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Preparation and Dissolution Pattern of Eudragit RS Microcapsules Containing Ketoprofen[1)]

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Microencapsulation of ketoprofen using Eudragit RS, which is a copolymer synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, was investigated. The preparation is based on dispersion of acetone containing the drug in liquid paraffin. Aluminium tristearate was used as an additive for the preparation of microcapsules. Good reproducibility in microcapsule preparation was observed. The microcapsules obtained were uniform and free-flowing particles. The dissolution rates of ketoprofen from these microcapsules were considerably decreased as compared with that from ketoprofen powder.

Keywords——microencapsulation; Eudragit RS; aluminium tristearate; ketoprofen; dissolution; scanning electron micrograph

Microencapsulation of drugs using Eudragit RS, a copolymer synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, was previously investigated in a methylene chloride/water system[2)] (this is an evaporation process in the water phase). However, Eudragit RS microcapsules containing drugs (sulfamethizole, furosemide and piretanide) were swollen just after being separated from the purified water phase. The crude product had to be dehydrated under reduced pressure for several days to obtain the microcapsules as a final product. Furthermore, the final product thus obtained was so fragile that it could be broken between the fingers.

A new attempt was made to overcome these defects, swelling and fragility, in order to produce practical Eudragit RS microcapsules containing drugs. This paper deals with the preparation of Eudragit RS microcapsules containing ketoprofen, an anti-inflammatory drug, by the evaporation process in an oil phase, using an acetone/liquid paraffin system.

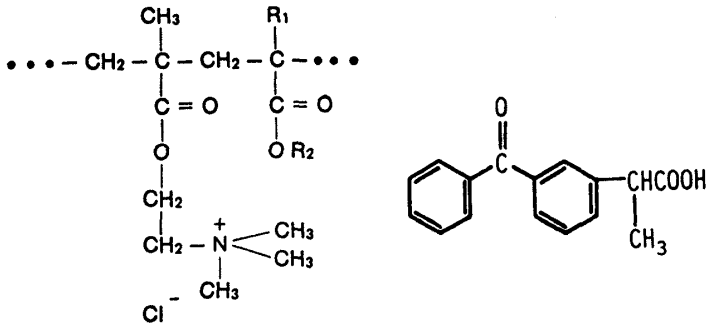
Experimental

Materials——Ketoprofen was supplied by Hisamitsu Pharmaceutical Co. Eudragit RS was a gift from Higuchi Co. The formulae are shown in Chart 1. Aluminium tristearate was a product of Nakarai Chemical Co. Other reagents were all of analytical grade.

Preparation of Microcapsules——The preparation procedure is outlined in Chart 2.

Eudragit RS (5.5 g) was added to 30 ml of acetone in a glass vessel and dissolved completely. Aluminium tristearate and ketoprofen were added, and the mixture was stirred at 250 rpm in a water bath at 10 °C over 20 min. The above solution was poured into 200 ml of liquid paraffin previously cooled to 10 °C and maintained at 35 °C with stirring at 190 rpm for 4 h. During this time, acetone used as a solvent of Eudragit RS could be completely removed by evaporation. The microcapsules were separated by filtration, washed five times with 50 ml of *n*-hexane at room temperature and allowed to dry in a desiccator under reduced pressure (<15 mmHg). The particle size of microcapsules used in the present study ranged from 250 to 1000 μm as determined by sieving with JP X standard sieves.

Various percentages (w/w) of aluminium tristearate were added in order to investigate the effect of aluminium



$R_1 = H$ or CH_3
$R_2 = CH_3$ or C_2H_5

Eudragit RS Ketoprofen

Chart 1. Chemical Structures of Eudragit RS and Ketoprofen

5.5 g of Eudragit RS dissolved in acetone 30 ml
↓
add aluminium tristearate
↓
add drug powder 1.4 g (less than 149 μm particle diameter)
↓
stir (10 °C, 1 propeller, 250 rpm, 20 min)
↓
pour into liquid paraffin 200 ml
↓
stir (gradually heat to 35 °C, 3 propellers, 190 rpm, 4 h)
↓
filter
↓
wash with 50 ml of *n*-hexane (5 times)
↓
dry (12 h, under reduced pressure)

Chart 2. Preparation of Eudragit RS Microcapsules by a Solvent Evaporation Process in Liquid Paraffin

tristearate on microencapsulation as follows: 0.72, 1.43, 2.82, 4.17, 6.76 and 9.21%.

Dissolution Studies——The procedure and apparatus were essentially the same as described in JP X. The dissolution medium (No. 2 solution, pH 6.8, used in the JP X "disintegration test") was introduced (500 ml) into a beaker and stirred at 50 rpm. An accurately weighed amount (10 mg) of ketoprofen was gently spread over the surface of the dissolution medium at 37 °C. At appropriate intervals, 5 ml samples were withdrawn by means of a pipette. The solution was filtered through a dried filter paper to remove any solid drug particles, and the filtrate was taken for analysis. An equivalent volume (5 ml) of fresh dissolution medium was added to keep the volume of dissolution medium in the beaker constant (500 ml). The released ketoprofen concentration was determined spectrophotometrically by measuring the absorption at 254 nm. The release results were plotted as percentage of ketoprofen extracted into the dissolution medium from the microcapsules *versus* time.

Scanning Electron Microscopy——The microcapsules were coated with gold using an Eiko Engineering 1B-3 ion coater under a high vacuum (0.1 Torr) and at high voltage (800—1500 V and 8 mA). Samples obtained were examined with a scanning electron microscope, Hitachi S 510, at 25 kV.

Results and Discussion

Ketoprofen has a very short biological half-life in humans ($t_{0.5}$, 1—2 h) requiring that the drug be administered 3 times a day. Consequently, it is desirable to prepare a sustained release preparation of ketoprofen.

As stated in the previous paper,[1] two problems, swelling and fragility, were found in the Eudragit RS microcapsules prepared by the evaporation process in the water phase.

Therefore, the evaporation process in an oil phase, using an acetone/liquid paraffin system, was examined in this experiment to prepare Eudragit RS microcapsules containing ketoprofen. This method proved to be much more satisfactory.

Flocculation occurred when no aluminium tristearate was added to the microencapsulation system. With the addition of aluminium tristearate, the microcapsules were completely formed. Therefore, it became clear that aluminium tristearate was indispensable for the formation of spherical microcapsules. The ketoprofen content of the microcapsules was always held at about 15% (w/w). Eudragit RS content in the microcapsules amounted to approximately 75—85% (w/w) in theory. The weight percent of microcapsule particles lying in the range of 0—2000 μm is plotted against size in Fig. 1. Reproducible frequency distribution data for different lots of microcapsules prepared on different days were obtained. As shown in Fig. 1, the particle size of spherical microcapsules became smaller with increasing amount of aluminium tristearate. This seemed to be a result of accelerated dispersion of microcapsules in the microencapsulation system by addition of excess aluminium tristearate.

Dissolution tests were carried out to compare the dissolution rates of ketoprofen powder and microcapsules containing ketoprofen. Figure 2 shows the dissolution pattern of ketoprofen from Eudragit RS microcapsules containing various amounts of aluminium tristearate in pH 6.8 buffer solution at 37 °C and 50 rpm. The microcapsules considerably suppressed the dissolution of ketoprofen at pH 6.8 as compared with the powder. Thus, these microcapsules may be useful for biopharmaceutical studies related to sustained release formulations.

It is also evident from Fig. 2 that the release of ketoprofen increased with increasing percentage of aluminium tristearate added to the microcapsules. The above results can be explained well in terms of reduced particle size of Eudragit RS microcapsules, producing a greater surface area per unit weight of microcapsules, with increasing percentage of

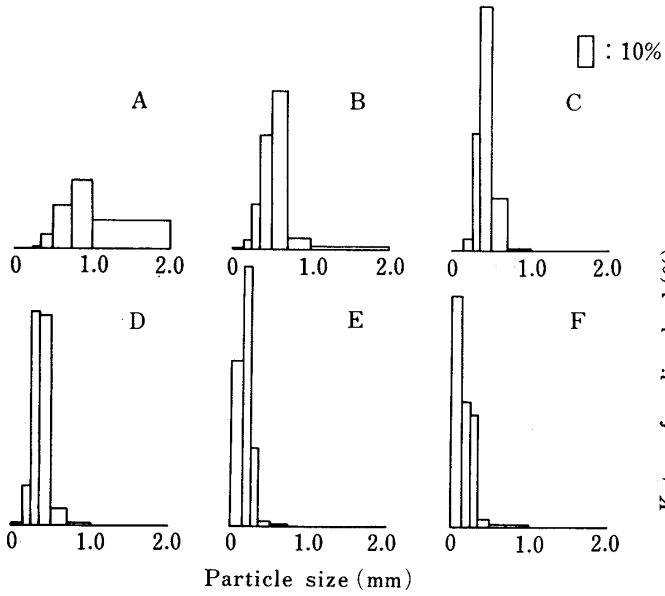


Fig. 1. Frequency Distribution for Microcapsules Containing Ketoprofen

Percentages of aluminium tristearate are as follows: A (0.72%), B (1.43%), C (2.82%), D (4.17%), E (6.76%), F (9.21%).

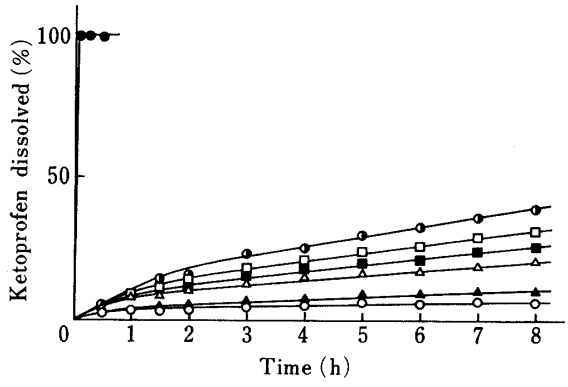


Fig. 2. Dissolution (%) Curves of Ketoprofen from Microcapsules and Powder (—●—) at 37 °C, pH 6.8 and 50 rpm

Percentages of aluminium tristearate are as follows: —○— (0.72%), —▲— (1.43%), —△— (2.82%), —■— (4.17%), —□— (6.76%), —◑— (9.21%).

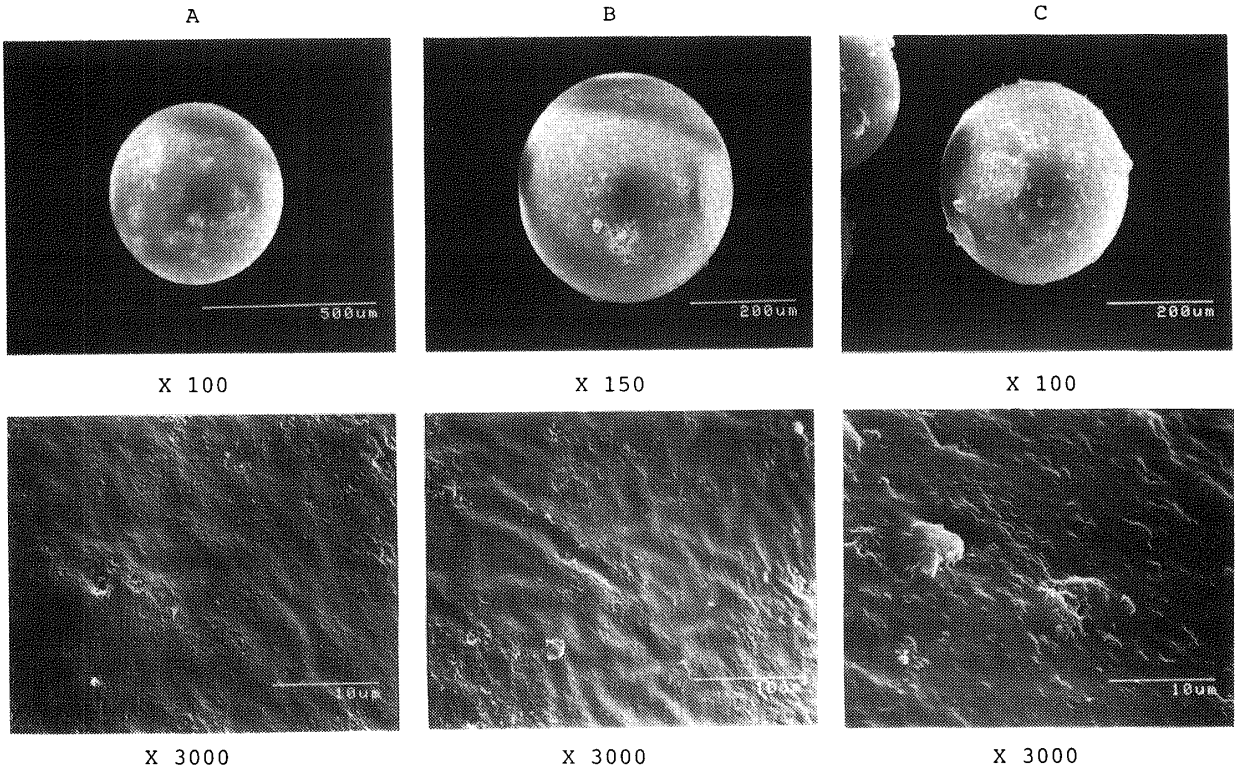


Fig. 3. Scanning Electron Micrographs of Microcapsules Containing Ketoprofen

Percentages of aluminium tristearate are as follows: A (0.72%), B (1.43%), C (2.82%).

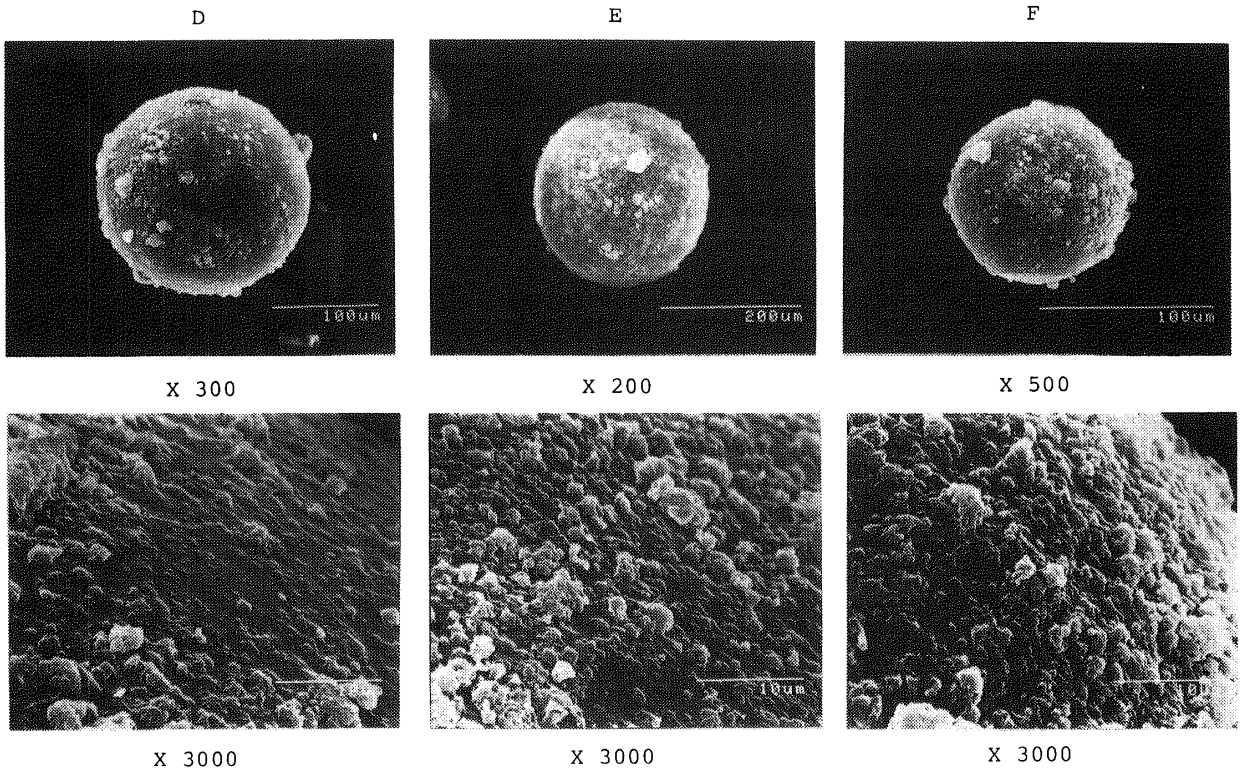
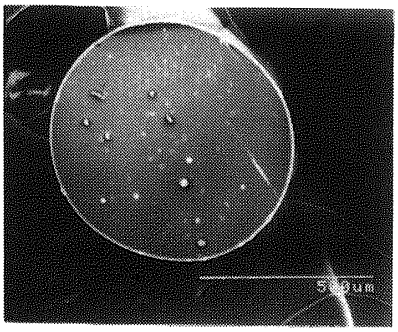


Fig. 4. Scanning Electron Micrographs of Microcapsules Containing Ketoprofen

Percentages of aluminium tristearate are as follows: D (4.17%), E (6.76%), F (9.21%).



X 100

Fig. 5. Scanning Electron Micrograph of a Ketoprofen-Containing Microcapsule Sliced with a Razor Blade

Percentage of aluminium tristearate is 0.72%.

aluminium tristearate. Thus, in oral administration studies in animals, the drug release rate can be easily controlled by modifying the percentage of aluminium tristearate added to the microcapsules.

All Eudragit RS microcapsules obtained were free-flowing spherical particles, as shown in Figs. 3 and 4. The surfaces of microcapsules containing a small amount of aluminium tristearate were relatively smooth (Fig. 3) in contrast to those of microcapsules containing a large amount of aluminium tristearate (Fig. 4). Increasing the content of aluminium tristearate in the Eudragit RS microcapsules appears to induce coarseness of the surfaces of microcapsules.

A scanning electron micrograph of a ketoprofen-containing microcapsule sliced with a razor blade is also shown in Fig. 5. The microcapsule had some pores in the matrix which might have been formed during the solvent evaporation process but the structure of the cross section was relatively fine. It is therefore presumed that the microcapsules prepared by the present method did not have the defects seen in the microcapsules obtained by the evaporation process in the water phase. These microcapsules were also superior in terms of spherical shape to the microcapsules prepared by the coacervation method.[3)]

In general, aluminium tristearate is used as a dispersing agent in the preparation of water in oil (w/o) emulsion. In this experiment, aluminium tristearate was used to prevent electrification and flocculation[4,5)] during the preparation of Eudragit RS microcapsules. Satisfactory results were obtained; that is, unswollen, spherical, solid microcapsules could be prepared by adding a small amount of aluminium tristearate. As shown in Fig. 4, it was recognized that aluminium tristearate existed on the surface of the microcapsules. However, it can be presumed that a part of the aluminium tristearate used also exists in the liquid paraffin because aluminium tristearate is known to dissolve in liquid paraffin. Therefore, the interesting phenomenon described above may be due to reduced interfacial tension between solid particles (Eudragit RS microcapsules) and the vehicle (liquid paraffin) in the preparation of a suspension. Excess addition of aluminium tristearate to the CH_2Cl_2/H_2O system caused large amounts of flocculate, which was due to progressive reduction of the electric charge of Eudragit RS as a result of adsorption of aluminium tristearate, as shown in the previous paper.[1)] It is interesting that the results in this experiment are in marked contrast to those obtained by the evaporation process in the water phase.

The method described here is quite simple and economical, and should be very useful for the future development of sustained release dosage forms. Further results on microcapsules prepared by using Eudragit E, S, L and RL will be reported in subsequent papers.

References

1) This paper forms Part XV of series entitled "Evaluation of Microcapsules." The preceding paper, Part XIV:

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