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RESEARCH PAPER

Development of Terbutaline Sulfate Sustained-Release Coated Pellets

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ABSTRACT

Sustained-release coated pellets containing terbutaline sulfate (TS) 1.8% w/w were prepared. The suitable core formulation that gave round-shape TS pellets was preformulated and was composed of microcrystalline cellulose:lactose 38.61%: 57.92%, hydroxypropyl cellulose (HPC-M®) 1.67%, and water 40%, respectively. The core pellets containing active drug were coated with various amounts of ethylcellulose (EC) and a combination of EC/HPC-M polymers. The effects of fluidized bed polymeric film coats on drug release were studied in vitro. The dissolution characteristics were also investigated. The release of the active drug decreased as the amount of EC increased. This may be due to water-insoluble EC film, leading to decreased permeability in water. In the case of the combination of EC/HPC-M, the release of the active drug increased as the amount of HPC-M in the coating solution increased. Since HPC-M is a water-soluble polymer, it may be suggested that formation of pores were increased in the coating layer. Among five coating formulas in this study, formulation 1 (F1) (at 1.1% EC concentration) shows a similar dissolution profile to Bricanyl Durules®; however, lag time for the release occurred. In conclusion, the formulation that gave an insignificant release profile ($p < .01$) when compared with commercial product was the capsule containing F1 (at 1.1% EC concentration) mixed with uncoated pellets at a ratio of 7:1, and the release was found to be reproducible.

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INTRODUCTION

The therapeutic range and duration of action of drugs are important for consideration in drug therapy. Therefore, sustained-release products have received substantial attention in recent years. A multiple-unit dosage form is one of several sustained-release dosage forms. The multiple-unit dosage form could readily separate into sustained-release units throughout the gastrointestinal (GI) tract after ingestion. One of the multiple-unit dosage forms is the pellet, which reduces variations in gastric emptying and transit time, is less susceptible to dose dumping, and provides less irritation from high local concentrations of drugs. Sustained-release pellets made by a coating process are composed of two important parts, the core of the pellets and the coated layer. For the core of the pellets, we previously reported the influence of process variables, including the spheronization speed, the spheronization time, the binder type, and the amount of moisture content, on the physical properties of pellets (1). We concluded that the suitable conditions to produce core pellets containing lactose:microcrystalline cellulose in a 60:40 ratio consisted of 2% w/w of hydroxypropyl cellulose (HPC-M®), 40% w/w water, and 15 min of spheronization time at a 951 rpm spheronizer speed. For the coating layer, various polymers could be employed in the coating process, such as ethylcellulose (EC), Eudragit RS®, and the like. Utilizing EC as a polymer in the coating solution has an effect on the dissolution rate of sustained-release pellets. The increased coating level of polymers will decrease the drug release rate from film-coated pellets (2–4). Chetty and Dangor (5) showed that the rate of release was a function of film thickness and the composition of the membrane. The size of the pellets and the composition of the coating formulation also have an important effect on the dissolution rate of sustained-release pellets. Smaller beads have a greater surface area per unit mass than the larger beads, and the release rate of drug from the smaller beads was faster than that from the larger beads. When reducing the particle diameter to half of its original value, four times more coating solution is needed to maintain the release rate per gram of coated cores (5).

The aim of this study was to develop sustained-release terbutaline sulfate (TS) pellets using the extrusion and spheronization process. In addition, the influence of the amount of EC and a mixture of EC and HPC-M on the release of TS were determined. The optimal level of polymer that exhibits a satisfactory release profile compared to commercial product (Bricanyl Durule®) was selected.

MATERIALS AND METHODS

Materials

Materials used were terbutaline sulfate (USP, India), lactose hydrous (USP/NF/BP/EP, Lactose Company of New Zealand, New Zealand), microcrystalline cellulose (Avicel pH 101®, Asahi Chemical Industry Co., Ltd., Japan), hydroxypropyl cellulose (HPC-M®, Nippon Soda Co., Ltd., Japan), and ethylcellulose 10 cps (Dow Chemical Company). All others reagents used were commercial grade and were used without further purification.

Equipment

Equipment used were planetary mixer (Gypto-Peerless Ltd., England), extruder (Pharmaceutical and Medical Supply Co., Ltd., Thailand), spheronizer (Pharmaceutical and Medical Supply Co., Ltd., Thailand), scanning electron microscope (JEOL, JSM-T220, Japan), cube mixer (Kasuga E. W. Ltd., Japan), fluidized bed air suspension (Uni-Glatt, Gatt® GmbH, Germany), dissolution apparatus (Hanson Research Model SR-2), and ultraviolet (UV) spectrophotometer (Beckman DU-68). High-performance liquid chromatography (HPLC) equipment used was as follows: pump, Shimadzu LC-3A, Japan; injector, Rheodyne 7125; column, Lichrosphere® 100 RP-18 (5 μm) 125 × 4 mm, Lichro CART®, Merck 50943; fluorometric detector, Fluoro Monitor 4100 LCD Analytical; integrator, Shimadzu C-RIA, Chromatropac, Japan.

Preparation of Terbutaline Sulfate Pellets

The amount of excipients employed in the core formulation was based on ingredients previously developed (1). The suitable compositions for placebo pellets composed of microcrystalline cellulose at a ratio of 60:40, 2% w/w of HPC-M, and 1.8% w/w of TS. It was found that the drug itself also had a binding property. In this case, excipients and process modifications were somewhat necessary. The amount of ingredients used in the formulation (batch size 3.5 kg) were TS, 1.80% w/w; Avicel PH 101®, 38.61% w/w; lactose, 57.92% w/w; HPC-M, 1.67% w/w; water, 40.00% w/w by dry weight of powder.

The TS, lactose, and Avicel PH 101 were mixed. The mixture of powder and binder solution was blended until a wet mass was obtained. The wet mass was transferred to a double-screw drive extruder and screened through a 1-mm sieve at an extruder speed of 26 rpm. Extrudates were obtained and transferred to the spheronizer. A

spheronizer speed of 1010 rpm and 15 min of spheronization time were used to prepare the pellets. Finally, the TS pellets were dried in a hot air oven at 50°C for 12 hr.

Evaluation of Terbutaline Sulfate Pellets

Physical properties of TS pellets, such as pellet appearance by scanning electron microscope, particle size distribution, bulk density and tapped density, percentage compressibility, flow rate, angle of repose, and percentage friability were evaluated according to our previous study (1).

Measurement of Terbutaline Sulfate Content in Pellets

About 300 mg of 14/20 mesh-cut TS pellets (equivalent to 5.4 mg of TS) were transferred to a 50.0-ml volumetric flask. Then, 30 ml of 0.01 N hydrochloric acid was added to the flask. The mixture was stirred for 30 min, with 0.01 N hydrochloric acid added to maintain volume, and mixed. The mixture was filtered, and the filtrate was collected. The absorbance of the filtrate was determined by spectrophotometer at 278 nm.

Preparation of Film-Coated Pellets

The amount of ingredients used in the film-coating formulation are presented in Table 1. The 500 g of 14/20 mesh cut TS pellets were placed in the bottom spraying of a fluidized bed coating machine (Wurster type). The film-coating solution was sprayed to the pellets under an inlet air temperature of 50°C–55°C, an outlet air temperature of 48°C–50°C, an inlet air volume of 45, a spraying pressure of 1.5 bar, a spraying rate of 10 ml/min, and a partition height of 2.5 cm.

Table 1

Amount of Ingredients Employed to Prepare Film Coated Solution for Terbutaline Sulfate Pellets

	Formulation				
Ingredient (% w/v)	1	2	3	4	5
Ethylcellulose 10 cps	2.5	2.5	2.25	2.0	1.75
HPC-M	—	—	0.25	0.5	0.75
Propylene glycol	0.25	0.5	0.5	0.5	0.25
Ethanol 95%	20	20	20	20	20
Chloroform qs to.	100	100	100	100	100

Evaluation of Terbutaline Sulfate Content

The method of determination of TS content was similar to that for TS pellets but chloroform was added to dissolve the film out before 0.01 N hydrochloric acid was added for continuing assay of the drug as mentioned above. The mixture was heated about 60°C to get rid of chloroform before the mixture was filtered. The percentage of film based on weight increase was calculated.

Dissolution Study

A dissolution test was determined using the dissolution apparatus II (paddle), with 500 ml of dissolution medium equilibrated to 37°C ± 0.5°C. The dissolution medium consisted of 0.05 M potassium phosphate monobasic adjusted to pH 1.2 with concentrated hydrochloric acid, which was adjusted over 1 hr to pH 7.5 using 50% NaOH solution. The apparatus was operated at 50 rpm. An accurately weighed portion of about 300 mg of film-coated TS pellets equivalent to about 5 mg of TS was added to each dissolution vessel. Samples were taken at predetermined times . These samples were assayed by HPLC with a fluorometric detector. The TS was detected using an excitation wavelength (λex) of 280 nm and an emission wavelength (λem) of 310 nm.

Microscopic Determination

Photomicrographs of the pellet samples were taken with a scanning electron microscope as previously mentioned.

RESULTS AND DISCUSSION

Physical Properties and Dissolution Profiles

Uncoated Terbutaline Sulfate Pellets

The microscopic appearance of uncoated TS pellets is presented in Fig. 1. The physical properties of uncoated TS pellets are shown in Table 2. The results indicated that uncoated TS pellets had a narrow size distribution. The mean particle size was approximately 0.96 mm, and the sieve fraction on the 14/20 mesh cut was about 77%. The pellets had a good flow rate and a low percentage of friability (≤0.43%). These studies revealed that uncoated TS pellets had good physical properties. A dissolution profile of uncoated TS pellets is presented in Fig. 2. The results indicated that the release of TS from uncoated TS pellets was very fast. About 90% of the TS was released with about 1 min. However, the TS was not

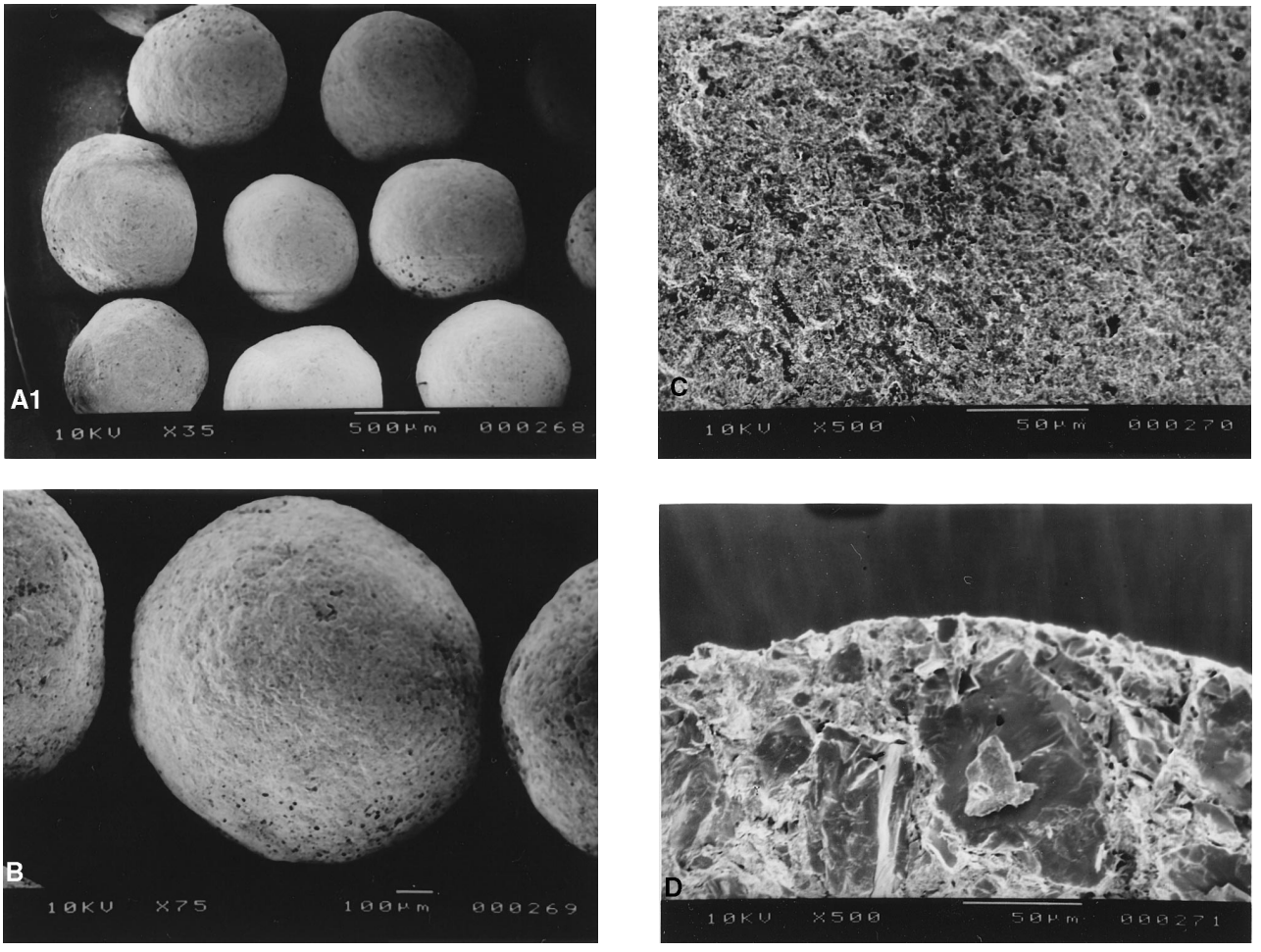

Figure 1. Photomicrographs of uncoated terbutaline sulfate (TS) pellets at various magnifications (A = ×35; B = ×75; C = ×500; D = ×500 (cross section).

completely released after 12 hr of dissolution study. The reason may be that the drug remained intact with microcrystalline cellulose during the dissolution test. The result is in agreement with results of Millili and Schwartz (6).

Coated Terbutaline Sulfate Pellets

The microscopic appearance and dissolution profiles of film-coated TS pellets with EC and a combination of EC/HPC-M are presented in Figs. 3–16. The microscopic appearance and dissolution profiles of film-coating solution formulations 1 and 2 (F1 and F2, respectively) at a 5.4% coating level were similar. Formulations 1 and 2 had 10% and 20% propylene glycol (PG) by weight of EC, respectively. Film-coated pellets before the dissolution test of both formulations had a round shape with a fairly smooth surface. After the dissolution test of both formulations, the pellets still had a round shape, but with a little collapsed film and some pores on the film-coating layer. In the cross-section view, there were some channels in the film-coating layer. These appearances showed that drug may be released by passing through the channels during dissolution; however, PG may have an effect on the pores of the film-coating layer. It may be seen that F1 (10% PG) and F2 (20% PG) possibly gave parallel percentage cumulative release, which may indicate that 10% and 20% are PG suitable. However, from preliminary results, if the concentration of PG is too high,

Table 2

Physical Properties of Uncoated Terbutaline Sulfate Pellets

Physical Properties	
Sieve analysis[a]	
Percentage weight retained on	
Sieve 14	6.78
Sieve 18	40.19
Sieve 20	36.81
Sieve 40	15.00
Sieve 60	1.17
Sieve pan	0.05
Granule size (mm)[a] by sieve analysis	0.96
Percentage sieve fraction on 14/20 mesh cut pellets[a]	77.00
Bulk density (g/ml, ±SD)[b]	0.83 (0.01)
Tapped density (g/ml, ±SD)[b]	0.86 (0.01)
Flow rate (g/ml, ±SD)[b]	280.97 (6.31)
Angle of repose (°, SD)[b]	27.38 (1.54)
Percent friability (%)[a]	0.43

[a] Averaged from two determinations.
[b] Averaged from three determinations.

it might block and retard the release of TS through the channels.

The results from scanning electron microscopic studies showed that film-coated pellets had a round shape with a fairly smooth surface. A relatively thicker film layer was obtained by increasing the percentage of film-coating solution. The release of TS from film-coated pellets depended on the percentage of the film-coating layer.

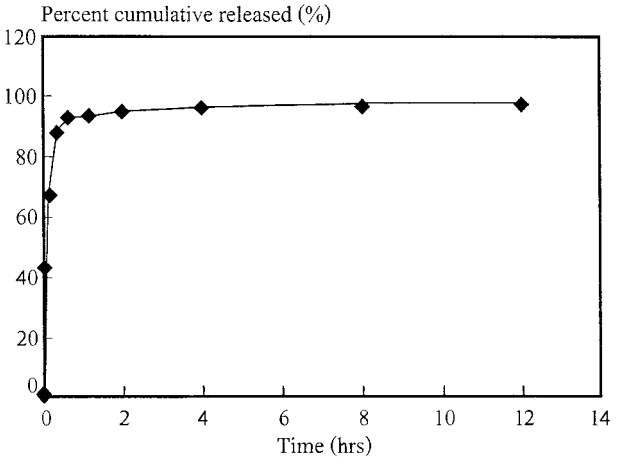

Figure 2. Dissolution profile of TS from uncoated pellets.

The results from dissolution tests showed that increasing the coating level decreased the drug release from film-coated pellets, which suggests that the film may controlling the release process. Therefore, the drug solution had to diffuse through a thicker membrane before it dissolved in the surrounding medium (5,8,9).

The microscopic appearance and dissolution profiles of coating formulations 3–5 at a 3.2% coating level were compared. Formulations 3-5 contained ratios of HPC-M and EC of 1:9, 2:8, and 3:7, respectively. Film-coated pellets before the dissolution test also had a round shape with a fairly smooth surface. After the dissolution test, the pellets still appeared to be round; however, there were some pores on the film-coating layer and channels in the cross-section view of the film-coating layer. This appearance showed that drug may be released through the channels during the dissolution test. The release of TS from film-coated pellets depended on the ratio of HPC-M in the coating layer; when the amount of HPC-M increased, it suggested that the formation of pores increased in the coating layer. In this case, drug could be dissolved and pass through the pores to the dissolution medium (5,8,9).

The release of drug from the 1.1% and 1.5% EC coating levels of formulation 1 was lower than that for a commercial product. It was found that increasing the initial drug release by reducing the EC concentration had no effect on the later period of the dissolution test (Fig. 12, at 1.1% and 1.5% w/w of EC).

In addition, for the above coating levels, a lag time for drug release occurred, which might be because, at initial release, the drug required time for diffusion through the film.

The results from the dissolution test indicated that a combination of uncoated TS pellets and film-coated TS pellets resulted in an increased initial drug release and the disappearance of the lag time (Fig. 14). It is suggested that uncoated pellets can be employed as a loading dose for initial drug release. The formulation selected to compare with a commercial product (Bricanyl Durules) was the capsules containing a mixture of 1.1% EC coated pellets (formulation 1) and uncoated pellets at a ratio of 7:1. This formulation gave a satisfactory profile with less standard deviation, high drug release at 12 hr (about 97.59%), and a dissolution profile that was insignificant in comparison to the commercial product ($p < .01$).

The dissolution profiles of the selected formulation were reproducible (Fig. 16), an indication that the extruder and spheronizer used for these studies were quite efficient for the production of the spherical granules or pellets. The fluidized bed with Wurster column used for these studies was also quite efficient in applying the coat-

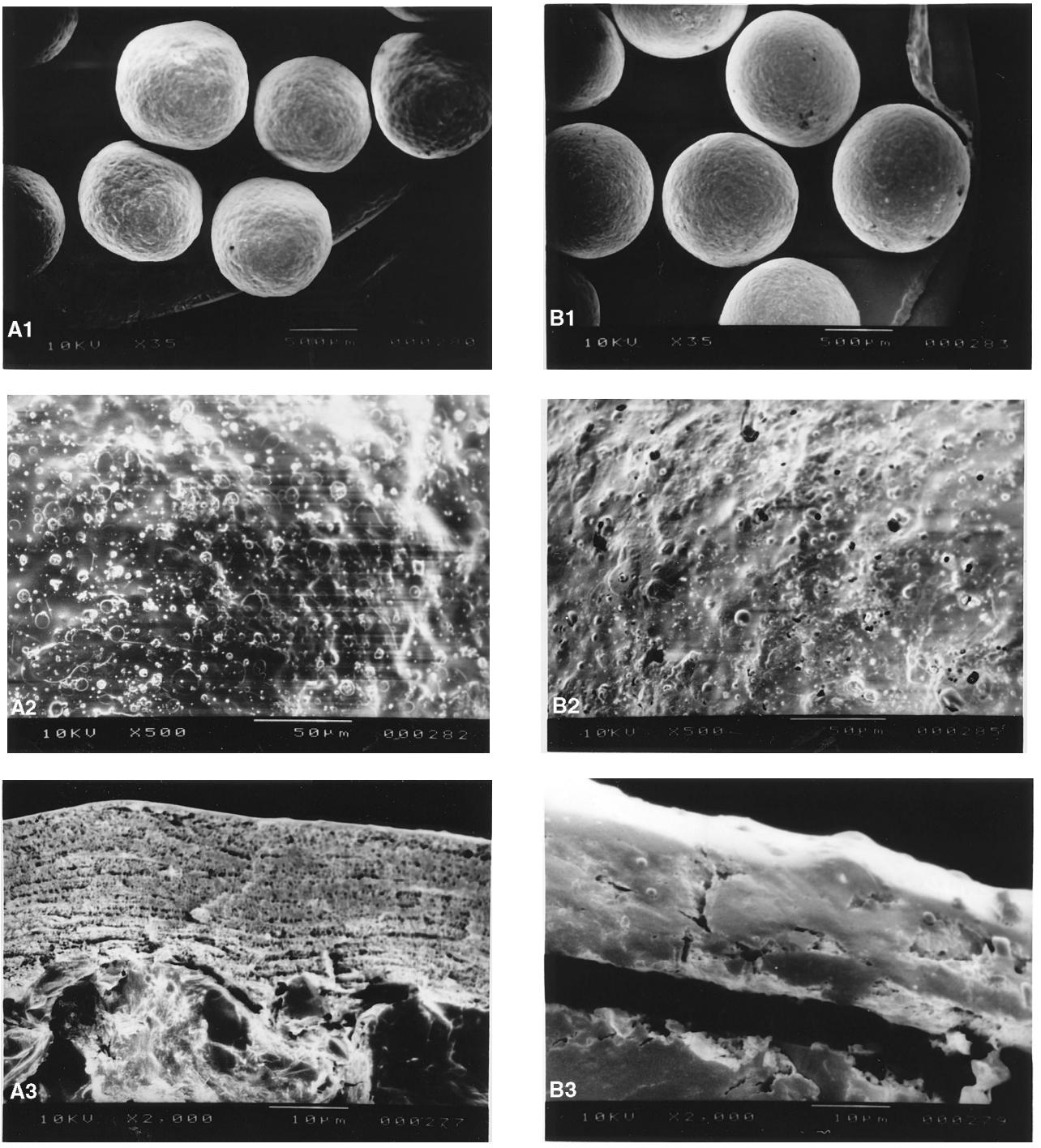

Figure 3. Photomicrographs of 5.4% w/w film-coated TS pellets with EC (formulation 1) (1) before and (2) after dissolution test, with 10% propylene glycol by weight of polymer (A1, A2, A3 are before dissolution test at ×35, ×500, ×2000 cross-section magnification; B1, B2, B3 are after dissolution test at ×35, ×500, ×2000 cross-section magnification).

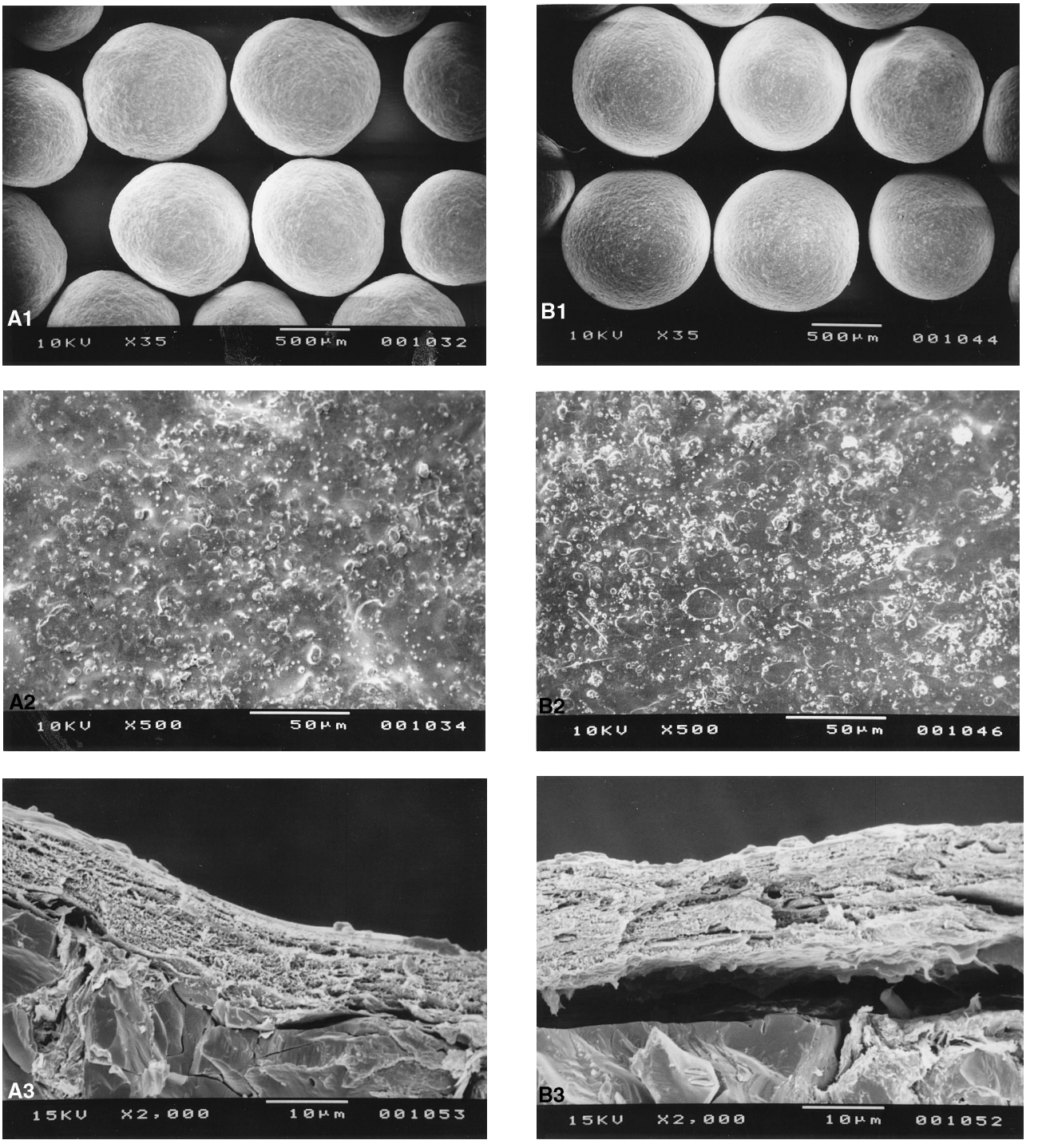

Figure 4. Photomicrographs of 5.4% w/w film-coated TS pellets with EC (formulation 2) (1) before and (2) after dissolution test with 20% propylene glycol by weight of polymer (A1, A2, A3 are before dissolution test at ×35, ×500, ×2000 cross-section magnification; B1, B2, B3 are after dissolution test at ×35, ×500, ×2000 cross-section magnification).

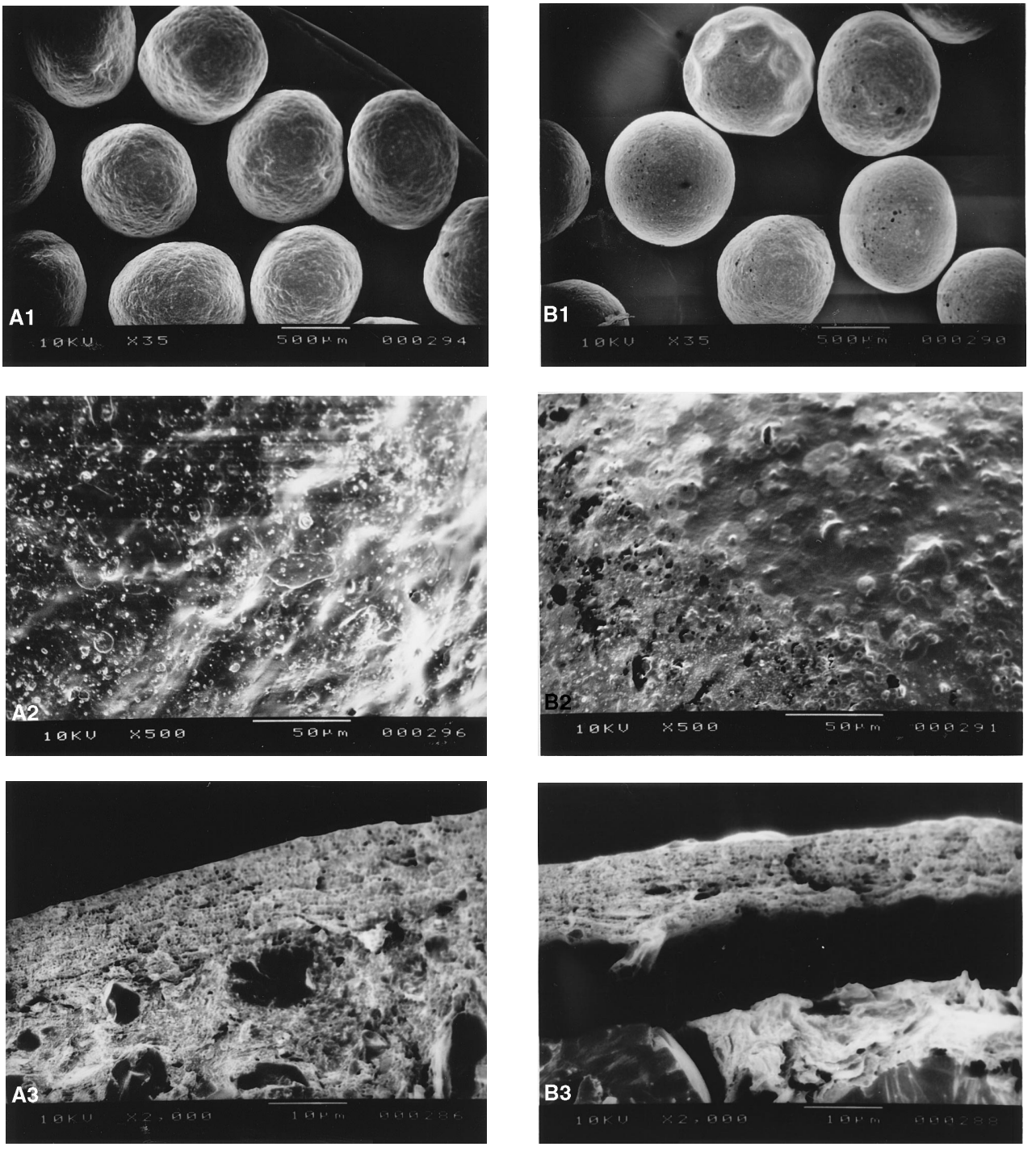

Figure 5. Photomicrographs of 3.2% w/w film-coated TS pellets with EC (formulation 1) (1) before and (2) after dissolution test (A1, A2, A3 are before dissolution test at ×35, ×500, ×2000 cross-section magnification; B1, B2, B3 are after dissolution test at ×35, ×500, ×2000 cross-section magnification).

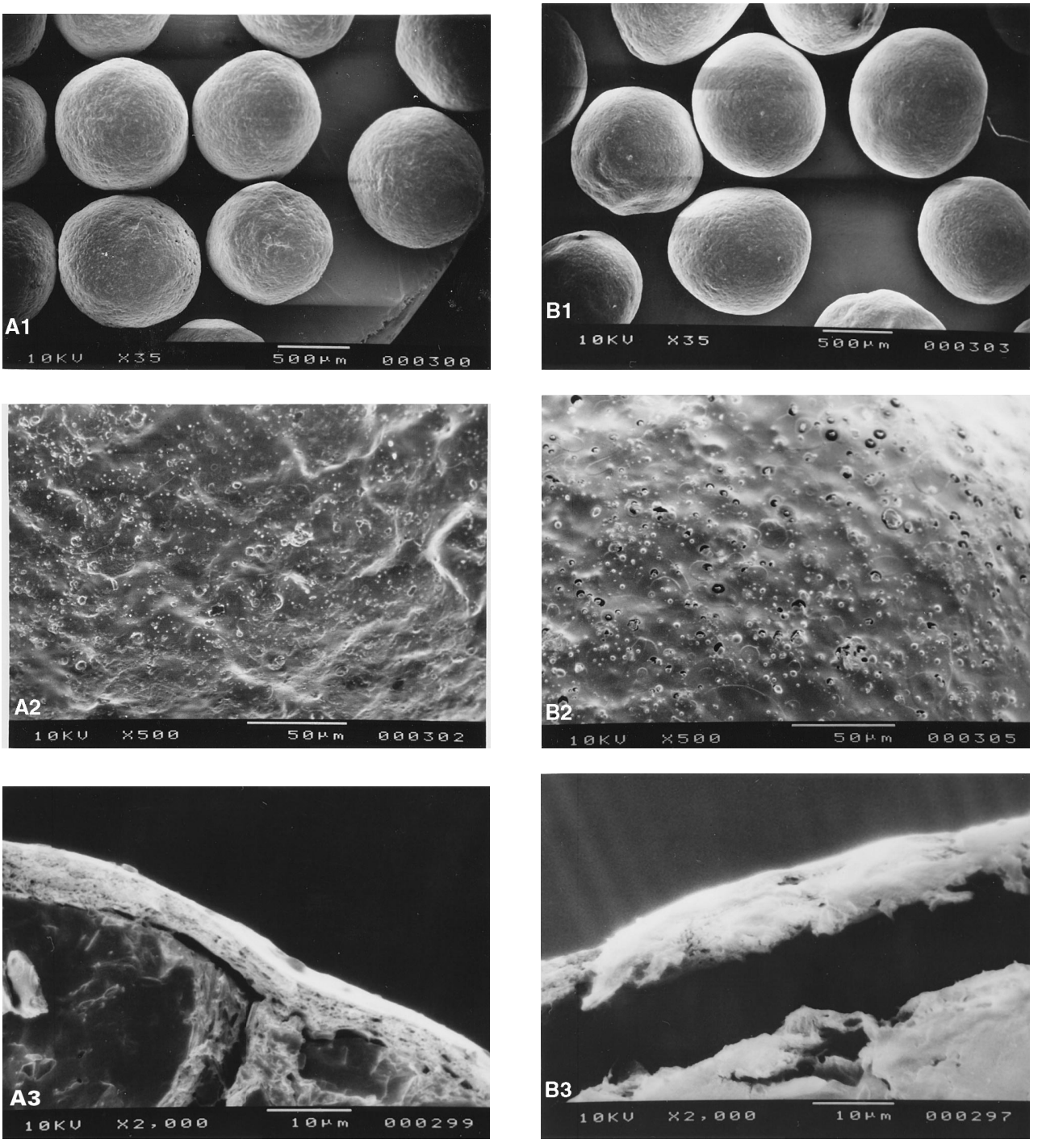

Figure 6. Photomicrographs of 1.5% w/w film-coated TS pellets with EC (formulation 1) (1) before and (2) after dissolution test (A1, A2, A3 are before dissolution test at ×35, ×500, ×2000 cross-section magnification; B1, B2, B3 are after dissolution test at ×35, ×500, ×2000 cross-section magnification).

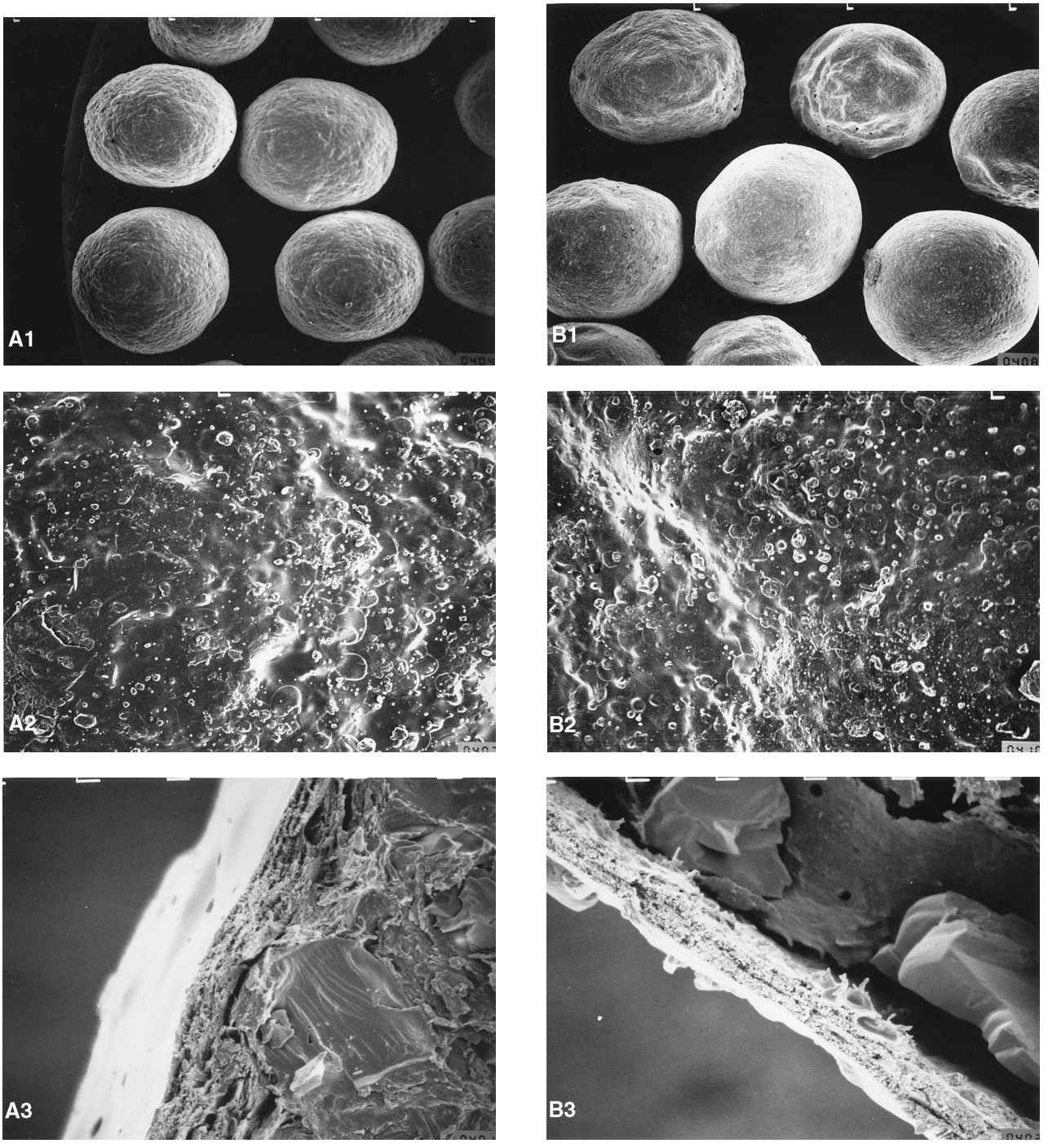

Figure 7. Photomicrographs of 1.1% w/w film-coated TS pellets with EC (formulation 1) (1) before and (2) after dissolution test (A1, A2, A3 are before dissolution test at ×35, ×500, ×2000 cross-section magnification; B1, B2, B3 are after dissolution test at ×35, ×500, ×2000 cross-section magnification).

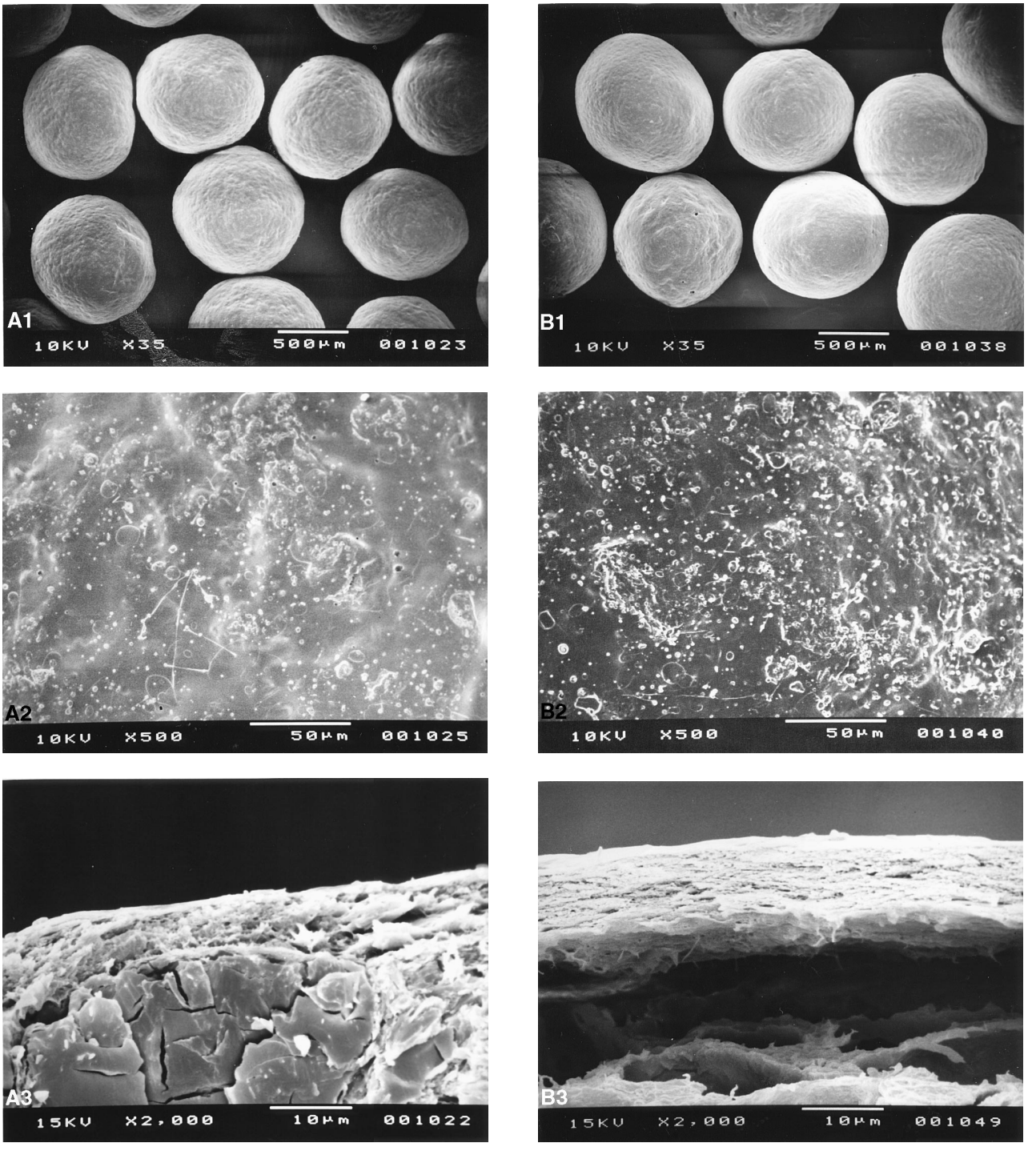

Figure 8. Photomicrographs of 3.2% w/w film-coated TS pellets with EC/HPC-M (formulation 3) (1) before and (2) after dissolution test (A1, A2, A3 are before dissolution test at ×35, ×500, ×2000 cross-section magnification; B1, B2, B3 are after dissolution test at ×35, ×500, ×2000 cross-section magnification).

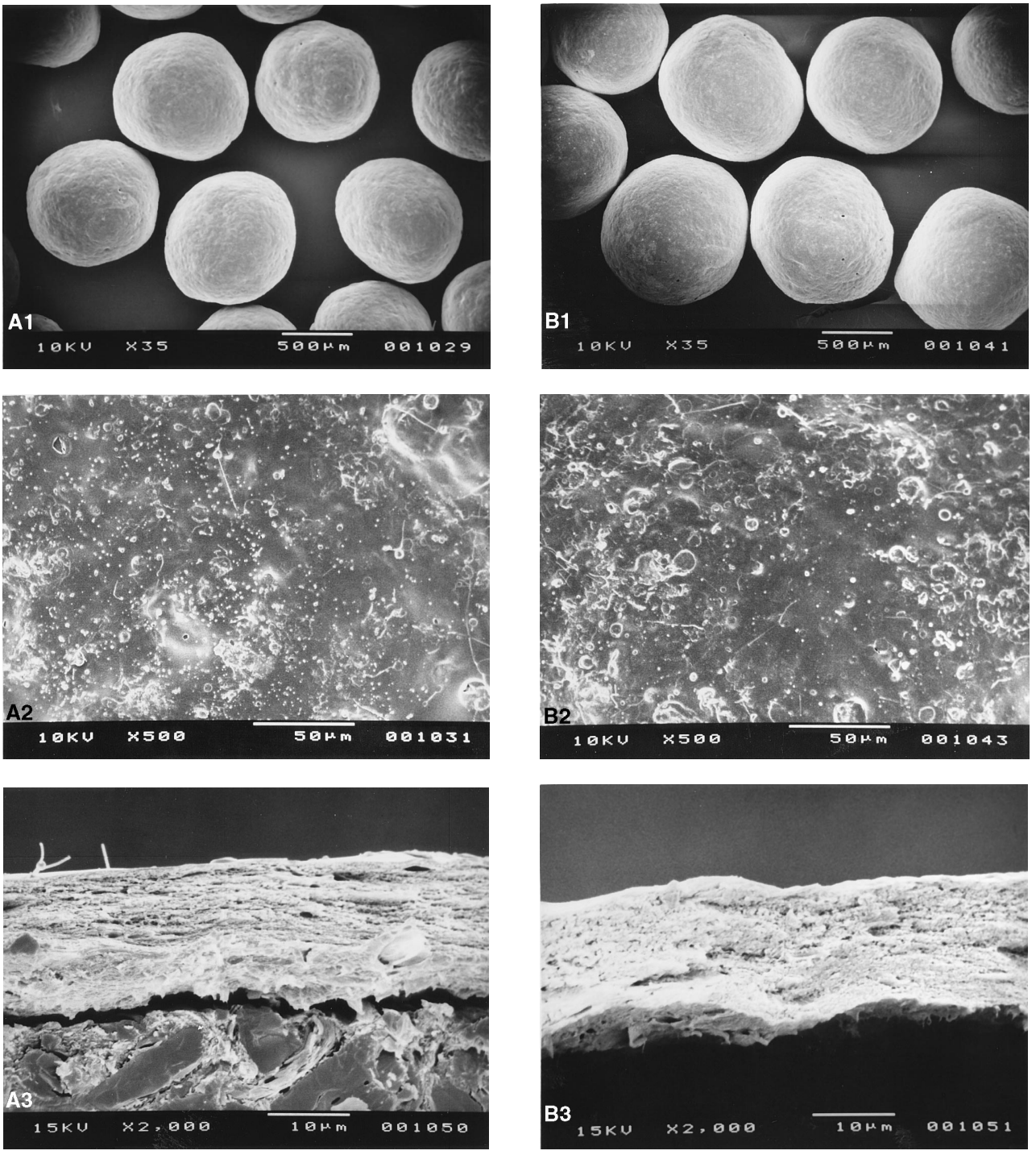

Figure 9. Photomicrographs of 3.2% w/w film-coated TS pellets with EC/HPC-M (formulation 4) (1) before and (2) after dissolution test (A1, A2, A3 are before dissolution test at ×35, ×500, ×2000 cross-section magnification; B1, B2, B3 are after dissolution test at ×35, ×500, ×2000 cross-section magnification).

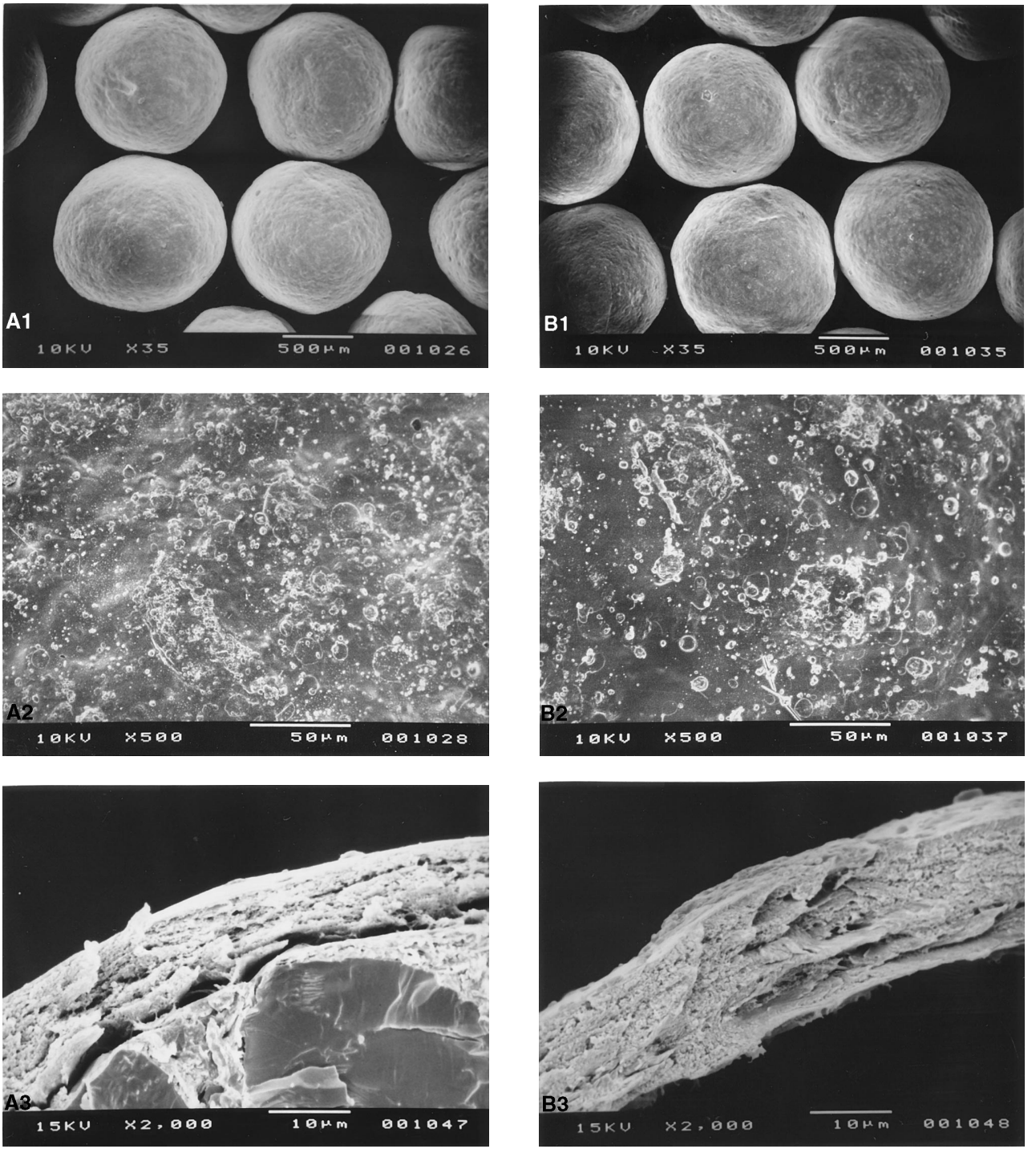

Figure 10. Photomicrographs of 3.2% w/w film-coated TS pellets with EC/HPC-M (formulation 5) (1) before and (2) after dissolution test (A1, A2, A3 are before dissolution test at ×35, ×500, ×2000 cross-section magnification; B1, B2, B3 are after dissolution test at ×35, ×500, ×2000 cross-section magnification).

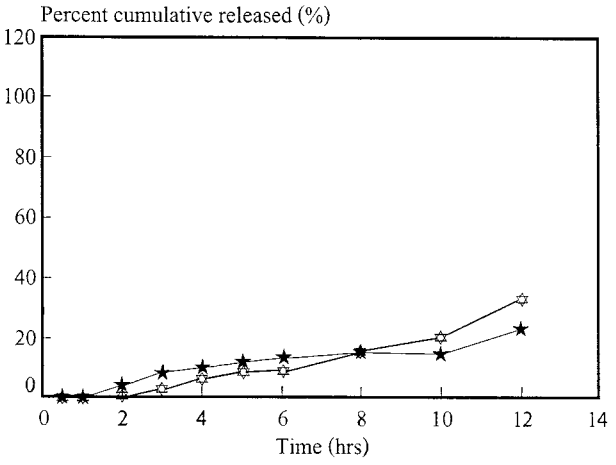

Figure 11. Dissolution profile of TS pellet formulations 1 and 2 from 5.4% w/w EC coating level with 10% and 20% propylene glycol by weight of polymer (★, F1; ☆, F2).

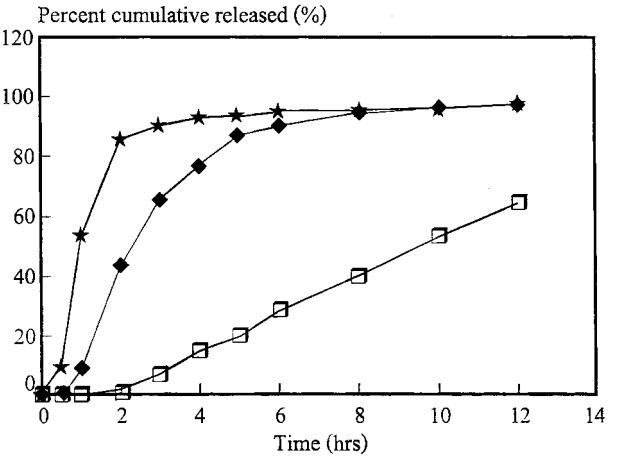

Figure 13. Dissolution profile of TS pellet formulations 3–5 from 3.2% w/w EC/HPC-M coating level (□, F3; ◆, F4; ★, F5).

ing solution to the surface of the pellets and producing a satisfactory coating.

CONCLUSIONS

In this study, TS sustained-release coated pellets were developed. It was indicated that the binding property of the drug itself had an effect on the roundness of the core pellets. The release of drug from film-coated TS pellets decreased with an increasing amount of EC. In the case of HPC-M, when its amount in the mixture of coating polymer was increased, the drug release from the film-coated pellets was also increased. This may suggest that pore formation in the coating layer occurred. In summary, the formulation that gave an insignificantly different release profile ($p < .01$) compared to a commercial

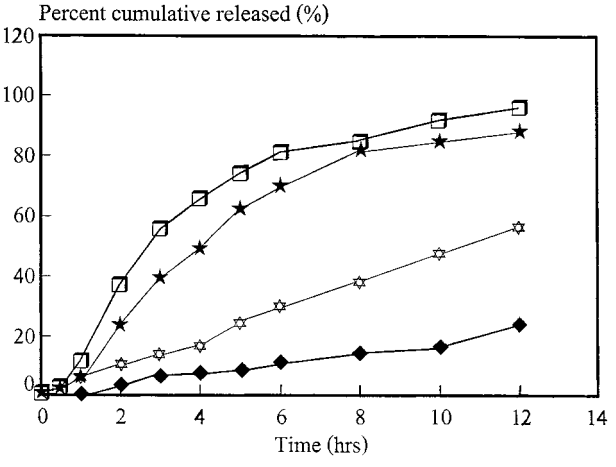

Figure 12. Dissolution profile of TS pellet formulation 1 film coated at various concentrations of polymer (◆, 5.4% w/w; ☆, 3.2% w/w; ★, 1.5% w/w; □, 1.1% w/w).

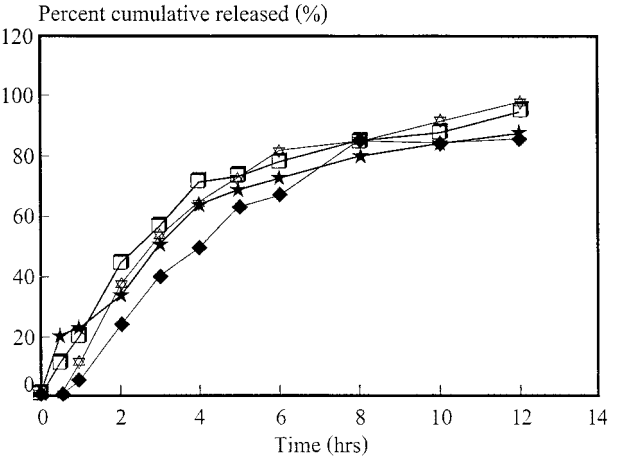

Figure 14. Dissolution profile of TS pellets from 1.1%, 1.5% w/w of EC coating (formulation 1) and mixture of 1.1%, 1.5% w/w of EC coating with uncoated terbutaline sulfate pellets at a ratio of 7:1 (◆, 1.5% w/w; ★, 1.5% w/w + uncoated; ☆, 1.1% w/w; □ 1.1% w/w + uncoated).

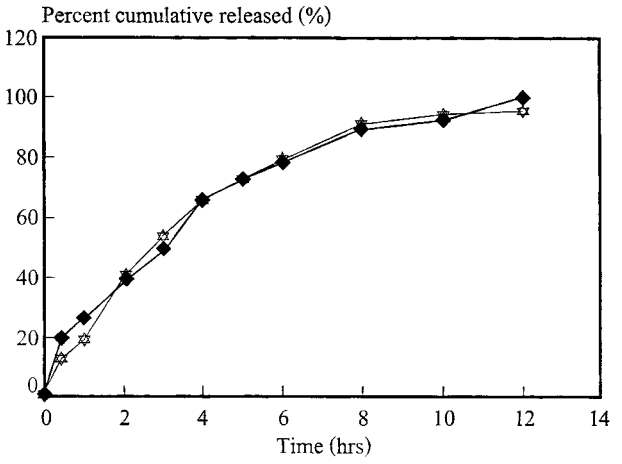

Figure 15. Dissolution profile of TS from Bricanyl Durules (BD) and selected film-coated formulation containing 1.1% EC coated pellets mixed with uncoated pellets at a ratio of 7:1 (◆, BD; ☆, selected formulation).

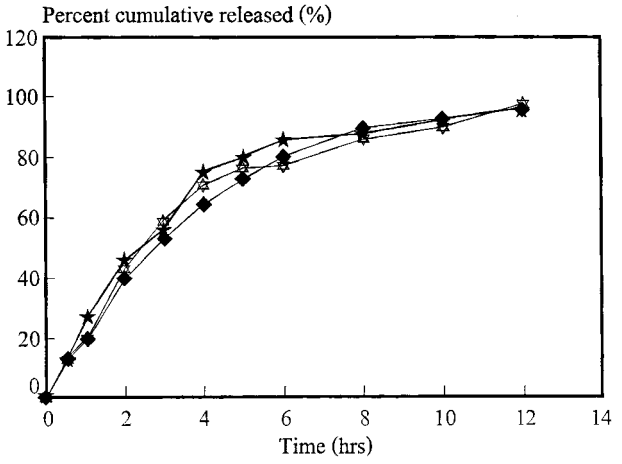

Figure 16. Dissolution profiles of TS pellets from three batches of selected film-coated pellets as indicated in Fig. 15 fill in capsule to confirm repeatability of drug release.

product was the capsule containing F1 mixed with uncoated pellets at a ratio of 7:1. It was found that both extrusion and spheronization processes and coating with a Wurster column process could be reproduced.

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