WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 4, 1281-1291. Research Article ISSN 2277 – 7105

DEVELOPMENT AND EVALUATION OF A SUSTAINED RELEASE MICROENCAPSULES OF THEOPHYLLINE

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Article Received on
30 April 2014,

Revised on 19 May 2014,
Accepted on 14 June 2014

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ABSTRACT

A sustained release dosage form of Theophylline in the form of microspheres was prepared by the solvent evaporation method. Solvent evaporation method was attempted in oily manufacturing vehicles. Different polymers such as Ethyl Cellulose, *Eudragit® RS PO, Eudragit® RL PO, Eudragit® S 100,Eudragit® RL 100* and different combinations of these polymers were tried and the resulting microspheres were evaluated for entrapment efficiency, drug loading and percent yield of the process and dissolution profile. The aim was to develop a multiparticulate sustained release drug delivery system to be converted to a orally disintegrating formulation, so that patient suffering from dysphagia, stroke, difficulty in swallowing, paediatric, geriatric patients etc. may consume it easily and long term therapy may be maintained as required in patients suffering from osteoarthritis, diabetes.

Keywords: Theophylline, microspheres, solvent evaporation, taste masking, orally disintegrating, factorial design.

INTRODUCTION

Much of the research efforts in developing novel drug delivery systems have been focused on *per oral* sustained or controlled release dosage forms. Among the oral dosage forms, multiunit formulations such as microparticles have become more popular becauseof their advantages over single unit dosageforms. They may be spread out more uniformlyin the gastrointestinal tract leading to moreuniform drug absorption, reduced localirritation, and decreased retention of polymericmaterials. They have been reported to berelatively

unaffected by digestive tractactivities, causing less variation in the resultsof pharmacokinetic studies. Attention hasbeen recently devoted to liquid sustainedrelease preparations that are more palatable topaediatric and convenient to geriatric patients. This formulation may also help in givingdrug delivery to patients suffering fromdysphagia; stroke where consuming a tabletwill be very difficult. This problem becomesmore acute for the administration of sustainedaction dosage forms due to the increase in thevolume of the delivery system and necessity totake it intact without breaking. Formulating such systems as an orally disintegrating tablet presents anovel means of circumventing the potentialproblems associated with the administration ofsuch system. Multiparticulate systems could also be formulated as an orally disintegrating tablet allowing ease of swallowing and flexibility inthe dose adjustment for pediatric and geriatric patients. Many techniques for thepreparation of micro capsules have been developed and reviewed.Theophylline, a xanthine bronchodilator, is used in a dose of 100mg, 200mg 300mg, 400mg, 450mg t.i.d to prevent and treat wheezing, shortness of breath, and difficulty in breathing caused by asthma, chronic bronchitis, emphysema, and other lung diseases. Amongst the currently available means of treatment, oral dosage forms are associated with lag time and delayed onset of action. However, aerosols and parenterals have rapid onset of action but strongly affect patient compliance. Theophylline is available as conventional as well as sustained release tablets, syrups, elixirs, capsules and injections for the use by all age groups. However it is not yet marketed as mouth disintegrating tablets. Also, Asthmatic patients have to strictly follow daily dosage regimen for preventing occurrence of acute attacks. Hence, possibilities of missing out the doses should be minimized. Theophylline is also used to treat breathing problems in pediatric patients. Thus, an attempt was made to prepare taste masked sustained releasemicrospheres of Theophylline which would then be incorporated in orally disintegrating tablets to improve patient compliance. This drug delivery system would be an effective alternative for administration of theophylline.[1,2,3,4,5,6] Hence the aim of investigation was to formulate effective, palatable fast disintegrating tablets of theophylline for target patients like pediatrics.

MATERIALS

The drug Theophylline was procured from Glenmark Ltd, Mumbai. The polymer Ethyl Cellulose, Eudragit® RS PO, Eudragit® RL PO, Eudragit® S 100, Eudragit® RL 100 were received as a gift sample from Evonik Industries, Mumbai. All the other chemicals used were of analytical grade.

METHOD

Preformulation

The drug was identified by means of melting point, colour reaction and FTIR. The physical characterization of the drug was carried out. The pH solubility profile was also obtained. The interaction between the drug and polymer was assessed by means of differential scanning calorimetry.[7,8]

Formulation

The drug was formulated into microspheres which helped in masking the highly bitter taste of theophylline.

Preparation of Microspheres

Theophylline microspheres were prepared by solvent evaporation technique. The polymer Ethyl cellulose was dissolved in organic solvent by using a magnetic stirrer (REMI, Mumbai). Powdered theophylline was dispersed in the polymeric solution. The polymeric solution was then poured in liquid paraffin while stirring by over head mechanical stirrer (VEEGO, Mumbai). Stirring was continued until complete evaporation of organic solvent took place resulting in microspheres formation. The microspheres obtained were filtered under suction. The filtrate was evaluated for the presence of drug by extraction with water. The microspheres were washed with 0.5% sodium lauryl sulphate and dried in ovenat 60°C for one hour. The microspheres were then passed through mesh # 44.[9, 10, 11, 12, 13]

Optimization of the process

The method was optimized for various processing variables, viz; type of organic solvent, volume of liquid paraffin, speed of agitation, duration of stirring and drug: polymer ratio. The resultant microspheres were subjected to particle size distribution studies and *in vitro* drug release studies. Table 1 gives trials conducted with different organic solvents. The optimization was carried out for various parameters viz. duration of stirring, speed of stirring, volume of liquid paraffin and drug polymer ratio.[14, 15] Table 2

Table 1 Formulations trials for microspheres using different organic solvents

Ingredients	F-1	F-2
Theophylline	1g	1g
Ethyl Cellulose	1g	1g
Isopropyl alcohol	10ml	-
Acetone	-	10ml
Liquid paraffin	60ml	60ml
Speed	700 rpm	700 rpm
Duration	45mins	45mins

Table 2 Optimization of microsphere formula

Optimization parameter	Formulation	Value
Duration of stirring (In 60 ml liquid paraffin and 700 rpm)	F2	45 mins
	F2 a	60 mins
	F2 b	90 mins
Speed of stirring (for one and half hour i.e. 90 min and 60 ml liquid paraffin)	F2 b1(i.e. F15b)	700 rpm
	F2 b2	900 rpm
	F2 b3	1200 rpm
	F2 b4	1400 rpm
	F2 b5	1600 rpm

Further F2b5 formulation was optimized using two factors speed of stirring and volume of liquid paraffin. The particle size and yield was considered as response. A 3^2 factorial design was carried out using Design Expert 8.0 software Table 3 and 4.

Table 3 Factors, Responses and levels

Levels / Factors	-1	0	+1
Liquid paraffin(X1)	40ml	50ml	60ml
Speed (X2)	1400 rpm	1600 rpm	1800 rpm
Response (Y)	Particle size (Y1)	Yield (Y2)	-

Table 4 Optimization formulations

Ingredients	A1	A2	A3	A4	A5	A6	A7	A8	A9
	++	- -	+-	-+	00	+0	0+	-0	0-
Theophylline (gms)	1	1	1	1	1	1	1	1	1
Ethyl cellulose (gms)	1	1	1	1	1	1	1	1	1
Acetone (ml)	10	10	10	10	10	10	10	10	10
Liquid paraffin (ml)	**60**	**40**	**60**	**40**	**50**	**60**	**50**	**40**	**50**
Speed (rpm)	**1800**	**1400**	**1400**	**1800**	**1600**	**1600**	**1800**	**1600**	**1400**
Duration of stirring (mins)	90	90	90	90	90	90	90	90	90

Preparation of sustained release microspheres

The optimized formula was tried with different sustained release polymers to assess the suitability of the formulation for sustained release. [16, 17] Also varying levels of finalized polymer were tried out Table 5 and 6.

Table 5 Effect of various sustained release polymer

Ingredients	A6 a	A6 b	A6 c	A6 d
Theophylline	1g	1g	1g	1g
Ethyl cellulose	1g	-	0.5g	0.4g
Eudragit RS 100	-	0.5g	-	-
Eudragit RL 100	-	0.5g	0.5g	-
Eudragit S 100	-	-	-	0.2g

Table 6 Effect of various levels of polymer Ethyl cellulose

Ingredients	A6 a1	A6 a2	A6 a3
Theophylline	1g	1g	1g
Ethyl cellulose	1g	0.5g	0.4g
Acetone	10ml	10ml	10ml
Liquid paraffin	60ml	60ml	60ml
Speed	1600 rpm	1600 rpm	1600 rpm
Duration	90mins	90mins	90mins

Evaluation of microspheres

1) Percentage yield

The percentage yield of microspheres was calculated using the following formula:

% Yield = (Practical Yield x 100) / Theoretical Yield

2) Drug Entrapment efficiency

The amount of drug entrapped was estimated by crushing the spherules and extracting with water. The concentration was determined spectrophotometrically against appropriate blank. The % DEE was calculated using the following formula:

% DEE = (Amount of drug actually present x 100) / Theoretical drug expected

3) Particle Size Analysis

The particle size analysis and particle size distribution of microspheres was carried out by means of optical microscopy method under 10 x 10 magnifications.

4) Scanning Electron Microscopy Analysis

The microspheres were characterized further using scanning electron microscopy. Shapes and surface characteristics of the microspheres were investigated and photographed. The coated microspheres were then placed in SEM (Model: JEOL JSM-5400 SEM) and the images were procured using Unimation Prime SEM software.

5) Subjective Taste Evaluation

Taste evaluation was done using the time intensity method on 10 healthy human volunteers from whom informed consent was first obtained. The microspheres equivalent to 100 mg of theophylline was held in the mouth for 60 seconds and then spat out. Bitterness was recorded at different time intervals, according to the bitterness intensity scale from 0 to 3 where 0, 1, 2, and 3 indicate bland taste, Partially masked, masked but an after taste and strong bitterness respectively. [18, 19]

6) *In Vitro* Drug Release Studies

Release of Theophylline from the microspheres was determined using USP type II apparatus at 50 rpm using 0.1N HCl for the first one hour and phosphate buffer pH 7.4 for the next six hours. The drug: polymer ratio was varied to achieve the USP specifications for Extended release Theophylline capsule. [20, 21]

7) Flowability of Microspheres

The static angle of repose was measured according to the fixed funnel and free standing cone method. The bulk density of the mixed powders before compression was calculated by determining the Hausner's ratio and Carr's index.

RESULTS AND DISCUSSIONS

Based on IP limits we can say that the drug has good solubility in water and organic solvents. pH solubility profile showed that the drug showed good solubility at pH 4 and 11 (figure 1). Solubility at gastric pH indicated that any acid soluble polymer can be used for taste masking. Also, the solubility profile indicated solubility of the drug over the entire gastro intestinal tract thus justifying its use in sustained release formulations. The DSC results indicated that

the drug showed an endotherm at 271 ^{o}C (figure 2). The mixture of drug and polymer also showed a distinct drug peak without change in position, which indicated that there was no interaction between the drug and the polymer.

For preparing microspheres, various trials were conducted and final selection was done on the basis of particle geometry and size distribution. The organic solvent evaporation method using iso propyl alcohol (F1) was not successful in formation of microspheres; while method using acetone (F2) yielded spherical particles as desired. Thus the method using acetone and 60 ml of liquid paraffin, stirred at 1600 rpm for 90 minutes duration yielded best microspheres of particle size 351± 10 µ. The final formulation containing Theophylline : Ethyl cellulose in the ratio 1:0.4 gave the desired release profile (Figure 3) and was subjected to assay, taste evaluation, flow characteristics (Table 7) and scanning electron microscopy and the results are as shown in Table 4. The yield was 96.57 ± 2 % (figure 5) and the assay results showed entrapment of 99.71 ± 0.53 % drug. No drug release was observed in simulated salivary fluid from microspheres, indicating complete masking of bitter taste has been achieved. Also, this was confirmed by subjective taste evaluation in healthy volunteers. The scanning electron microscopy was carried out for the final formula and the results were as shown in Figure 4. The photographs confirmed the spherical nature of microspheres.

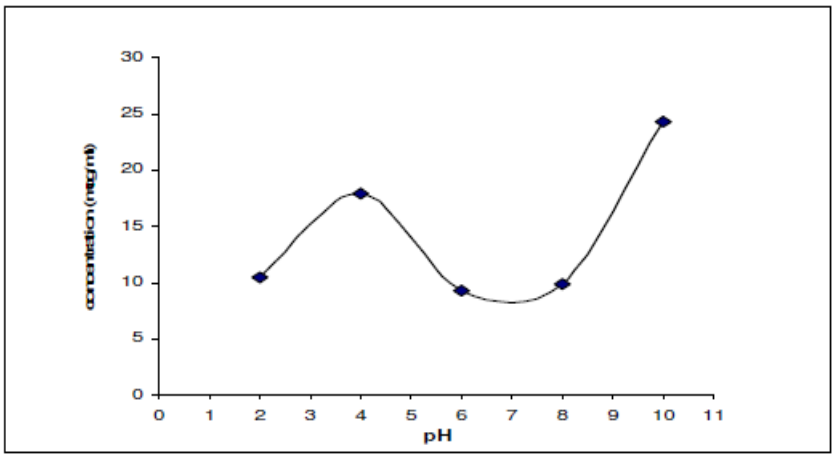


Figure 1: pH solubility profile curve

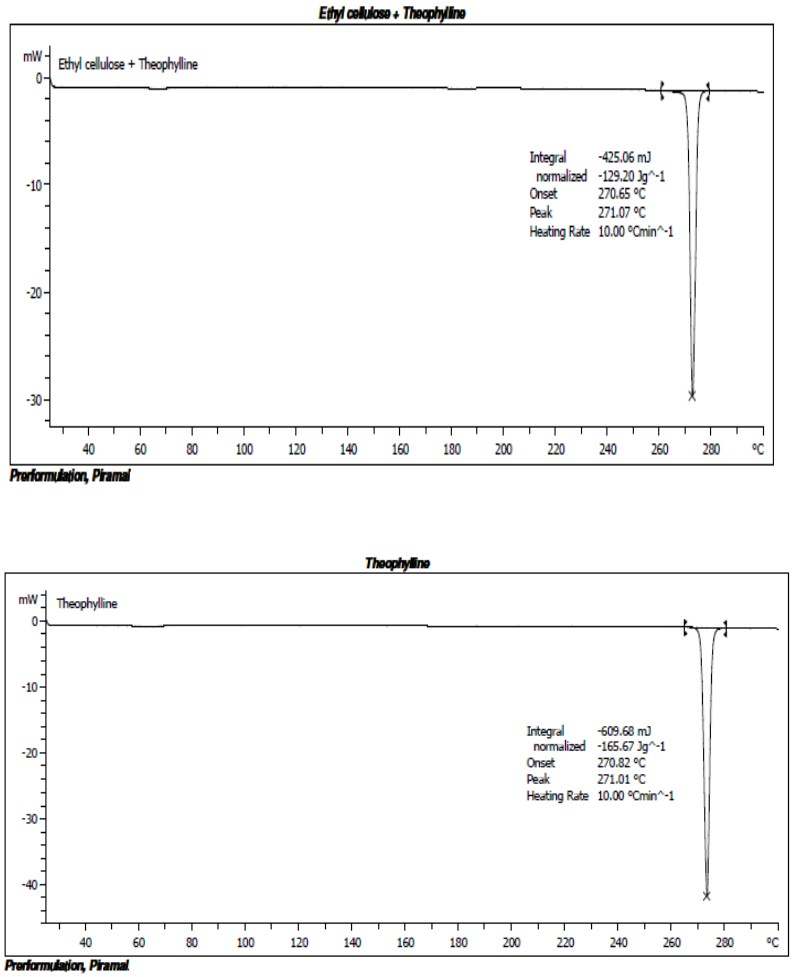


Figure 2: DSC Thermograms a) Thermogram of plain Theophylline b) Thermogram of Theophylline:Ethyl Cellulose (1:0.4)

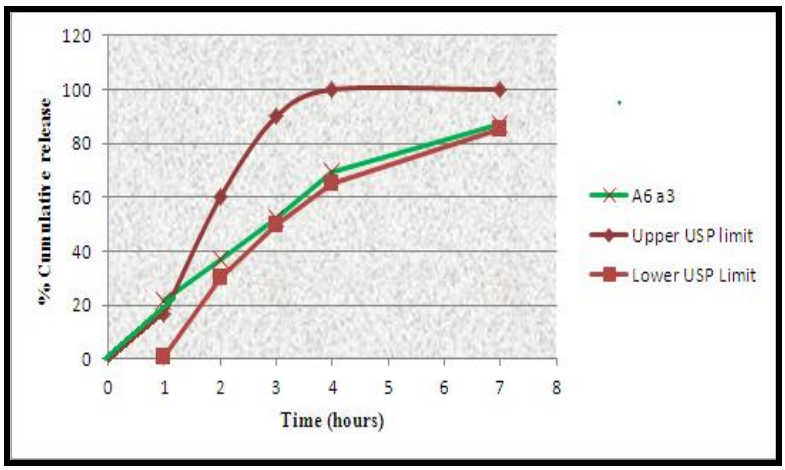


Figure 3: Drug release profile of batch A6 a3 (1:0.4) complying with the USP limits of Theophylline sustained release capsules

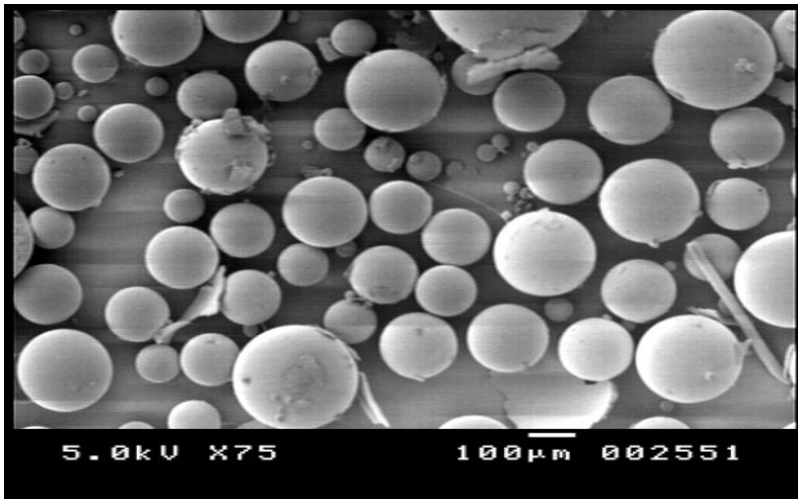
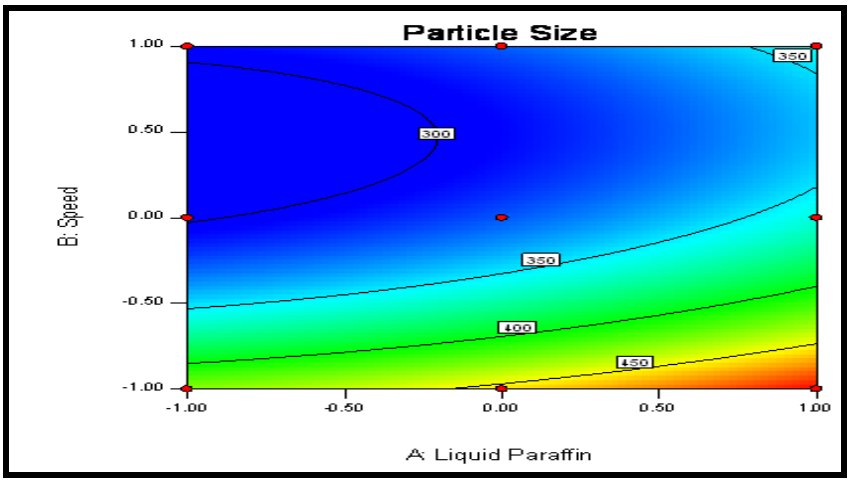


Figure 4: SEM image of microspheres



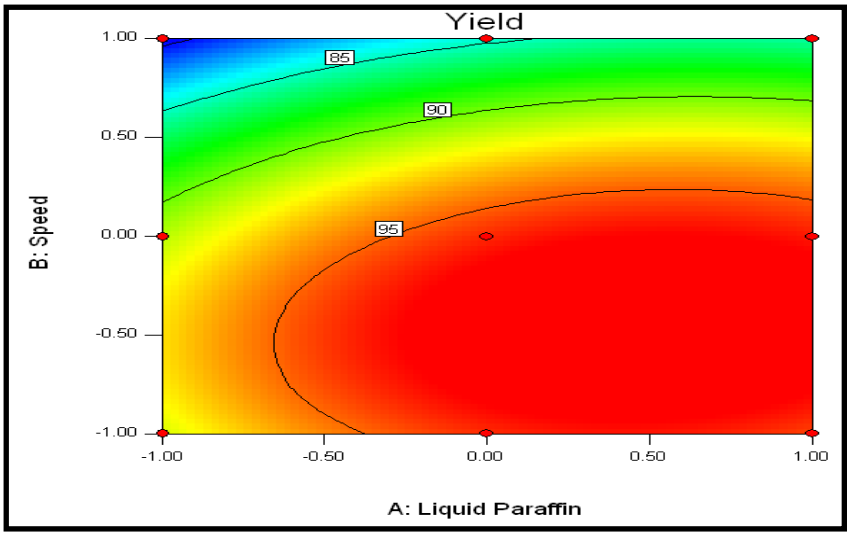


Figure 5: Contour plots a) For particles size as response b) For yield as response

Table 7 Flow properties

Parameter	Result
Taste	Good
Bulk density	0.53768± 0.003579 g/ml
Tap density	0.68432± 0.024537 g/ml
Compressibility	23.476± 1.8%
Hausner ratio	1.27 ± 0.15
Angle of repose	41.06 ± 0.66°
Flow rate	0.31 ± 0.01g/sec
Particle size diameter	351µ
Yield	96.01%

CONCLUSION

The method of volatile solvent evaporation emulsification was successful in yielding microspheres which made the drug palatable. The method using acetone/liquid paraffin gave better results as compared to that using isopropyl alcohol. The trial conducted for 90 minutes at 1600 rpm using 60 ml of liquid paraffin resulted into spherical microspheres of particle size 351 ± 10 µ. The formulation containing Theophylline : Ethyl cellulose in the ratio of 1: 0.4 produced not less than 87 % release at the end of 7 hours.

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