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Preparation and *in vitro* Evaluation of Eudragit Microspheres Containing Theophylline

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The aim of this study was to prepare and evaluate Eudragit (RS and RL) microspheres containing theophylline. Microspheres were prepared by solvent evaporation method using acetone/liquid paraffin system. The prepared microspheres were analyzed for particle size and shape, percentage yield, entrapment efficiency, stability study, *in vitro* release pattern and for release kinetics. The yield of preparation and the encapsulation efficiencies were high for all formulations. The maximum encapsulation efficiency was found to be 94.27 ± 1.36 % (w/w). No appreciable difference was observed in the extent of degradation of product during 60 d in the microspheres, which were stored at various temperatures. The *in vitro* release studies were carried out for a period of 7 h. Although theophylline release rate from Eudragit RS microspheres were very slow and incomplete, they were fast from Eudragit RL microspheres. When Eudragit RS was added to Eudragit RL microspheres formulation, release rate slowed down and achieved the release profile suitable for peroral administration. The release followed zero order kinetic.

Key Words: Microspheres, Theophylline, Eudragit.

INTRODUCTION

Asthma is a reversible obstructive airway disease characterized by bronchial hypersensitivity. Theophylline is a xanthine bronchodilator. It relaxes directly the smooth muscle of bronchial airways and pulmonary blood vessels. So it is used to relieve and/or prevent symptoms of asthma[1]. It has a short half-life which leads to repeated administration and increased cost of therapy. Therefore attempts have been made to develop sustain release formulations of theophylline.

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Microspheres are one of the multi-particulate delivery system and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance[2-4].

Eudragit polymers are series of acrylate and methacrylate polymers available in different ionic forms. Eudragit RL and Eudragit RS are insoluble in aqueous media but they are permeable and both have pH-independnt release profile. The aim of this study was to prepare Eudragit microspheres containing theophylline to achieve a controlled drug release profile suitable for peroral administration.

EXPERIMENTAL

Theophylline was obtained as a gift sample from Cipla pharmaceuticals, Mumbai. Eudragit RS and Eudragit RL were obtained from Rohm Pharma. Liquid paraffin and *n*-hexane were procured from Loba Chem. Pvt. Ltd., Mumbai. Other substances used were all of pharmaceutical grade.

Preparation of microspheres: Theophylline microspheres were prepared by solvent evaporation technique[5-8]. Different amount of polymer (Eudragit RS or Eudragit RL or mixture of both) as shown in Table-1 was dissolved in 27 mL of acetone by using a magnetic stirrer. Theophylline (1 g) and magnesium stearate (100 mg) were dispersed in the polymer solution, the resulting dispersion was then poured into a vessel of 1000 mL containing the mixture of 270 mL liquid paraffin and 30 mL *n*-hexane while stirring by a mechanical stirrer. Stirring was continued for 1 h until acetone evaporated completely. After evaporation of acetone, the microspheres formed were collected by filtration in vacuum and washed 4-5 times with 50 mL *n*-hexane each and dried at room temperature for 24 h. Microspheres dried at room temperature were then weighed and the yield of microspheres preparation was calculated using the formula

$$\% \text{ Yield} = \frac{\text{Amount of microspheres obtained (g)}}{\text{Theoretical amount (g)}} \times 100$$

TABLE-1
FORMULATION OF THE MICROSPHERES PREPARED

Formulation no.	Eudragit RL (g)	Eudragit RS (g)	Magnesium stereate (mg)	Drug (g)
F_1	–	2.0	100	1
F_2	2.0	–	100	1
F_3	1.8	0.2	100	1
F_4	1.6	0.4	100	1
F_5	1.4	0.6	100	1

Encapsulation efficiency of the microspheres: Theophylline was extracted from the microspheres after crushing with phosphate buffer pH 7.4 and absorbance was measured using UV/Vis spectrophotometer at 271 nm. Amount of theophylline in the microspheres was estimated with the help of a standard graph.

Determination of the shape and mean particle size of microspheres: The mean particle sizes were determined by separating microspheres into different size fractions by sieving for 15 min using standard sieves having apertures of 425, 355, 250 and 180 μm. The surface morphology and the internal textures of microspheres were observed under a scanning electron microscope.

Stability study: The microspheres were placed in a screw capped glass container and stored at ambient humidity conditions, at room temperature (27 ± 2 °C), oven temperature (40 ± 2 °C) and in refrigerator (5-8 °C) for a period of 60 d and the microspheres were analyzed for drug content[9].

***in vitro* Release studies:** The *in vitro* release studies of microspheres were carried in phosphate buffer pH 7.4 using the paddle method (US Pharmacopoeia XXIII, 1995) under sink conditions. Accurately weighed samples of microspheres (size fraction 250 μm) were added to dissolution medium kept at 37 ± 0.5 ºC. At preset time intervals aliquots were withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. After suitable dilutions, the samples were analyzed spectrophotometrically at 271 nm. The kinetic data obtained from release rates were also evaluated.

RESULTS AND DISCUSSION

Solvent evaporation method was used to prepare theophylline microspheres. Magnesium stearate was added to the formulations as droplet stabilizer to overcome the problem of droplet coalescence during solvent evaporation[10]. The scanning electon microphotograph of microspheres (Fig. 1) indicated that microspheres were sphericial and discrete. Most of the microspheres were collected above the sieve of 250 μm by all formulation. The mean particle size of the microspheres are shown in Table-2, among the 5 drugs to carrier ratio, formulation no. F_3 showed maximum percentage yield of 91.52 ± 3.23 % and also showed highest drug entrapment of 94.21 ± 1.36 % (w/w) (Table-2). The yields of preparation and encapsulation efficiency were high for all microspheres obtained and were not affected by the type of polymer and polymer ratio. In the stability study, no appreciable difference was observed in the extent of degradation of product during 60 d in the microspheres, which were stored at various temperatures.

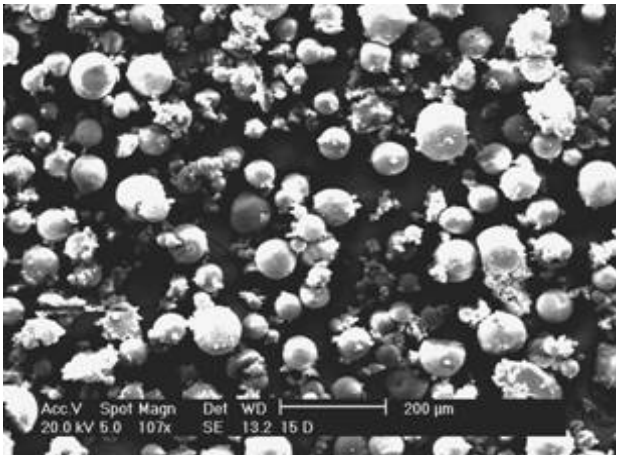

Fig. 1. Scanning electron microphotograph of theophylline loaded Eudragit microspheres

TABLE-2
MEAN PARTICLE SIZE, YEILD OF PREPARATION AND ENCAPSULATION EFFICIENCY

Formulation no.	Mean particle size* (µm)	Yield of preparation* (%)	Encapsulation efficiency* (% w/w)
F_1	275.31 ± 6.16	86.51 ± 1.85	88.25 ± 1.19
F_2	278.54 ± 8.79	87.59 ± 2.10	93.53 ± 1.87
F_3	282.87 ± 6.41	91.52 ± 3.23	94.21 ± 1.36
F_4	291.11 ± 9.24	88.12 ± 1.78	92.51 ± 1.75
F_5	281.87 ± 7.69	90.53 ± 1.23	93.42 ± 1.46

*Average of three preparation ± SD

Theophylline release rate from microsphere was dependent on the type of polymer used. In order to keep the total surface area of the microspheres sample constant and thus to get comparable result the release studies all were carried out with 250 µm size fraction of the microspheres prepared.

Theophylline release rate from Eudragit RS microspheres was very low and incomplete, whereas release rate from Eudragit RL microspheres was fast and the amount released in 7 h reached 99 % (Fig. 2). This is due to the fact, that the amount of quaternary ammonium groups of Eudragit RS is lower than that of Eudragit RL, therefore, Eudragit RL is more permeable to water, so that release is less retarded[11,12]. The gastrointestinal transit time is 6-8 h[13] for young healthy man. Considering the gastrointestinal transit time, release profile from Eudrgit RL microspheres seem to be too fast for controlled release. To decrease the release rate Eudragit RL and Eudragit RS were mixed at different amounts. When Eudragit RS was added

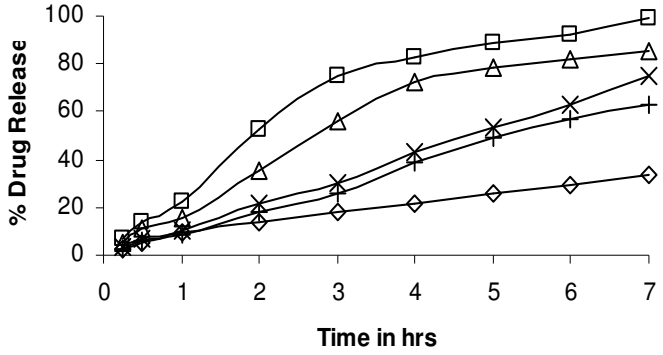

Fig. 2. *in vitro* Release of theophylline from Eudragit RS/ Eudragit RL microspheres in pH 7.4 buffer solution
Formulation F_1 (-◇-), F_2 (-□-), F_3 (-Δ-), F_4 (-×-) and F_5 (-+-)

to Eudragit microspheres formulation, release rates slowed down and the amount of theophylline released in 7 h was between 62.29 to 85.21 % for different formulations and achieved the release profile suitable for peroral administation. The release of theophylline from microspheres followed zero order kinetic.

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