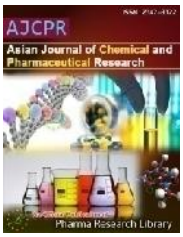
Asian Journal of Chemical and Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ajcpr



Research Article **Open Access**

Formulation and Evaluation of Colon Targetted Drug Delivery System of Theophylline for the Treatment of Nocturnal Asthma

Y. Swetha, Venugopalaiah .P*, D. Sravanthi

Ratnam Institute of Pharmacy, Pidathapolur, Muthukur, Nellore, Andhra Pradesh, India

A B S T R A C T

The site specific release in the colon affects a time delay between administration and onset of action, which can be useful for diseases with various degrees of severity, such as asthma and arthritis. In the present study development of time controlled formulation to treat the nocturnal symptoms of asthma was formulated and administered in the night at 10.00 pm, symptoms that are experienced in early morning hours could be avoided. Theophylline possesses good oral bioavailability and adequate colon absorption. Hence it is selected as an ideal candidate for the colon targeted drug delivery system. This system when administered in evening is aimed to achieve an elevated Theophylline levels overnight where the risk of asthma is found to be maximum. Matrix tablets and Compression coated tablets of Theophylline are proposed to be developed by employing guar gum as rate controlled polymer. Tablets were prepared by wet granulation method and granules were evaluated for various physicochemical properties. Results revealed that matrix tablets prepared with guargum which are compression coated with CAP released the drug up to 24 hrs which were found to be suitable for chronotherapeutic delivery of theophylline to treat the symptoms of nocturnal asthma. Drug release kinetics revealed that F6 follows Zero Order Kinetics with R^2=0.98. Diffusional exponent 'n' and mechanism of diffusional release from swellable controlled release systems was found to be Super Case-2 transport.

Keywords: Theophylline, Guargum, Cellulose acetate phthalate (CAP), Chronotherapeutics etc

A R T I C L E I N F O

CONTENTS

Article History: Received 18 January 2017, **Accepted** 28 February 2017, **Available Online** 12 April 2017

***Corresponding Author**
Venugopalaiah .P
Ratnam Institute of Pharmacy,
Pidathapolur, Muthukur, Nellore,
Andhra Pradesh, India
Manuscript ID: AJCPR3291

PAPER-QR CODE

Citation: Venugopalaiah .P, *et al.* Formulation and Evaluation of Colon Targetted Drug Delivery System of Theophylline for the Treatment of Nocturnal Asthma. *A. J. Chem. Pharm, Res.*, 2017, 5(1): 01-05.

1. Introduction

Colon targeting is naturally of value for the local treatment of colonic diseases like inflammatory bowel disease, Crohn's disease and for the Chronotherapeutic delivery of drugs. Bowel diseases can be effectively treated by local delivery of drugs to the large intestine. By this technique absorption of the drugs from the stomach and small intestine can be minimized until the drug reaches the large intestine [1].

Asthma is a chronic obstructive lung disease characterized by airways inflammation and hyper reactivity. In most of the patients the condition worsens at night with acute exacerbation being most common. The risk of asthma at night coincides with trough of the circadian rhythms of airway potency, cortisol, epinephrine and sympathetic tone, along with peak of rhythms in airway inflammation, hyper reactivity and cholinergic tone [2,3].

Chronotherapeutics refers to a clinical practice of synchronizing drug delivery in a manner consistent with body's circadian rhythm indicating disease state to produce maximum health benefit and minimum harm [4].Colon drug delivery system is valuable design, when a delay in absorption is therapeutically vital in the treatment of chronic medical conditions like nocturnal asthma. Theophylline possesses good oral bioavailability and adequate colon absorption. Hence it is selected as an ideal candidate for the colon targeted drug delivery system. This system when administered in evening is aimed to achieve an elevated Theophylline levels overnight where the risk of asthma is found to be maximum. Matrix tablets and Compression coated tablets of Theophylline are proposed to be developed by employing guar gum as rate controlled polymer [5].

2. Materials and Methods

Materials: Theophylline, Guargum was obtained from Natco Pharma, Potassium hydrogen ortho phosphate was obtained from Qualigens fine chemicals, Cellulose acetate phthalate was obtained from Burgoyme Burbidges & co, Magnesium stearate and Talc was obtained from S.D Fine chemicals pvt. Ltd. All the other chemicals used were of analytical grade.

Method

From the study of drug properties, it was revealed that, the drug has poor flow properties, so the tablets were prepared by wet granulation technique. Theophylline (200 mg), Guar gum, PVPk-30 sufficient for 50 tablets according to the formula shown in the table 1 were weighed and granulated by using a blend of 1:1 ratio of Iso propyl alcohol and water to form a damp mass and passed through sieve no:16. The granules were dried until constant weight was achieved and passed through sieve no: 44. Then the flow properties of granules were determined and the powder blend was then lubricated with magnesium stearate and talc. The tablets were compressed by using 9 mm round shaped punches on a 16 station rotary tablet punching machine (Cadmach, Ahmedabad). The average hardness of all the tablets was 7-9 kg/cm².

Compression coating:

Half the quantity of coating material was placed in the die cavity and the core tablet was placed at the centre and then the remaining half of the coating material was placed. The tablets were compressed by using 16mm round shaped punches on a 16 station rotary tablet punching machine.

Evaluation of Tablets [6-11]:

The tablets were also subjected various quality control tests such as uniformity of weight, hardness, friability and drug content uniformity.

Uniformity of weight:

According to I.P 20 tablets were selected at random, weighed together and then individually for the determination of uniformity of weight of tablets. The mean and standard deviation were determined. The results were given in Table 1.4.

Hardness: Ten tablets were selected at random and the hardness of each tablet was measured on a Monsanto tablet hardness tester.

Friability:

The friability test was carried out in Roche Friabilator. Ten tablets were weighed (Wo) initially and put in rotating drum. Then, they were subjected to 100 falls of 6 inches height. After the completion of rotations, the tablets were weighed (W). The percent loss in weight or friability (f) was calculated by the formula given below

$$f = (1-W/Wo) \times 100$$

Estimation of drug content:

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to 200 mg was transferred to 250 ml volumetric flask.50 ml of p^H 6.8 phosphate buffer was added and then the solution was subjected to Sonication for a period of about 30 min. The solution was made up to 250 ml with 6.8 phosphate buffer.The solution was filtered and suitable dilutions were prepared with p^H 6.8 phosphate buffer and then drug content was estimated by recording the absorbance at 271 nm by using UV-visible spectrophotometer. The results were given in Table 1.4.

Percent drug content = (drug content/label claim)×100

***In-Vitro* Dissolution Studies**

Dissolution studies were carried out using USPXXII, Basket method (apparatus **I**). The stirring rate was 100 rpm. The tablets were placed in 0.1N Hydrochloric acid for 2 hours then the dissolution medium was replaced with pH7.4 phosphate buffer and tested for 3 hrs. As the average small intestine transit time is about 3 hrs. Then the dissolution medium was replaced with 6.8 pH phosphate buffer and study was continued for a period of 19 hrs. At the regular intervals of time 5 ml of sample was collected and analyzed for drug content. The susceptibility of guar gum to the enzymatic action of colonic bacteria was accessed by continuing the drug release studies in 100 ml of pH 6.8 phosphate buffer saline containing 2% w/v rat caecal contents. The caecal contents were obtained from male albino rats after pretreatment for 7 days with guar gum. Thirty minutes before the commencement of drug release studies two rats were killed by spinal traction. Their abdomens were opened the caecum were isolated, ligated at

both ends, dissected and immediately transferred in to pH 6.8 phosphate buffer saline previously bubbled with co_2 the caecal bags were opened and their contents were individually weighed, pooled and then suspended in PBS to give a final dilution of 2%w/v. continuous supply of co_2 was provided throughout the study period.

Release Kinetics:

As a model dependent approach, the dissolution data are fitted to three popular release models such as zero order, first order, diffusion equations. The order of drug release from matrix systems was described by using zero order or first order kinetics. The mechanism of drug release from matrix systems was by Higuchi or Korsemayer and Peppas equation.

3. Results and discussion

The present study was aimed to develop Colon targeted formulation of theophylline by using guar gum in the form of matrix tablets. FT-IR spectrum of the pure drug by which the compatability of drug to all other excipients were evaluated and found that there is no incompatibility between drug and excipients. Results were shown in Fig 1,2. From the study of guar gum and drug properties (table 2), it was found that both drug and polymer will have poor flow properties. Hence the tablets were prepared by wet granulation method. Granules were evaluated for flow properties and results indicated that there was increase in these properties when compared to pure drug.(table 3). The matrix tablets were prepared by using maximum force of compression and the hardness was found to be 7-9 Kg/cm^2. All the prepared tablets were evaluated for weight variation, friability and Assay. Results were found to be within the limits and indicated in table-4. The formulations were subjected to drug release studies in varied dissolution media namely 0.1NHCl (for 2 hrs), p^H 7.4 phosphate buffer (for 3 hrs) and p^H 6.8 phosphate buffer (till the end). The formulations F1, F2 containing 60, 80 mg of guar gum released more amount of drug in 0.1N HCl and the release was not extended for 24 hrs. So, proportion of guar gum was further increased in F3. In this formulation, the release was not controlled in 0.1 N HCl. Hence in formulation F4, the proportion of guar gum was increased much more and prepared by employing 120 mg of guar gum. In this formulation the drug released in 0.1NHCl was only 28.9 % as shown in table 4. The release profile was extended up to the desired time. Hence F4 was selected for compression coating with CAP to decrease the release rate in 0.1NHCl. Two formulations F5, F6 were prepared with varying concentrations of CAP.

In F6 the percentage of drug released in 0.1 N HCl was very less (only 0.7%) upto the period of 5 Hrs in p^H 7.4 phosphate buffer. After incorporation of 2% rat caecal content in the dissolution medium the drug release was increased and release was extended up to 24 hrs as shown in table-5 and figure 3,4, due to the degradation of guar gum by the rat caecal content in the medium. Drug release kinetics revealed that F6 follows Zero Order Kinetics with R^2=0.98. Diffusional exponent 'n' and mechanism of diffusional release from swellable controlled release systems was found to be Super Case-2 transport. Results are shown in figure no-5-8.

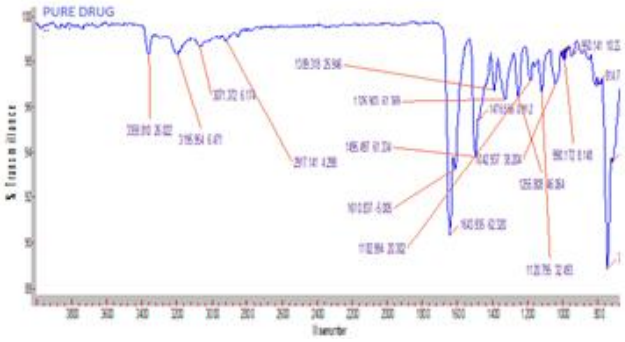


Figure 1: FIG-1 FT-IR spectrum of the pure drug

Figure 2: FT-IR spectrum of pure drug and excipients

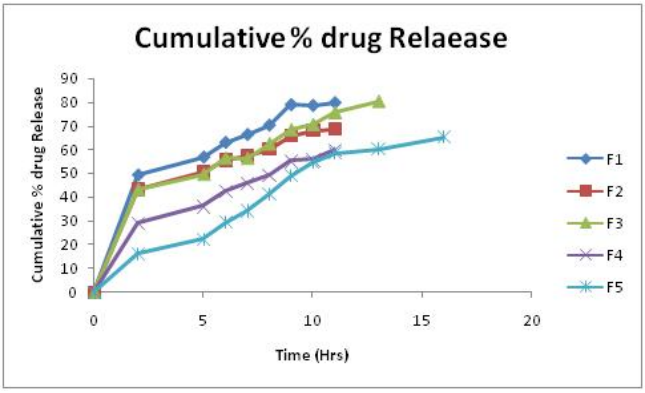


Figure 3: Cumulative drug release plot for Compression Coated Tablet (Cumulative % drug release Vs Time)

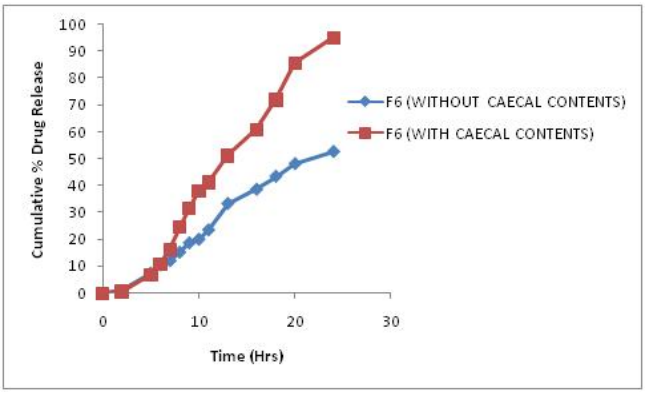


Figure 4: Comparision of F6 (with and without cecal contents) (Cumulative % drug release Vs Time)

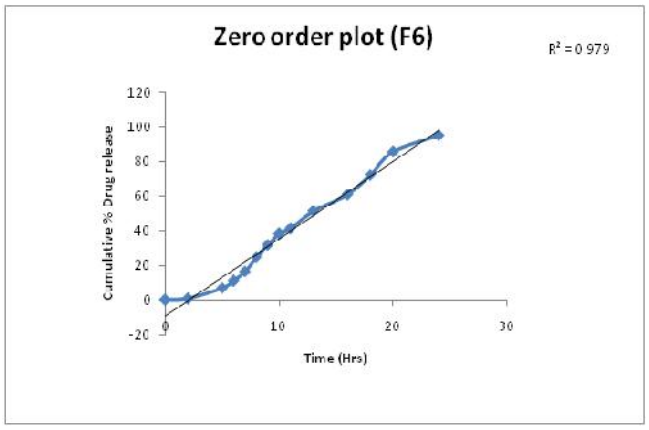


Figure 5: Zero Order plot for Compression Coated Tablet (Percent drug released Vs Time)

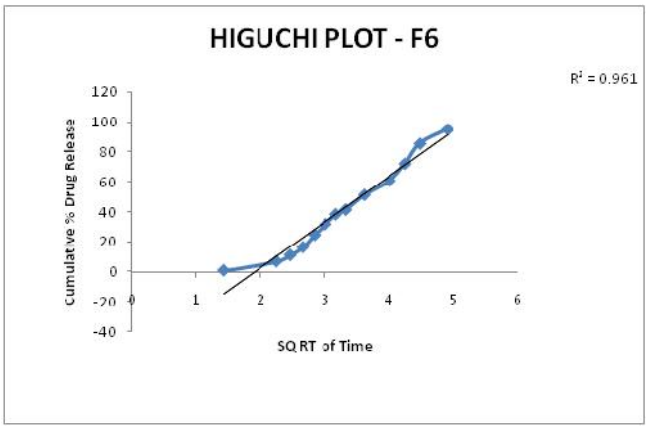


Figure 7: Higuchi's plot for Compression Coated Tablet (% drug release Vs Sq.rt of Time)

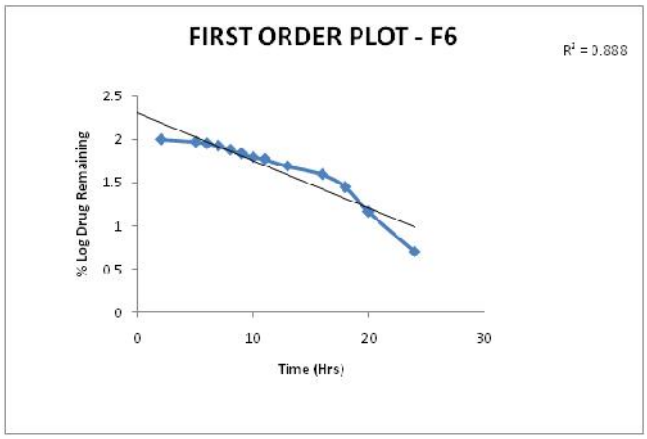


Figure 6: First Order plot for Compression Coated Tablet (%log drug remaining Vs Time)

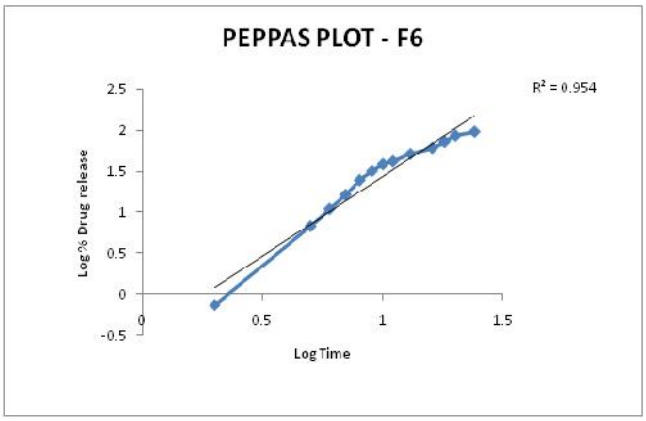


Figure 8: Peppas plot for Compression Coated Tablet (Log% drug release Vs log Time)

Table 1: Formulae of Theophylline CTDDS Prepared With Guar Gum

Ingredient (mg)	F1	F2	F3	F4	F5	F6
Theophylline	200	200	200	200	200	200
Guar gum	60	80	100	120	120	120
Pvp K-30	10	10	10	10	10	10
Magnesium stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Cellulose acetate phthalate	_	_	_	-	200	300
Total weight(mg)	272	292	312	332	532	632

Table 2: Study of Drug and Polymer Properties

S.No	Parameter	Theophylline	Guar gum
1.	Bulk density	0.625 gm/ml	0.555 gm/ml
2.	Carr's index	27.2 %	21.7 %
3.	Hausner's ratio	0.72	0.782
4.	Angle of repose	45^0	38^0

Table 3: Characterization of Powder Blend

S.N	Parameter	F1	F2	F3	F4	F5	F6
1.	Granule density(mg/ml)	0.23	0.28	0.34	0.34	0.32	0.29
2.	Carr's index	0.9 %	0.8 %	1.1 %	1.1 %	1.0%	0.9
3.	Hausner's ratio	14	14.5	15	15	14.5	15
4.	Angle of repose	18^0	19^0	17^0	17^0	19^0	15

Table 4: Evaluation of Different Formulations

Formulation	Weight variation (mg)	Hardness (Kg/cm^2)	Drug content (%)	Friability
FI	272±0.3	7.0±0.22	98.0	0.89
F2	292±2.01	7.5±0.26	97.0	0.95
F3	312±1.1	7.2±0.46	98.5	0.83
F4	412±1.3	7.5±0.45	99.1	0.94
F5	512±1.02	7.5±0.63	98.9	0.86
F6	612±1.6	7.5±0.56	99.2	0.84

Table 5: In-Vitro Dissolution Profile

Dissolution Medium	Time In hrs	Cumulative % drug release of all formulations						
		F1	F2	F3	F4	F5	F6 (without caecal content)	F6 (with caecal content)
Simulated Gastric Fluid	02	49.31	43.15	43.2	28.97	16.3	0.82	0.738
Simulated Intestinal Fluid	05	56.82	50.76	49.6	36.18	22.4	7.54	6.79
Simulated Colonic Fluid	06	62.96	55.63	56.4	42.41	29.5	10.68	10.96
	07	66.25	57.62	56.3	45.91	34.3	12.17	16.25
	08	70.21	60.30	62.4	49.11	41.2	15.30	24.54
	09	78.81	65.79	68.3	55.18	49.2	18.80	31.60
	10	78.46	68.21	70.4	55.66	54.6	20.12	38.23
	11	79.651	68.60	75.5	59.84	58.6	23.6	41.29
	13	–	–	80.2	–	60.4	33.4	51.22
	16	–	–	-	–	65.3	38.7	60.81
	18	–	–	-	–	-	43.5	72.12
	20	–	–	-	–	-	48.2	85.53
	24	–	–	-	–	-	52.7	95.01

4. Conclusion

Matrix tablets and compression coated tablets containing various proportions of guar gum were prepared and subjected to *in-vitro* drug release studies. Theophylline matrix tablets containing 60, 80, 100mg guar gum was found to be unsuitable as they released more amount of drug in 0.1NHcl. Though matrix tablets containing 120mg guar gum were prepared and release rate was extended but failed to stop the release of drug in 0.1N HCl. Hence this formulation was modified by compression coating with CAP. In presence of rat caecal content 95%of the drug was released in 24 hrs. Hence we concluded that matrix tablets prepared with guargum which are compression coated with CAP were found to be suitable for chronotherapeutic delivery of theophylline to treat the symptoms of nocturnal asthma.

5. References

[1] N.K.Jain, Advances In Controlled and Novel Drug Delivery., First Edition, CBS publishers& distributors, New Delhi, Pg. No: 89-112.

[2] Vyas and Khar, Controlled Drug Delivery Concepts & Advances.,First Edition ,Vallabh prakashan publishers, Pg No: 218-253.

[3] The United States Pharmacopoeia. USP 27, 2004; Asian Edition 16.

[4] Medical Publishers (p) Ltd, 5th edition, 201-204.

[5] S.Sarasija and A. Hota, Indian Journal of Pharmaceutical Sciences., 2000, 62(1): 1-8.

[6] H.N Shiva Kumar, Sarasija Suresh and B.G.Desai, Indian Journal of Pharmaceutical sciences., 2007, 69(1), 73-79.

[7] Leon Lachman, Herbert A. Lieberman, The Theory and Practice of Industrial Pharmacy., Third edition, 430-436.

[8] Michael E Aulton,Pharmaceutics ,The Science of Dosage Form Design Second Edition, Harcourt Publishers Limited, London 2002.

[9] D. M. Brahmankar, Sunil B. Jaiswal, Biopharmaceutics and Pharmacokinetics A Treatise, First Edition, Vallabh Prakashan Publishers.

[10] Yiew Chein, Novel Drug Delivery Systems, second edition, marcel dekker 2003.

[11] Remington, The Science and Practice Of Pharmacy., B.I.Publications Pvt Ltd., 21st edition, vol II , 1373-1374.

[12] KD Tripathi, Essentials of Medical Pharmacology., Jaypee Brothers,