

Fast Disintegrating Palatable Theophylline Tablets For Pediatrics

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Abstract

In the present scenario, there is an ever-increasing demand for more patient compliant dosage forms. One important innovation in this direction considering pediatric patients is the development of fast dissolving/disintegrating oral dosage forms that dissolve or disintegrate instantly upon contact with recipient's tongue or buccal mucosa. Theophylline, a xanthine bronchodilator, is used to prevent and treat wheezing, shortness of breath, and difficulty in breathing caused by asthma, chronic bronchitis, emphysema, and other lung diseases. It finds application in pediatrics but lacks patient compliance due to its bitter taste. Therefore, to provide this drug in a more accessible and patient compliant form, in the present study an attempt has been made to mask its bitter taste and formulate it into mouth disintegrating tablet. The fast disintegration was achieved by incorporation of subliming agent like camphor. Tablet weight variation, hardness, disintegration time, wetting time and friability were measured. [1- 6]

INTRODUCTION

Many pharmaceutical dosages are administered in the form of pills, tablets, capsules, and liquids. However, some patients, particularly pediatric have difficulty swallowing or chewing solid dosage forms. Many pediatric patients are unwilling to take these solid preparations due to fear of choking. Syrups are best for pediatrics but they are bulky and drugs are not as stable in liquid form as in solid form like tablets. Also, there is risk of spillage with respect to liquid dosage forms, especially during traveling. In order to assist these patients, several fast-dissolving drug delivery systems have been developed. Fast disintegrating tablets (FDTs) disintegrate rapidly in the saliva without the need for water. The major advantage of the FDT formulation is that it combines the advantages of both liquid and conventional tablet formulations, while also offering advantages over both traditional dosage forms. It provides the convenience of a tablet formulation, while also allowing the ease of swallowing provided by a liquid formulation. FDTs allow the luxury of much more accurate dosing than the primary alternative, oral liquids. [1,2,3,4,5, 6]

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 improve the onset of action of theophylline used commonly in the treatment of asthma and to improve patient compliance. This drug delivery system would be an effective alternative for administration of theophylline. But the drug has a high bitter taste which makes the dosage form non compliant. So this necessities taste masking to be carried out during the formulation process. [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 Cipla Ltd, Mumbai. The polymer Eudragit E 100 was obtained from

Degussa Ltd, Mumbai. All the other chemicals used were of analytical grade.

METHOD

PREFORMULATION

The drug was identified by means of melting point, color 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 Eudragit E 100 was dissolved in organic solvent by using a magnetic stirrer (REMI, Mumbai). Powdered theophylline was dispersed in the liquid paraffin containing Span 80. 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 petroleum ether and dried in desiccator. The microspheres were then passed through mesh # 44.

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 and different volumes of liquid paraffin. Also different drug: polymer ratios were tried out.

Figure 1

Table 1: Formulations trials for microspheres using different organic solvents

Ingredients	F -1	F - 2
Theophylline	1 g	1 g
Acetone	-	10 ml
Isopropyl alcohol	10 ml	-
Eudragit E 100	1 g	1 g
Liquid paraffin	50 ml	50 ml
Stirring speed	900 rpm	900 rpm
Duration of stirring	60 minutes	60 minutes

Figure 2

Table 2: Formulations trials for microspheres using different speed of rotation

Ingredients	F - 2	F - 2a	F - 2b	F - 2c
Theophylline	1 g	1 g	1 g	1 g
Acetone	10 ml	10 ml	10 ml	10 ml
Eudragit E 100	1 g	1 g	1 g	1 g
Liquid paraffin	50 ml	50 ml	50 ml	50 ml
Stirring speed	900 rpm	1200 rpm	1400 rpm	1600 rpm
Duration of stirring	60 minutes	60 minutes	60 minutes	60 minutes

The formulation showing best results (F 2) was further optimized for the speed of stirring, by subjecting it to 900, 1200, 1400 and 1600 rpm speeds of rotation. The trials were also conducted for 45, 60 and 90 minutes to optimize the duration of stirring. Different volumes of liquid paraffin were also tried viz. 40 , 50 and 60 ml. The trials were finally conducted with different drug: polymer ratios viz. 1:1, 1:0.5 and 1:0.25 to optimize the ratio. Various evaluations were carried out for the microspheres.

INCORPORATION INTO FAST DISINTEGRATING TABLET

Tablets were prepared by direct compression process using sublimable components viz. camphor and ammonium bicarbonate. Four different tablets having different combination of sublimable excipients were prepared [Table - 3]. Excipients were screened through sieve 44 and mixed with microspheres and compressed into tablets. Tablets were subjected for drying at a temperature of 50 o to facilitate the volatilization of sublimable components added. The tablets were weighed at regular intervals until constant weight was achieved ensuring complete removal of the sublimable component. The tablets were then subjected to the various evaluations.

Figure 3

Table 3: Various formulation trials for fast disintegrating tablet of Theophylline

Ingredients	A 1 (mg)	A 2 (mg)	A 3 (mg)	A 4 (mg)	A 5 (mg)	A 6 (mg)
Microspheres equivalent to 100 mg	160	160	160	160	160	160
Microcrystalline cellulose	-	40	40	40	-	40
Camphor	-	-	24(15 %)	-	24(15 %)	24(15 %)
Ammonium bicarbonate	-	-	-	24(15 %)	24(15 %)	24(15 %)
Sodium saccharin	0.5	0.5	0.5	0.5	0.5	0.5
Trusil Flavour	0.05	0.05	0.05	0.05	0.05	0.05
Total weight	160.55	200.55	225.05	224.55	208.55	248.55

EVALUATION

EVALUATION OF MICROSPHERES [,]

1) Percentage yield

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

$$\% \text{ Yield} = (\text{Practical Yield} \times 100) / \text{Theoretical Yield}$$

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:

$$\% \text{ DEE} = (\text{Amount of drug actually present} \times 100) / \text{Theoretical drug expected}$$

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 magnification.

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) In Vitro Taste Evaluation

In vitro taste was evaluated by determining drug release in simulated salivary fluid (SSF) (pH 6.2) to predict release in the human saliva. Microspheres, equivalent to 100 mg of

theophylline, were placed in 10 ml of SSF and shaken for 60 seconds. The amount of drug released was analyzed at 270 nm.

6) In Vivo 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. The method was approved by institutional ethical committee.

6) In Vitro Drug Release Studies

The drug release from the microspheres was studied using 0.1 N HCl for one hour using the paddle method under sink conditions. Accurately weighed sample of microspheres equivalent to 100 mg of drug was added to dissolution medium kept at $37 \pm 0.5^\circ\text{C}$. After suitable dilution, the samples were analyzed spectrophotometrically at 270 nm.

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.

EVALUATION OF TABLETS [,,,,,]

1) Hardness

The fracture strength, which is defined as the force, required to break a tablet by radial compression, was measured with a Monsanto tablet hardness tester.

2) Friability: Friability was determined using Roche Friability tester.

3)Wetting time

To measure tablet wetting time, a piece of tissue paper placed in a small culture dish (i.d.= 5 cm) containing 6 ml of water, a pre-weighed tablet was put on the paper, and the time for complete wetting was measured.

4) In vitro disintegration

Tablet was placed in 6 ml of simulated saliva and the time required for the tablet to disintegrate into a dispersion was noted down.

5) In vivo disintegration

The test was carried out in 5 healthy volunteers from whom informed consent was first obtained. The tablet was held in the mouth for 60 seconds and then spat out. The time required for disintegration was noted down. The method was approved by institutional ethical committee.

5) In vitro drug release

The drug release from the tablet was studied using 0.1 N HCl for one hour using the paddle method at $37 \pm 0.5^\circ\text{C}$ under sink conditions. After suitable dilution, the samples were analyzed spectrophotometrically at 270 nm.

6) Assay

5 tablets were crushed and powder equivalent to one tablet was taken and extraction was carried out. The concentration was determined spectrophotometrically against appropriate blank

STATISTICAL ANALYSIS

The drug release of the best formulation was compared with that of the marketed immediate release formulation of dose 100 mg and student t test was applied at 0.05 level of significance for comparison.

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. 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 270°C . 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 40 ml of liquid paraffin, stirred at 1600 rpm for 90 minutes duration yielded best microspheres of particle size $315 \pm 10.84 \mu$. The final formulation was subjected to assay, taste evaluation, scanning electron microscopy and particle size analysis and the results are as shown in Table 4. The particle size distribution was as shown in Fig 1. The yield was $85 \pm 2 \%$ and the assay results showed entrapment of $93.77 \pm 0.53 \%$ 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 in vivo taste evaluation in healthy volunteers as shown in Table 5. The scanning electron microscopy was carried out for the final formula and the results were as shown in Fig 2. The photographs confirmed the spherical nature of microspheres.

Figure 4

Table 4: Evaluation results of Microspheres

Evaluation Test	Result
Percentage Yield	$85 \pm 2 \%$
Drug Entrapment Efficiency	$93.77 \pm 0.53 \%$
SEM	Spherical shape
Particle Size	$315 \pm 10.84 \mu$
In vitro evaluation	No drug detected in the sample
In vivo evaluation	Was palatable

Figure 5

Figure 1: Particle size distribution of Theophylline microspheres

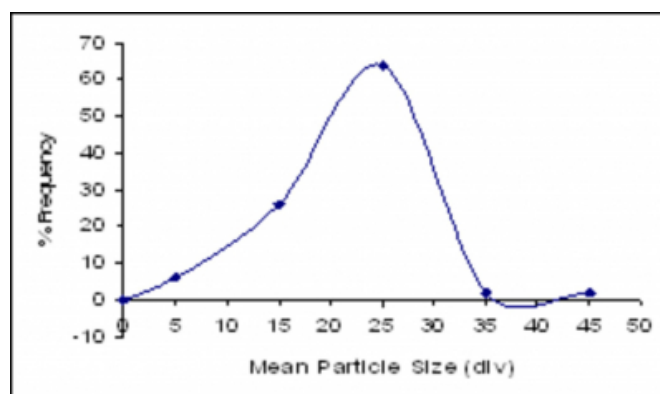


Figure 6

Figure 2: Scanning electron microscopy image of Theophylline microspheres

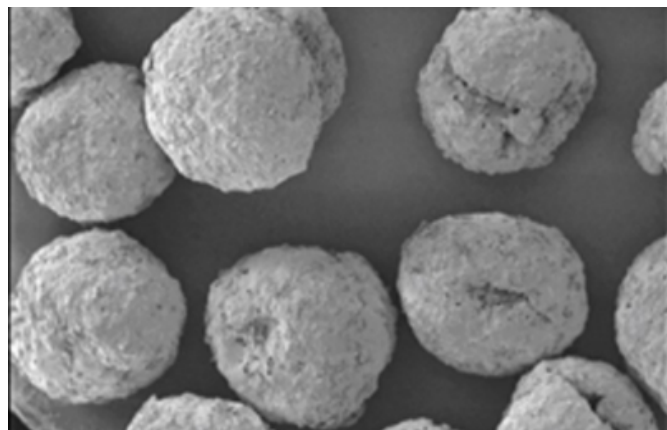


Figure 7

Table 5: Subjective taste evaluation of Theophylline microspheres of different drug : polymer ratio

Volunteer	1	2	3	4	5	6	7	8	9	10
(1:1)	0	0	0	0	0	0	0	0	0	0
(1:0.5)	0	0	0	0	2	0	0	0	0	0
(1:0.25)	3	3	3	1	3	3	3	2	3	3

3 = No change (Highly bitter), 1 Partially masked (less bitter),
2 Masked but an aftertaste, 0 = Completely masked

Drying of the prepared tablets at 50 °C rendered them porous by allowing the volatile components to escape through the tablet matrix. The tablets were found to be porous after drying thus facilitating their easier breakup in water. The formulations containing only microcrystalline cellulose, only camphor, only ammonium bicarbonate showed longer disintegration times greater than one minute. The combinations of microcrystalline cellulose with subliming agents decreased the disintegration time. However, the formulation containing microcrystalline cellulose as filler and camphor as subliming agent (A 3) showed minimum disintegration time which could be attributed towards disintegrating property of microcrystalline cellulose and porosity imparted due to camphor sublimation. The results for various evaluation tests are given in Table 6.

Figure 8

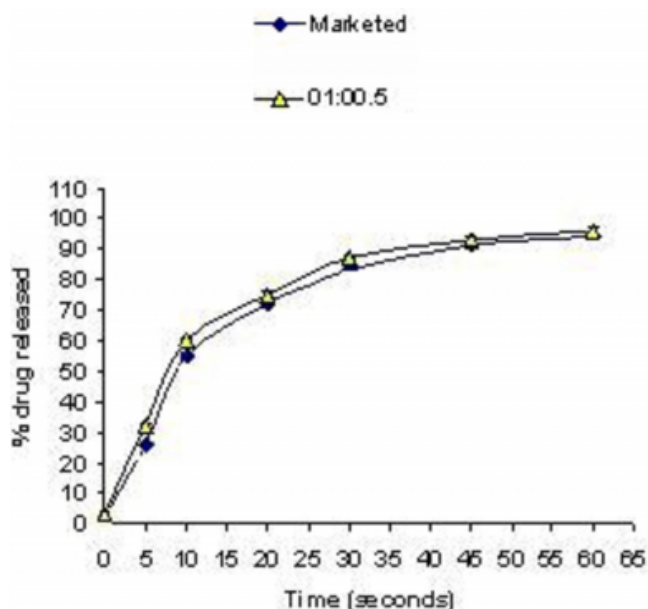
Table 6: Evaluation results of tablets

Evaluation Test	Result
Hardness	3 ± 0.5 kg/cm
Friability	0.7 ± 0.1 %
Wetting time	20 ± 2 seconds
In vitro disintegration time	25 ± 2 seconds
In vivo disintegration time	30 ± 3 seconds
In vitro drug release	87 ± 3 % at the end of 30 minutes
Assay	99 ± 0.5 %

Dissolution studies for comparative evaluation of marketed and fast disintegrating tablets were conducted and showed no differences between release rates as shown in Fig 3.

Figure 9

Figure 3: Drug release from fast disintegrating comparable to marketed



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 40 ml of liquid paraffin resulted into spherical microspheres of particle size 315 ± 10.84 μ . The formulation produced not less than 87 % release at the end of 30 minutes. Thus, the pleasant tasting fast disintegrating tablet of theophylline intended for pediatrics, disintegrating in 30 seconds, having hardness of 3 kg/cm was successfully formulated.

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