TASTE MASKED, ORALLY DISINTEGRATING TABLET CONTAINING MICROSPHERES FOR IMMEDIATE RELEASE

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Received on: 24-06-2008; Accepted on :28-09-2008

ABSTRACT

The purpose of this study was to evaluate the potential of microspheres for taste masking when incorporated into orally disintegrating tablets. The microspheres were produced by emulsification solvent evaporation method using a model drug theophylline with a taste masking polymer. The solvent evaporation method was optimized to obtain microspheres with desirable characteristics. The microspheres were mixed with other excipients to form orally disintegrating tablets. Optimization using two factors and three levels using factorial approach was carried out. The microspheres were best formed using acetone in 40 ml liquid paraffin at 1600 rpm speed of stirring for 90 minutes. The yield was 85 ± 2 %, particle size was 315 ± 10.84 µ and the assay results showed entrapment of 93.77 ± 0.53 % drug. The tablets formed showed a hardness of 3 ± 0.5 kg/cm^2 and in vitro disintegration of 25 ± 3 seconds. The in vitro drug release was 88 ± 4 % at the end of 30 minutes. In conclusion, microspheres can effectively mask the bitter taste of the active pharmaceutical ingredients in combination with the orally disintegrating tablets.

Key words: Theophylline,microspheres, solvent evaporation, taste masking, orally disintegrating, factorial design, superdisintegrant.

INTRODUCTION

Although tablets and capsules constitute a major portion of the drug delivery systems, some patient groups, such as pediatrics, geriatrics, and bedridden or disabled patients, may have difficulties in swallowing tablets or capsules. To meet these medical needs, formulators have devoted considerable efforts to develop a novel dosage form known as orally disintegrating tablet (ODT), which can disintegrate rapidly in the saliva without need of water[1]. However, taste masking for some pharmaceutical actives with bitter or unpleasant taste can be challenging for this dosage form to achieve patient acceptability.

In recent years, microspheres and microencapsulations have been developed for taste masking by creating a physical barrier to protect the bitter drugs from coming in contact with the patients' taste buds. It has also been reported that these micro particles remained intact without undergoing merging or rupturing during tabletting. The potential of microspheres for taste masking when incorporated into orally disintegrating tablets will be investigated[2-10]. Solvent evaporation method is a very easy and convenient method to prepare microspheres[11-13]. In this investigation, polymethacrylate (Eudragit E 100) was used. E 100 is soluble only in acidic pH; hence the microspheres will remain intact in oral cavity thus masking the taste.

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[14-17]. 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. Thus, an attempt to make orally disintegrating taste masked tablet was carried out.

Materials

The drug, theophylline was procured from Cipla Pharmaceuticals Ltd, Mumbai, India. Eudragit E 100 was obtained from Degussa Polymers, Mumbai, India. Other reagents used were of analytical grade.

Methodology

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[18 - 20].

Preparation of Microspheres

Theophylline microspheres were prepared by solvent evaporation technique incorporating ingredients shown in Table 1. The polymer Eudragit E 100 was dissolved in organic solvent by using a magnetic stirrer (REMI, Mumbai). Powdered theophylline was dispersed in the polymer solution. The resulting dispersion was then poured in liquid paraffin while stirring under an over head mechanical stirrer (VEEGO, Mumbai) with a blade of 3 cm diameter. Stirring was continued until complete evaporation of organic solvent 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 initially with 100 ml of 0.5 % SLS solution until free from oil and then with 100 ml distilled water and dried in oven at 60^0 C for one hour. The microspheres were then passed through mesh # 44. The method was optimized for various processing variables, viz; type of organic solvent, speed of agitation, volume of liquid paraffin, duration of stirring and drug: polymer ratio. The resultant microspheres were subjected to particle size distribution studies and in vitro drug release studies. The trials were also conducted with different drug: polymer ratios to optimize the ratio.

Evaluation of Microspheres

The microspheres were evaluated for taste, percentage yield, entrapment efficiency, particle size distribution, surface morphology, assay and drug release studies[11-13].

Preparation of orally disintegrating tablets

ODT was formulated using microspheres, blend of sweeteners and flavor, starch as disintegrant, sodium starch glycolate (SSG) as superdisintegrant and talc as lubricant. The tablets were then directly compressed using 9 mm concave punch on single station machine. Optimization of the formula was carried out considering two factors, the concentration of superdisintegrant SSG and disintegrant starch at 3 levels as mentioned in Table 2. The evaluation parameter for optimization was disintegration time and friability.

Evaluation of tablets

The ODT were evaluated for weight variation, hardness, friability, wetting time, in vitro disintegration, in vivo disintegration, in vitro drug release and assay [21-25].

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.

Result and Discussions

Based on IP limits we can say that the drug has good solubility in water and organic solvents. The 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. The DSC results indicated that the drug showed an endotherm at 270^0C. 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 method using acetone as organic solvent and 40 ml of liquid paraffin, stirred at 1600 rpm for 90 minutes duration yielded best microspheres of particle size 315 ± 10.84 µ. The final formulation was subjected to assay, taste evaluation, scanning electron microscopy and particle size analysis. The yield was 85 ± 2 %, particle size was 315 ± 10.84 µ and the assay results showed entrapment of 93.77 ± 0.53 % drug. No drug release was observed in simulated salivary fluid from microspheres, indicating complete masking of bitter taste has been achieved. The drug: polymer ratio of 1:0.5 was found to be successful in masking the taste as per the in vivo taste evaluation. Also, this was confirmed by *in*

Table 1: Ingredients used in microsphere formation

Ingredients	Quantity
Theophylline	1 g
Acetone	10 ml
Eudragit E 100	0.5 g
Liquid paraffin	40 ml
Stirring speed	1600 rpm
Duration of stirring	90 minutes

Table 2: Optimization formulations of ODT

Ingredients	A1 (mg) + +	A2 (mg) + 0	A3 (mg) + -	A4 (mg) 0 +	A5 (mg) 0 0	A6 (mg) 0 -	A7 (mg) - +	A8 (mg) - 0	A9 (mg) - -
Microspheres(equivalent to 100 mg of drug)	160	160	160	160	160	160	160	160	160
* Blend of sweetener and flavor	20	20	20	20	20	20	20	20	20
Sodium starch Glycolate	12	12	12	10	10	10	6	6	6
Starch	10	8	5	10	8	5	10	8	5
Talc	2	2	2	2	2	2	2	2	2
Total	204	202	199	202	200	197	198	196	193

*** = Blend of sweetener and flavor - Pearlitol + mint flavor + sodium saccharin) (93.33: 3.33: 3.33)**
+ indicates higher concentration level,- indicates low concentration level,0 indicates intermediate concentration level

Table 3: Evaluation of ODT

Parameter	Result
Friability	0.8 ± 0.04 %
Hardness	**3 ± 0.5 kg/cm²**
Weight variation	Passes
Loss on drying	2.23 %
In vitro disintegration time	25 ± 3 seconds
Drug release	88 ± 4 % in 30 minutes.
Assay	98 ± 2 %, Passes
In vivo disintegration time	30 ± 5 seconds
Taste	Pleasant

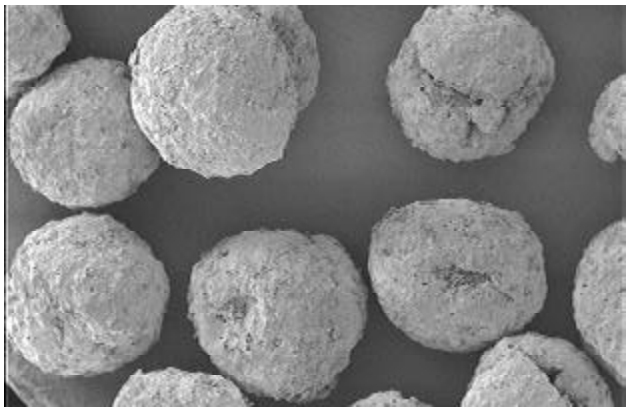
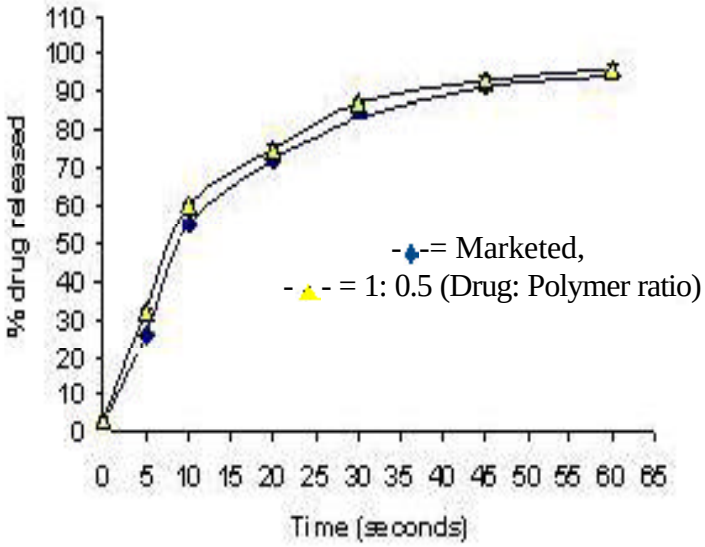


Fig 1: Scanning electron image of Theophylline microspheres

Fig 3: Drug release from ODT comparable to marketed



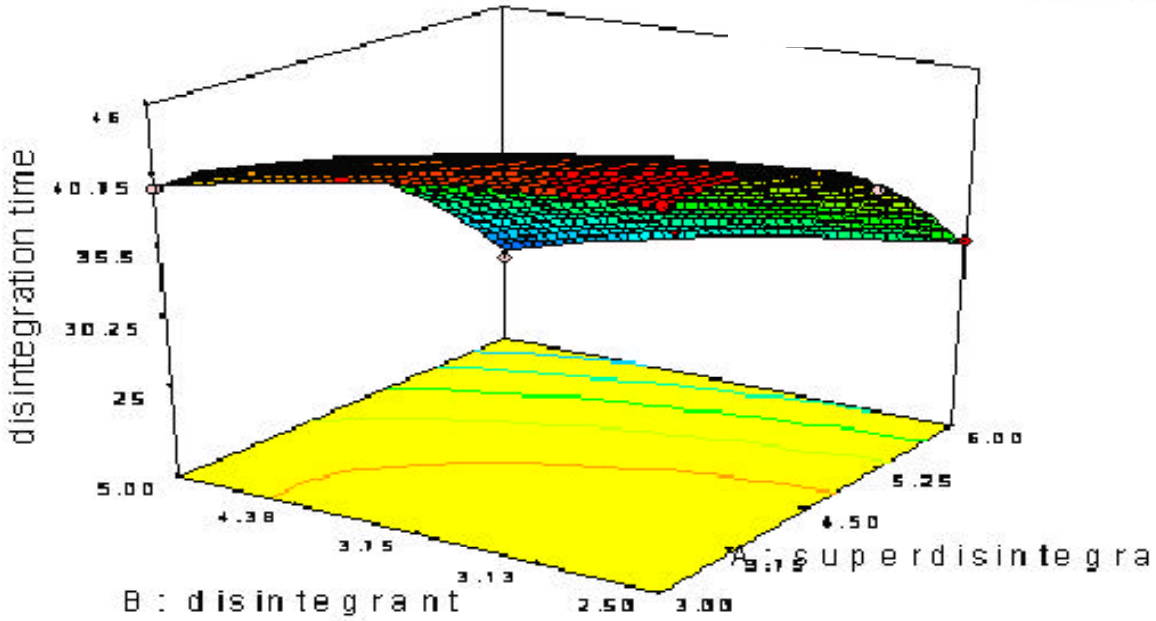


Fig 2: Surface response curve for factorial design

vivo taste evaluation in healthy volunteers by subjective taste evaluation method. The scanning electron microscopy was carried out for the final formula and the observation was as shown in Fig 1. The photographs confirmed the spherical nature of microspheres. The results of tablet evaluation are as shown in Table 3.

The optimization results indicated that in the model for disintegration time it gives a F-value of 92.14 which implies the model is significant. The final equation in terms of actual factors is as below:

Disintegration time = +19.125 + 12.838 x superdisintegrant + 3.828 x disintegrant -0.334 x superdisintegrant x disintegrant - 1.777 x superdisintegrant ^{2} - 0.622 x disintegrant^2

The equation indicates that the concentrations of superdisintegrant and of disintegrant are significant factors affecting disintegration. The surface plot diagram is as shown in fig 2.

Dissolution studies for comparative evaluation of marketed and fast dissolving tablets were conducted and showed no differences between release rates. (Fig 3)

Conclusion

The method of volatile solvent evaporation emulsification was successful in yielding microspheres. The ODT prepared were effective, palatable and showed a good balance between the disintegration time and hardness. The present investigation explores the idea of incorporating taste masked micro particles in ODT thus giving a new way in the field of novel drug delivery. Also such products find a good position in the competitive market of today.

Acknowledgement

The authors thank University of Mumbai for the financial support for the project.

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Source of support: University of Mumbai , Conflict of interest: None Declared