J. Pharm* **2001**, *220*, 77-83.
[13] P Costa and Sousa Lobojy, *European. J. Pharm. Sci*. **2001**, *13*, 123-133.