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Preparation and evaluation of sustained release microspheres of terbutaline sulfate

Chong-Kook Kim *, Mi-Jung Kim, Kyoung-Hee Oh

College of Pharmacy, Seoul National University, San 56-1, Shinrim-Dong, Kwanak-Ku, Seoul 151-742, South Korea

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Abstract

Terbutaline sulfate (TBS) microspheres were prepared from Eudragit RS® by an emulsion-solvent evaporation method. In the presence of aluminium tristearate, used as a smoothing agent, the micropellets formed were very spherical and their size distribution was within a narrow range. The mean size of microspheres decreased as the polymer/drug ratio increased. The microspheres showed pH-independent dissolution behavior. As the mean size of microspheres decreased, the release of TBS was retarded. Maximum retardation occurred with 5% aluminium tristearate. The microspheres formulated at a polymer/drug ratio of 9:1 produced a typical 12 h sustained release pattern. Compared with commercial TBS of the PVC matrix type, the microspheres showed equivalent release characteristics.

Key words: Terbutaline sulfate; Sustained release; Eudragit RS®; Microsphere; Solvent evaporation method; Aluminum tristearate

1. Introduction

Terbutaline sulfate (TBS), an adrenergic agonist, is an effective bronchodilator following oral administration. Because of its short biological half-life of 3–4 h and a low daily oral dose of 5 mg (Ruiz et al., 1990), TBS should be formulated in a sustained release dosage form to improve patient compliance. Spherical pelletization with polymers is one method used to modify the drug dosage form and to retard the drug release rate. Since the micropellets can be widely distributed throughout the gastrointestinal tract, microspheres provide several advantages over other sustained release systems, especially matrix-type tablets. They improve drug absorption and minimize side effects due to the localized build up of irritating drugs against the gastrointestinal mucosa (Li et al., 1988).

In this study, TBS sustained release microspheres were prepared with Eudragit RS® by an emulsion-solvent evaporation method. This method is generally known to be simple, reproducible and economical (Goto et al., 1984, 1985a). Eudragit RS® is widely used as a coating material in the pharmaceutical industry. It is a copolymer synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. Since Eudragit RS® film is only

* Corresponding author.

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slightly permeable, drug release through the film is relatively retarded. Several sustained release formulations using Eudragit RS®, such as coated tablets and matrix type tablets, have been reported (Goto et al., 1985b).

The objectives of this study were to prepare microspheres containing TBS, and to investigate the variables affecting the preparation, the release properties and the morphology of the TBS microspheres, and finally to establish a sustained release formulation specifically with drug release no greater than 60% release in 6 h and not less than 80% in 12 h to produce a 12 h sustained release oral dosage form.

2. Materials and methods

2.1. Materials and apparatus

Terbutaline sulfate (Yu Hahn Co., Seoul, South Korea), Eudragit RS® 100 (Rohm Pharm. Co., Allemagne, Germany) and aluminium tristearate (Nakarai Chem. Co., Tokyo, Japan) were used. Acetone (Duksan Chem. Co., Seoul, South Korea) and mineral oil (liquid paraffin, Shinyo Chem. Co., Tokyo, Japan) were used as dispersion media. *N*-Hexane (Duksan Chem. Co., Seoul, South Korea) was a washing agent. All other chemicals were of reagent grade and used without further purification. A six-baffle cylindrical vessel (inside diameter and height 7.5 and 16 cm, respectively) and a mechanical stirrer with three screw-type blades (5 cm diameter) were used.

2.2. Methods

Microcapsules were prepared by an emulsion-solvent evaporation technique (Fukushima et al., 1975; Arshady, 1990; Kim et al., 1990). Eudragit RS® was completely dissolved in acetone (30 ml). Aluminium tristearate and TBS were then added. The mixture was stirred at 250 rpm in a 10°C water bath for 20 min and poured into a six-baffle vessel filled with light mineral oil (liquid paraffin, 150 ml) and Span 80 (1.5 ml). The system was gradually heated to 35°C in order to evaporate the acetone. The microspheres were filtered, washed five times with *n*-hexane (50 ml) at room temperature and dried in a desiccator under reduced pressure (< 15 mmHg). The preparative variables of polymer/drug ratio (1:1, 3:1 and 9:1) and aluminium tristearate concentration (1.45, 3.0, 5.0, 10.0 and 20.0 wt%) were investigated.

The distribution of particle size was evaluated by sieve analysis using 16, 18, 20, 25, 30, 35, 45 and 60 mesh screens and a pan (KP IV standard sieves). The charge weight on the 7.5 cm diameter screen was 10 g.

The drug content of the microspheres was determined by an extraction method. The microspheres (25 mg) were added into chloroform (20 ml) to dissolve the polymer matrix and TBS was then extracted with distilled water (100 ml). The amount of TBS in the aqueous phase was assayed spectrophotometrically at 276.6 nm.

The release properties of the microspheres were studied in distilled water, 0.1 N HCl (pH 1.2) or sodium phosphate buffer solution (pH 7.4) using the USP XXI basket method. An accurately weighed amount of microspheres equivalent to 50 mg of TBS was added to 500 ml of dissolution medium at 37 ± 0.5°C and stirred at 100 rpm. Samples of 5 ml were removed and replaced with fresh medium at appropriate time intervals. All samples were run in triplicate and assayed spectrophotometrically at 276.6 nm.

Scanning electron microscopy (SEM) was used to characterize the microspheres. The microspheres were coated with pure gold using an ion coater (Eiko Engineering IB-3, Tokyo, Japan) under vacuum (0.1 Torr) at high voltage (800–1500 V and 8 mA). The shape, size and surface of the microcapsules were observed with a scanning electron microscope (Hitachi S 510, Tokyo, Japan).

3. Results and discussion

3.1. Effects of operating conditions and variables on the pelletization of TBS

An emulsion-solvent evaporation method comprises dispersing drug-polymer solution into an

immiscible vehicle to form an emulsion. As the solvent is evaporated, the droplets become gradually concentrated and the nucleation takes place. Drug-loaded microspheres are thus produced (Kitajima et al., 1973; Kim et al., 1990). Micropelletization using Eudragit RS® was previously investigated in a methylene chloride/water system and the two problems of swelling and fragility have been reported (Goto et al., 1985b). In this study, the evaporation process in an oil phase (external phase) using liquid paraffin was employed. Since solvents with dielectric constants

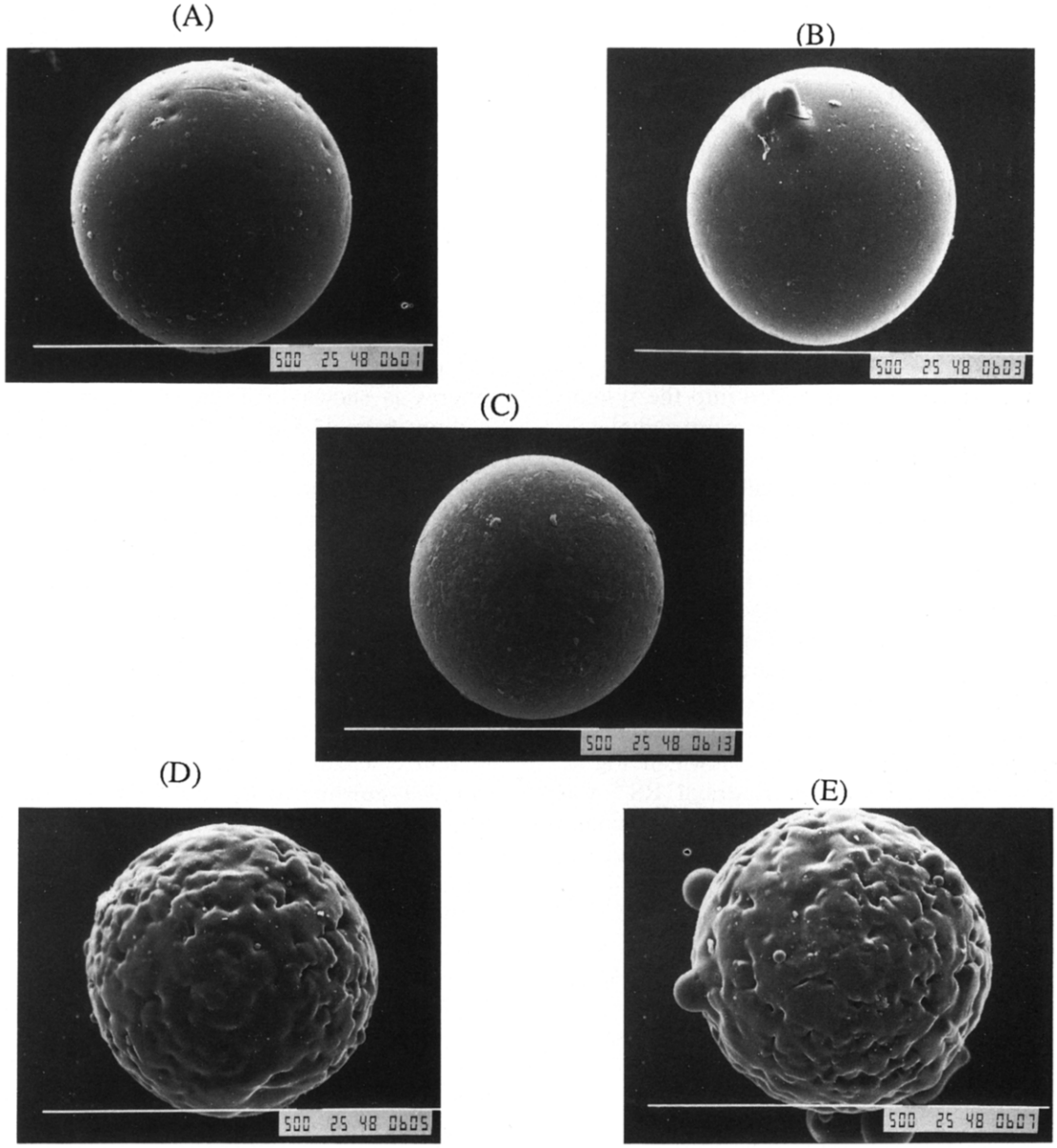

Fig. 1. Scanning electron micrographs of TBS-Eudragit R® microspheres (magnification, ×75). Percentage of aluminium tristearate: (A) 1.45%; (B) 3.0%; (C) 5.0%; (D) 10.0%; (E) 20%.

between 10 and 40 show poor compatibility with liquid paraffin and the systems of these solvents/liquid paraffin were reported to be applicable to the micropelletization process (Goto et al., 1986a), acetone with a dielectric constant of 20.7 was used as a dispersed phase (internal phase).

Factors affecting the particle size and shape, the size distribution and the yield of the microspheres can be the degree of agitation, the shape of the reactor and blade, the rate of heating, the polymer/drug ratio and the concentration of additives. Therefore, it is important to select the shape of reactor and operating conditions. In this experiment, micropelletization was carried out in a specially designed six-baffle vessel (Kim et al., 1990; Kim and Yoon, 1991). The presence of side baffles in this apparatus increased the uniformity of the mixing force and led to a narrow size distribution as well as a high yield.

Flocculation was clearly recognized when no aluminium tristearate was added into the system. As shown in Fig. 1, microspheres were completely formed in the presence of a small amount of aluminium tristearate. Especially with 5% aluminium tristearate, the microspheres were nearly uniform and free-flowing with a good reproducibility. It has been reported that aluminium tristearate reduces the interfacial tension and prevents electrification and flocculation during the preparation of microspheres (Goto et al., 1986a). However, addition of excess aluminium tristearate (10–20%) to the system resulted in a large amount of aggregates as shown in Fig. 1, since the electric charge of Eudragit RS® was reduced progressively by adsorption of aluminium tristearate (Goto et al., 1986b; Kawata et al., 1986).

Table 1
Entrapment of drug within TBS-Eudragit RS® microcapsules

Amount of aluminium tristearate (wt%)	TBS content (wt%) (theoretical content = 50%)
1.45	11.51
3.0	25.03
5.0	19.75
10.0	44.53
20.0	47.41

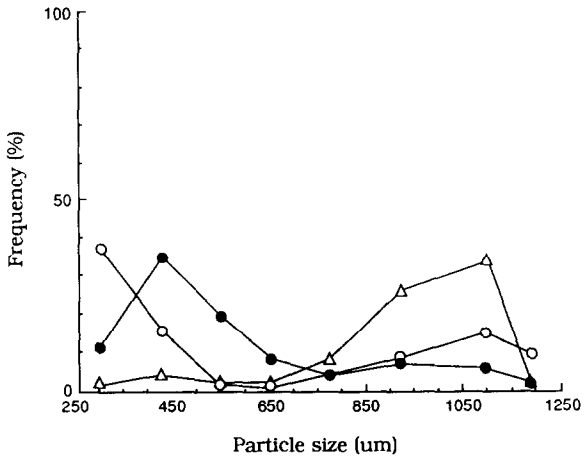

Fig. 2. Effect of polymer/drug ratio on the size distrbution of TBS-Eudragit RS® microspheres. Polymer/drug: (△) 1:1; (○) 3:1; (●) 9:1.

The effect of aluminium tristearate concentration on the actual drug contents in the microspheres is shown in Table 1. Acceptable drug loadings from 11.5 to 47.4% (theoretical content = 50%) were achieved and were reproducible. The actual drug content increased with the amount of aluminium tristearate added. It is considered that aluminium tristearate cooperates to build a dense surface of the microspheres and prevents leakage of the drug into the dispersion medium during the micropelletization process.

Fig. 2 illustrates the size distribution of microspheres, varying the ratio of polymer/drug but keeping the total amount of polymer and drug content constant. For the formulations with 1:1 and 9:1 polymer/drug ratio, the size distributions were within a narrow range. As the polymer/drug ratio increased, the mean size of microspheres decreased due to the reduced viscosity of the internal phase. Pongbaibul and Whitworth (1986) reported similar results.

3.2. Dissolution studies

Fig. 3 shows the release of drug from microspheres prepared with different concentrations of aluminium tristearate. It was found that the release rate of drug reached its minimum when 5% aluminium tristearate was added. This implies

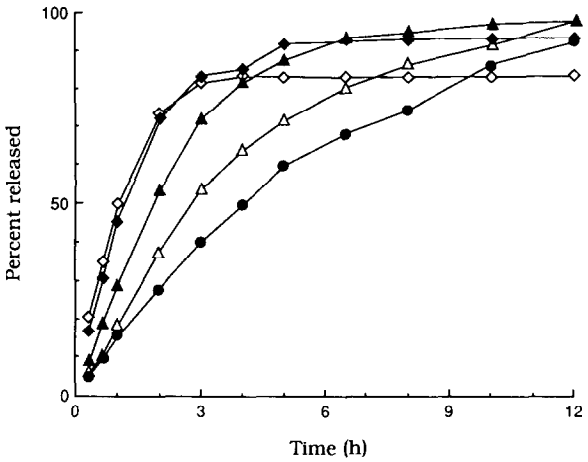

Fig. 3. Drug release from TBS-Eudragit RS® microspheres. Percentage of aluminium tristearate: (△) 1.45%; (▲) 3.0%; (●) 5.0%; (◇) 10.0%; (◆) 20.0%.

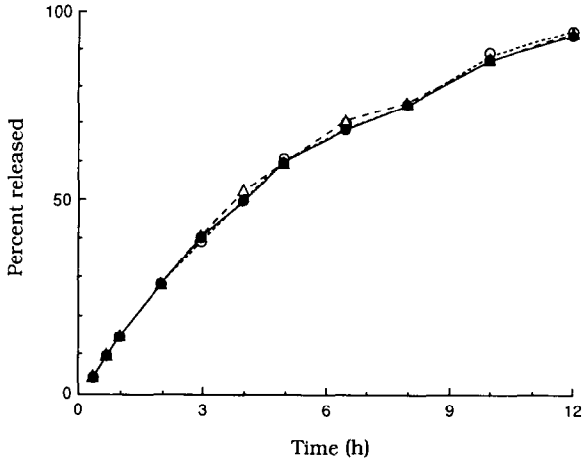

Fig. 5. Drug release from TBS-Eudragit RS® microspheres. Dissolution medium: (●) water; (○) 0.1 N HCl; (△) sodium phosphate buffer.

that the microspheres prepared under these conditions have very smooth and compact surfaces with few pores.

The effect of polymer/drug ratio on the drug release rate is shown in Fig. 4. As the polymer/drug ratio increased from 1:1 through 3:1 to 9:1, the drug release rate decreased dramatically. It is considered that a higher polymer/drug ratio results in a longer diffusion path, so that release is retarded. The same observation was also made in other studies (Jalsenjak et al., 1976; Mortada, 1982).

The effect of pH of the dissolution medium on drug release was investigated. As shown in Fig. 5, the release of drug from Eudragit RS® microspheres is independent of the pH of the dissolution media. Therefore, it is concluded that the drug permeability of Eudragit RS® matrix is con-

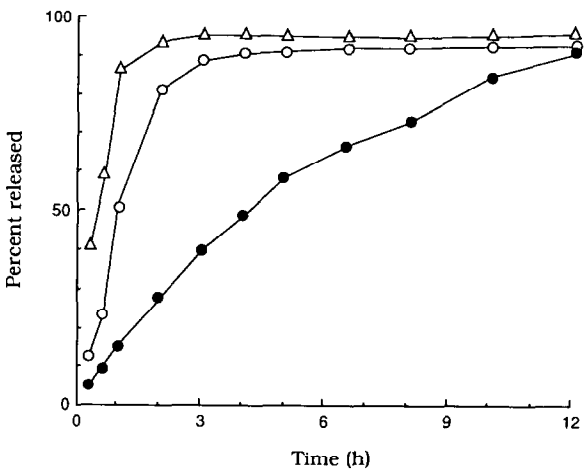

Fig. 4. Drug release from TBS-Eudragit RS® microspheres. Polymer/drug: (△) 1:1; (○) 3:1; (●) 9:1.

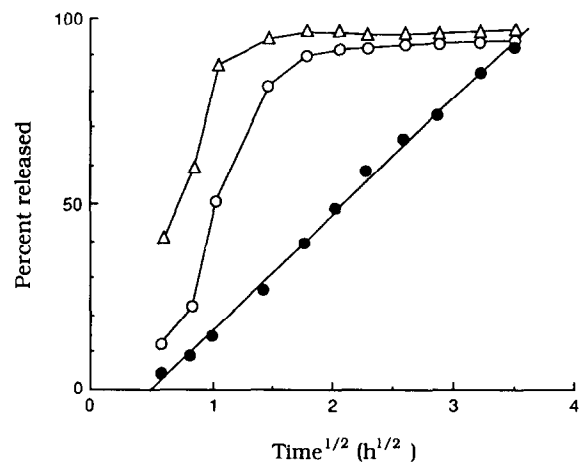

Fig. 6. Percent of drug released from TBS-Eudragit RS® microspheres with respect to square root of time. Polymer/drug: (△) 1:1; (○) 3:1; (●) 9:1.

sistent and that drug release is not affected by individual variations within the milieu of the digestive tract.

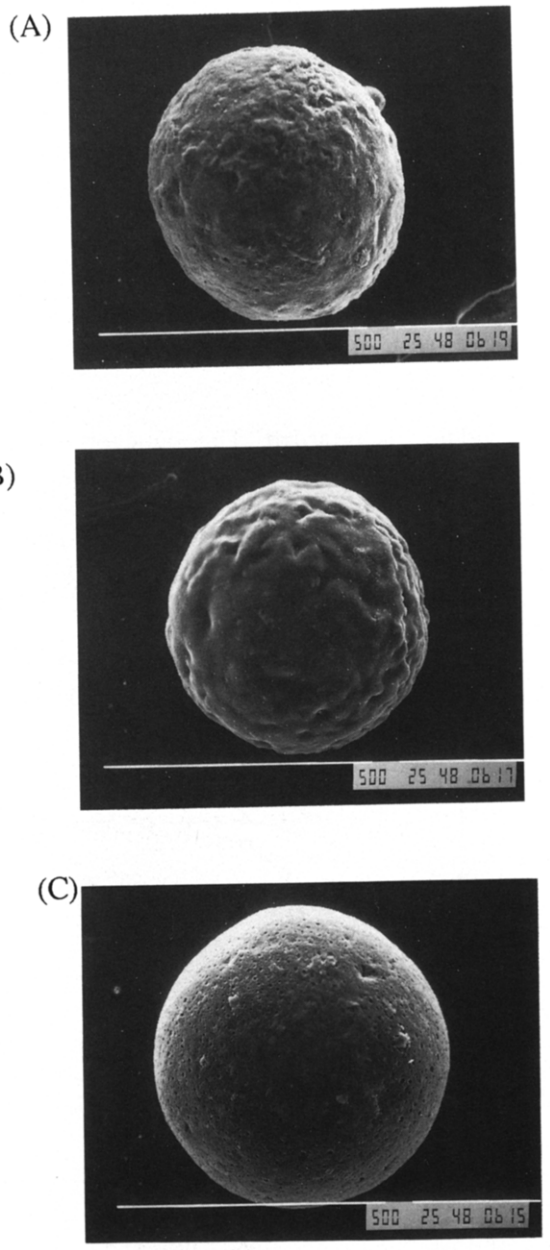

Fig. 7. Scanning electron micrographs of TBS-Eudragit RS® microspheres after dissolution studies (magnification, ×75). Polymer/drug: (A) 1:1; (B) 3:1; (C) 9:1.

3.3. Evaluation of sustained release formulation

The drug release profiles were fitted to square-root time release model in Fig. 6. For the formulation with a 9:1 polymer/drug ratio, release is expected to occur via a diffusion-controlled process as described by Higuchi (1963) and others (Schwartz et al., 1968). The scanning electron microscopic photographs of the microcapsules after completion of the dissolution study are shown in Fig. 7. The microcapsule prepared from the blend with 9:1 polymer/drug ratio had a smooth surface with many pores after the dissolution study. Irregular surfaces and smaller sizes were observed in the microcapsules prepared from polymer/drug ratios of 3:1 and 1:1.

The microcapsules prepared with the 9:1 polymer/drug ratio were evaluated by comparison with the matrix type of commercial TBS sustained release product. As summarized in Table 2, the differences in the percentage of drug released between the two sustained release products of the micocapsules and the matrix type tablet were about 1.5%. Therefore, it was ensured that the microcapsules prepared in this study are appropriate for a 12 h sustained release formulation.

In conclusion, TBS-Eudragit RS® microspheres were successfully prepared by the emulsion-solvent evaporation method. The microspheres showed pH-independent dissolution behavior and a typical 12 h sustained release. They could circumvent the potential toxicity problems inherent in other drug release systems, especially if these systems are designed for oral use.

Table 2
Percent of drug released from TBS-Eudragit RS® microcapsules in comparison with sustained release commercial product

Time (h)	% TBS released	
	Commercial product	Microcapsule
1	17.43	14.56
2	30.24	28.44
4	51.24	50.33
6	67.37	66.33
12	95.75	94.89

Acknowledgement

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