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COMMUNICATION

Development and Evaluation of Micropelleted Sustained-Release Suppositories of Terbutaline Sulfate*

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ABSTRACT

Terbutaline sulfate (TS), a β2 agonist, was fabricated in the form of micropelleted sustained-release suppositories. Micropellets of TS using Eudragit RS100 were prepared by emulsification-solvent evaporation technique and were incorporated into suppositories (PEG 4000 as base) by fusion method. Physical, in vitro and in vivo evaluations were carried out for both conventional (PEG 4000 base) and micropelleted sustained-release suppositories and were compared. Micropellets were scanned using electron microscopy to see the surface structure before and after the in vitro dissolution.

INTRODUCTION

Terbutaline sulfate (TS) is a selective β2 agonist used in the treatment of bronchial asthma. The therapeutic levels of TS in plasma for longer periods are desired in nocturnal asthmatics, so that the patient can have undisturbed sleep, particularly at night. The bioavailability of TS following oral route is much less (14 ± 2%) because it undergoes extensive first-pass metabolism and the onset of action may be delayed for 1-2 hr (1). It is well known that with rectal route, 60-70% of administered drug directly enters into the systemic circulation (2,3) and this avoids loss of drug due to first-pass effect. In the present investigation an attempt has been made to fabricate and evaluate a micropelleted sustained-release formulation of suppository of TS.

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MATERIALS AND METHODS

Terbutaline sulfate (Themis Ltd., Bombay), heavy liquid paraffin, Span-80, and polyethylene glycol, 4000 of AR grade (S.D. Fine Chemicals [P] Ltd., Bombay), Eudragit RS100 (Rhome Pharma, West Germany), and dialysis tubing (Sigma Chemical, MO, 33 mm width, 21 mm diameter) were used.

Preparation of Micropellets

Micropellets of TS were prepared by emulsification–solvent evaporation method (4). The internal phase a solution of Eudragit RS 100 and TS in acetone (Eudragit RS100: 1.5 TS: 1.5, and acetone 14 ml) was added in a thin stream to the ice-cold external phase (100 ml of heavy liquid paraffin containing 0.1 ml of span 80) which was stirred at 1000 rpm. The stirring was continued for 90 min to evaporate the solvent. Petroleum ether (150 ml) was added drop wise (2 ml/min) to extract the residual amount of acetone and to rigidize the resultant micropellets. The micropellets were separated and washed twice with petroleum ether and dried at room temperature for 24 hr. Size analysis of micropellets was performed and is given in Table 1. Micropellets of 18 mesh size were separated and used in the formulations.

Preparation of Conventional and Micropelleted Sustained-Release Suppositories

Conventional suppositories (CS) and micropelleted sustained-release suppositories (MSRS) were prepared by fusion method (5,6) with PEG 4000 as suppository base. The micropellets of TS were incorporated in suppositories during filling of the mold with PEG 4000. The ratios of micropelleted drug to free drug in the MSRS used were 8:2 and 5:5. Weight variation and content uniformity of CS and MSRS were performed. Table 2 gives the mean (±SD) of weight and content of TS suppositories.

Table 1

Sieve Analysis of Micropellets (Values Are Mean of Triplicated Batches)

Sieve No.	Size of Micropellets (μm)	Percent Retained
#16	991	14.52
#18	937	46.99
#22	792	17.40
#30	542	11.60
#44	323	09.48

Table 2

Weight and Content Uniformity of Formulated Suppositories (Values in Parentheses Represent Standard Deviation)

Formulation	Weight of Suppository	Terbutaline Sulfate Content (mg)
Conventional	0.9390 (±0.018)	10.199 (±0.184)
Formulation A	0.9590 (±0.028)	10.284 (±0.298)
Formulation B	0.9820 (±0.019)	10.218 (±0.121)

The ratio of micropelleted TS to intact TS in formulations A and B was 8:2 and 5:5, respectively.

In Vitro Liquifaction Time

Suppository under test was submerged in a glass beaker containing a minimum amount of pH 7.2 phosphate buffer maintained at 37°C, to simulate rectal condition. As peristaltic movements are virtually nonexistant in the rectum, agitation or shaking of beaker was not required during the liquifcation.

In Vivo Liquifaction Time

Three healthy male rabbits weighing about 2.8–3 kg were used in the study. The rabbits were fasted overnight and allowed water *ad libitum*. The test suppository was inserted into the rectum of the rabbit and the anal end was pinched with clip for 50 min to prevent expulsion of the suppository. This was done for all suppositories including placebo.

In Vitro Dissolution

The dissolution studies of CS and MSRS micropellets were carried out in 0.2 M phosphate buffer (pH 7.2) by modified Kcrowzynsky method (7). Accurately weighed micropellets containing 10 mg of TS were placed in a dialysis tubing (previously soaked in water for 24 hr) and then placed in 30 ml of phosphate buffer pH 7.2 at 37± 1°C. Samples were withdrawn at specified time

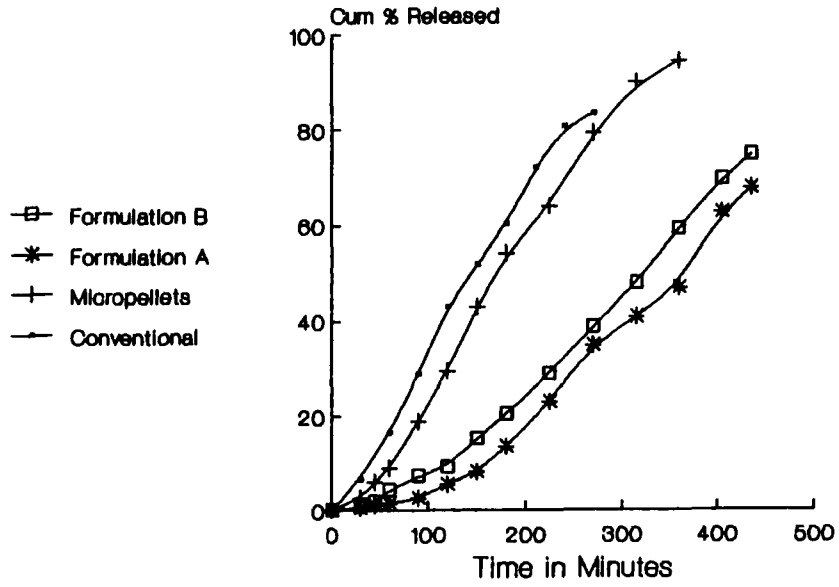

Figure 1. In vitro release profiles of micropellets and formulated suppositories.

intervals and the drug was estimated spectrophotometrically (8).

Scanning Electron Microscopy

Micropellets were studied using a scanning electron microscope (Hitachi, model no. S 415A, Japan) at accelerating voltage of 15 kV (ac) and at different magnifications to see the changes on the surface before and after in vitro dissolution. Samples (micropellets) were coated with gold by sputtering technique in an ion coater (EIKO Engineering, model no. IB2, Japan) at 1400 V (dc) with ionic current of 8 mA for 3 min. The thickness of gold coat was 150 Å. Necessary processing was done to eliminate the charging effect of the electron beam during scanning of the gold-coated micropellets. Samples were placed on a 15-mm stub with double-adhesive tape and the stub was placed in the speciman goniometer stage assembly of the microscope.

RESULTS AND DISCUSSION

The purpose of preparing MSRS is to provide therapeutic drug levels for longer periods and to avoid of first-pass metabolism of the drug.

Table 1 shows the percent of usable sieve fraction (18 mesh) obtained (46.99) and Table 2 gives the weight and content of TS in suppositories; both were satisfactory. The in vitro liquifaction time for the suppositories was found to be 75 min, i.e., suppository base was dissolved completely within 75 min in the phosphate buffer. The test suppositories were well tolerated by rabbits and were not expelled during the in vivo liquifaction study, and it was observed that suppositories (both CS and MSRS) were liquified completely within 50 min.

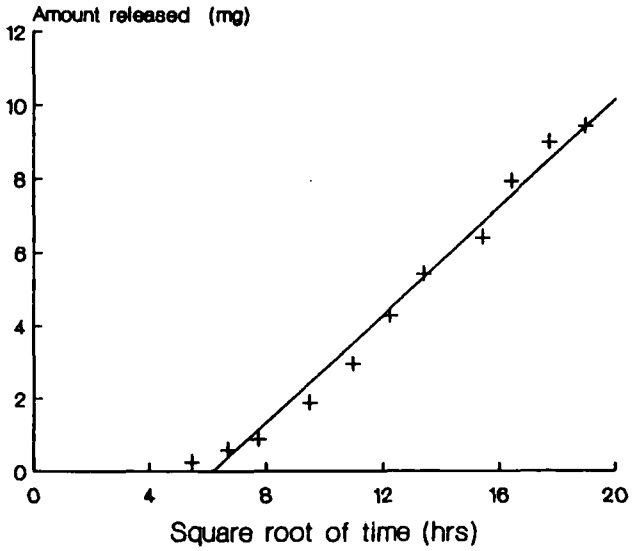

Figure 2. In vitro release of TS from micropellets.

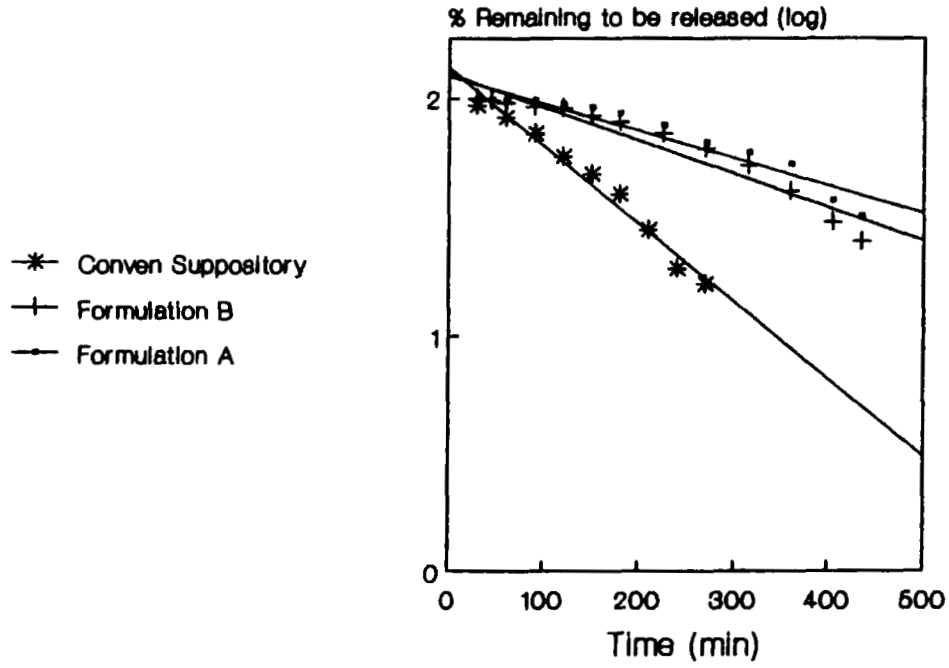

Figure 3. In vitro release of TS from conventional and micropelleted sustained-release suppositories.

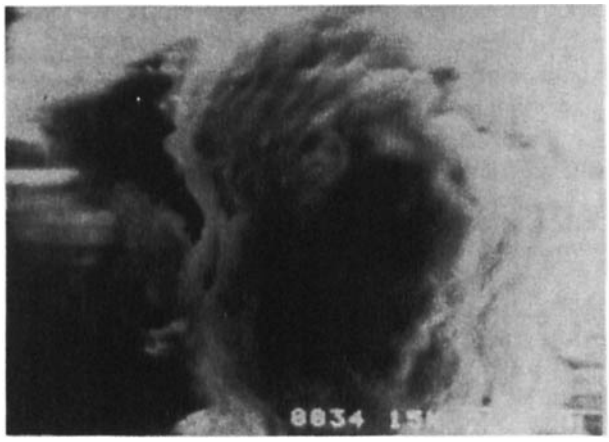

Figure 4. Micropellet surface structure before dissolution in phosphate buffer pH 7.2 at 37°C.

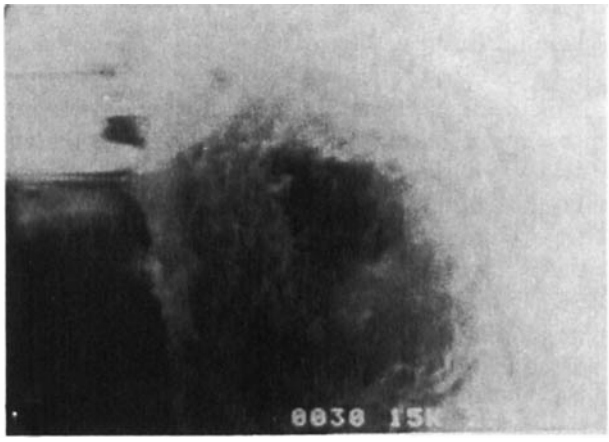

Figure 5. Structure of the micropellet surface of Fig. 4 after dissolution.

In vitro release profiles (Fig. 1) of TS from CS and MSRS micropellets show that time for 60% release ($T60\%$) of TS from micropellets was 3.5 hr, whereas for MSRS it was 6.5 hr, but in case of CS it was only 3 hr. It is evident from the profiles that the release of TS from MSRS was extended considerably when compared to CS. In Fig. 2 a plot shows the amount of TS released versus square root of time, is linear, i.e., TS is releasing from micropellets according to the Higuchi's equation (9,10). In Fig. 3, the release of TS is following Wagner's first-order kinetics (11,12) from CS and MSRS, where plots between percent remaining to be released on logarithmic scale against time on linear scale yielded straight lines.

Scanning electron microscopic photographs (Figs. 4 and 5) showed, initially, the surface of micropellets was

smooth and no channels were found, but after dissolution the size of micropellets was increased and surface of micropellets was eroded.

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