Preparation of Controlled Releasing Acrylic Polymer Microspheres of Acebutolol Hydrochloride and Those Powder Coated Microspheres with Sodium Alginate in a Polymeric Spherical Crystallization System

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Acrylic polymer (Eudragit-RS 100 or -RS PM) microspheres of acebutolol hydrochloride, a highly water soluble model drug, were prepared by the polymeric spherical crystallization technique with a good solvent (acetone + ethanol), a bridging liquid (water) and a poor solvent (cyclohexane) system. The microspheres were produced through coacervation of the drug and polymer in quasi-emulsion droplets of the good solvent and the bridging liquid mixture, but were dissolved when dispersed in the poor solvent. The preparation mechanism and the ratios of solvents employed for inducing the coacervation were determined by constructing a solubility phase diagram of the polymer in the good and poor solvent systems. To improve the sustained releasing properties of the microspheres, they were coated directly with sodium alginate powder in the same preparation batch of microspheres. The treatments of the microspheres and coated microspheres with triethyl citrate significantly retarded the drug release rates from each due to the improved embedding of the drug in the polymer. When they were formulated into capsules or tablets, the drug release rates were prolonged much further because of their gelled matrix structures formed during dissolution. The drug release mechanism was described by the square root time model by the diffusion of drug through the gelled layer of polymer.

Key words spherical crystallization; microsphere; powder coating; acebutolol hydrochloride; acrylic polymer; sodium alginate

The spherical crystallization technique has been accepted as a useful technique for particle design for pharmaceutical formulation.[2)] In this process, crystallization and agglomeration can be carried out simultaneously in a two (*i.e.*, poor solvent and bridging liquid) or three (*i.e.*, poor solvent, good solvent and bridging liquid) solvent system.[3)] The micromeritic designs (*e.g.*, agglomeration, spheronization) of precipitated crystals are conducted by agglomeration with the bridging liquid under shear force brought about in a stirring system. The resultant spherically agglomerated crystals can dramatically improve the original powder properties, such as flowability, packability and compressibility.[4)] By these micromeritic designs, capping which had occurred during compression of the unagglomerated original crystals was successfully prevented.[5,6)] This technique has been further developed for use with the polymeric spherical crystallization process, in which the precipitated crystals are designed to form functional drug devices, such as microsphere,[7)] microcapsule,[8)] microballoon[9)] and biodegradable nanosphere.[10)] In those systems, a satisfactorily sustained releasing device of a water soluble drug was not always prepared with a water-insoluble polymer for the lack of affinity between the drug and the polymer.[8)]

In the present study, acebutolol hydrochloride was used as a highly water soluble model drug. An improved process to prepare controlled release microspheres was explored in the polymeric spherical crystallization process with acrylic polymers. The preparation mechanism of this process was explained by the coacervation phenomena of polymers which occurred in the system. To accomplish the present objective, a functional additive, such as a plasticizer for the polymer, was introduced into the spherical crystallization system. Further improvements in sustained releasing properties of the resultant microspheres were accomplished by powder coating with sodium alginate after spherical crystallization in the same batch. The resultant coated microspheres were treated with a plasticizer to improve the plasticity of the acrylic polymer when necessary.

The drug release behaviors of the microspheres, coated microspheres and those microspheres treated with plasticizer were investigated. Further, the drug release behaviors from their dosage forms, such as capsules or tablets, were investigated. The mechanisms in the preparation of microspheres, coating, and drug releasing processes from the devices were also clarified.

Experimental

Materials Acebutolol hydrochloride was supplied by Rhône-Poulenc Rorer Co., Ltd. (France). The polymers for the matrix base and the coating material used in this study were acrylic polymer (Eudragit, EuRS 100 or EuRS PM, Röhm Pharma, Germany) and sodium alginate (Duck Algin NS PH^2, Kibun Food Chemifa Co., Kyoto, Japan), respectively. The plasticizers used were triethyl citrate (Nacalai Tesque, Inc., Kyoto, Japan) and polyethyleneglycol (PEG 6000, Kishida Chem., Co., Ltd., Japan). A mixed solvent of ethanol and acetone in a proper ratio was found to be an excellent solvent for dissolving both acebutolol hydrochloride and acrylic polymer. Cyclohexane was selected as a poor solvent, inducing the coprecipitation of both the drug and the polymer. Distilled water was chosen as a bridging liquid due to its good wettability to the drug and the polymer, and immiscibility to the poor solvent, *i.e.*, dispersing medium. A small amount of carboxyvinyl polymer (Carbopol 941, B. F. Goodrich Co., Ltd., U.S.A.) was added to enhance the bridging force of the water when necessary. All solvents were of analytical grade.

Preparation of Coprecipitated Microsphere (CM) of Acebutolol Hydrochloride and Acrylic Polymer The polymeric spherical crystallization technique employed for the preparation of microspheres was the emulsion–solvent–diffusion method developed by the present authors.[4)] The drug (3.0 g) and the polymers (EuRS 100, 3.0 g and PEG 6000, 0.6 g) were dissolved in the mixed solvent of good solvent (acetone and ethanol,

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10 ml each) and water (0.7 ml) at 50—60 °C. Cyclohexane (120 ml), placed in a 500 ml flask with three baffles inserted to improve the agitation of the system, was stirred with a propeller type agitator at 550 rpm. When the drug and polymer solution was poured into cyclohexane at room temperature, a quasi w/o emulsion was immediately formed in the flask. The emulsion droplets were gradually solidified through coacervated droplets along with the diffusion of the good solvent from the droplets into the poor solvent. Finally, the coprecipitated microspheres of the drug-polymer were filtered and air-dried at room temperature for more than 24 h, then stored in a desiccator with silica gel. When necessary, the microspheres filtrated from the preparation system were immersed into 20 ml of cyclohexane dispersing 10% triethyl citrate in a flask under periodic agitation for 1 h by hand. The treated microspheres (T-CM) were filtered and dried, and then stored similarly to the microspheres.

Preparation of Coated Microsphere (C-CM) with Sodium Alginate Powder The preliminarily prepared microspheres were coated in the same preparation batch of microspheres with powdered sodium alginate and magnesium stearate (to improve hydrophobicity). The geometric mean Heywood diameter of sodium alginate and magnesium stearate particles were about 20—30 μm and about 2 μm, respectively. In this process, the drug (3.0 g), EuRS PM (powdered form, 3.0 g), PEG 6000 (0.6 g) and Carbopol 941 (0.03 g) were dissolved in the mixed solvent (ethanol, 8 ml; acetone, 12 ml and water, 0.84 ml) at 50—60 °C. It was found that Carbopol significantly enhanced the cohesive force between the drug and the polymer compared to the use of distilled water alone as a bridging liquid. Similarly to the above method, the drug-polymer solution was poured into cyclohexane (120 ml) under agitation (650 rpm). Sodium alginate (0.5, 1.0 or 1.5 g) and magnesium stearate (0.15 g) were suspended in cyclohexane (7 ml). After completing the preparation of the microspheres, the resultant cyclohexane suspension was added dropwise immediately into the preparation system of microspheres under agitation. The suspended sodium alginate powder gradually adhered on the surface of microspheres and formed a coated microsphere (C-CM). A small amount of surplus water (*e.g.*, 0.14 ml) was preliminarily introduced to the preparation system of microspheres to improve the adherence of the sodium alginate powder on the surface of the microspheres. The treatment of coated microspheres with triethyl citrate was carried out after filtration of the coated microspheres in the similar manner to that used for the treatment of microspheres. The coated microspheres (C-CM) or the coat-treated microspheres (CT-CM) were filtrated and dried using the same procedure used for CM or T-CM. A flowchart of the preparation of microspheres and the coating procedure is shown in Fig. 1.

Measurement of Micromeritic Properties of the Resultant Microspheres The shape and surface topographies of microspheres (CM), coated microspheres (C-CM) and treated microspheres (T-CM, CT-CM) were observed with a scanning electron microscope (JSM-T330, Nihon Denki, Japan). The bulk density (ρ_b) and the mass median diameter (D_{50}) of the microspheres were measured by tapping and sieving methods, respectively. To investigate the thermal behavior and crystalline form of the drug in microspheres, differential scanning calorimetry (DSC-CN 808521, Rigaku Denki, Japan) performed at a heating rate of 10 °C/min, and X-ray diffractometry (RAD-1C, Rigaku Denki, Japan) performed at a scanning speed of 2 deg./min were employed, respectively. The zeta (ζ) potential of EuRS droplets in the dispersion medium was measured by using a Zetameter (PEN KEN 501, U.S.A.) with a non-water measurement system at 50 V of prism voltage and 8 V of application voltage.

Hard Capsule Filling and Preparation of Tablets with Resultant Microspheres The coat-treated microspheres (CT-CM) of $-20+42$ mesh (840—350 μm) sieve fraction were closely packed by hand in a gelatin hard capsule (No. 0, made in China). The weights of the microspheres coated with 0.5, 1.0 and 1.5 g of sodium alginate filled in the capsules were 224 mg, 244 mg and 286 mg, respectively (the weight of drug in each capsule corresponding to about 80 mg). The samples (300 mg, $-20+42$ mesh) of microspheres (CM), coated microspheres (C-CM), microspheres treated with triethyl citrate (T-CM, CT-CM) and the physical mixture (PH) of the drug and polymer corresponding to the formulation of microsphere (CM) were compressed into tablets (10 mm in diameter) using a hydraulic press (Tianjing Sci. Machin., China) at 100 MPa.

Drug Releasing Test Distilled water (900 ml) thermally controlled at 37 °C was used as a dissolution medium under stirring with a rotating basket or paddle at 100 rpm. The rotating basket was employed for both microspheres (with $-20+42$ mesh (840—350 μm) or $-16+20$ mesh (1000—840 μm) sieve fractions) and capsules. The paddle was used for the tablets placed in a sinker. Four ml of dissolution medium was withdrawn at suitable intervals from the system and the same amount of distilled water was added to the dissolution medium. The dissolved drug content was assayed spectrophotometrically at 233 nm (Spectrophotometer, WFZ 800-D2 UV, Shanghai, China). All drug releasing data were represented by the mean values of duplicate or triplicate runs. The maximum deviation was found to be less than 10%.

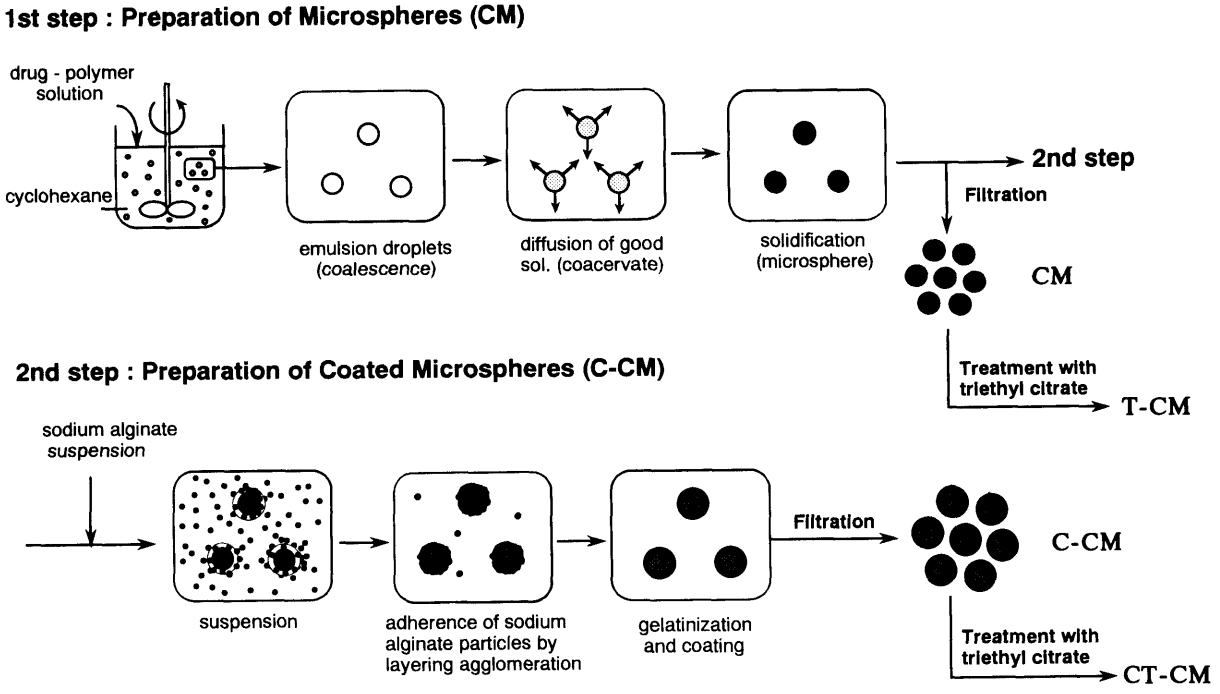

Fig. 1. Polymeric Spherical Crystallization for Preparation of Microspheres and Coating Process

1st step: preparation of microspheres (CM), 2nd step: preparation of coated microspheres (C-CM).

Results and Discussion

Preparation Mechanism of Coprecipitated Microsphere with Acebutolol Hydrochloride and Acrylic Polymer

When the drug-polymer solution was poured into the poor solvent under agitation at room temperature, the system immediately became semi-transparent, like oil. At this stage, small sized emulsion droplets (3—5 μm in diameter measured by an optical microscope) were formed, caused by the rapid diffusion of the good solvent into the poor dispersion medium, as found in the previous studies.[2] Gradually, the dispersion medium became transparent, and the emulsion droplets were coalesced to attain equilibrium in size, depending on the stirring speed. The diameter of emulsion droplets was determined by the balance between the interfacial tension of the emulsion droplets and the shearing force applied to the droplets under agitation. The resultant emulsion droplets could be observed visually. Along with the diffusion of the good solvent, drug crystallization and coacervation of the polymer occurred in the droplets, leading to coprecipitated microspheres. Prolonging the induction period of coacervation was favorable for forming uniform microspheres. The preparation mechanism of the microspheres is illustrated in Fig. 1.

To explain the phase separation phenomena of polymers in this process, a phase equilibrium diagram of EuRS 100 (15%) in the mixture of ethanol–acetone–cyclohexane was constructed in Fig. 2. In this system, the drug was not formulate otherwise, the drug precipitated by introducing cyclohexane disturbed the observation of the phase separation of the polymer. The acrylic polymer was dissolved freely in a mixture of ethanol and acetone because of their forming a cosolvent to the polymer. When introducing cyclohexane, *i.e.*, a dispersing medium, into the mixture, the solubility of EuRS in the system was decreased. In region [M] (*i.e.*, under phase separation line **a**), the polymer was dissolved in the three-solvent system. In the enclosed region [E] (*i.e.*, between coacervation line **b** and the phase separation line **a**), the polymer solution was separated from the system, forming emulsion droplets under agitation. When introducing more cyclohexane into the system, *i.e.*, in the upper region [C] (above line **b**), the emulsion droplets of EuRS were transformed into coacervate droplets. The coacervate droplets gradually coalesced to form a lumped form with increasing cyclohexane. When water (3.5%), the bridging liquid, was commixed in the good solvent mixture (ethanol–acetone), the phase separation line a shifted to the dotted line **a***, due to the decrease in solubility of the polymer in the system. When the polymer was removed from the system, the water phase separation line was represented by the dotted line **b***, on which water was separated and bridged the precipitated drug crystals and the polymer to form a microsphere. In this study, the preparation of microspheres was successfully carried out using the solvent combination in region [I] (oblique line region) in Fig. 2. With increasing the amount of ethanol in region [I], the system moved to a miscible region, where there is no available water capable to bridge between the drug and the polymer, yielding the dispersed drug and polymer powder. When the amount of ethanol

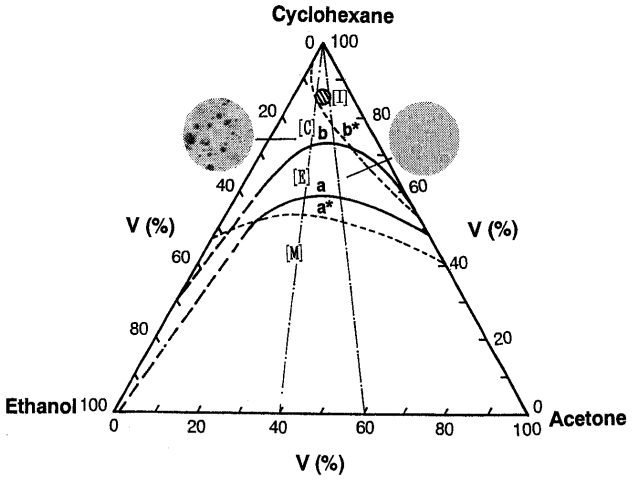

Fig. 2. Solubility Phase Diagram of EuRS 100 (15%) in Good Solvent (Ethanol–Acetone) with Increasing Poor Solvent (Cyclohexane) and That in a Water (3.5%) Containing System

Non-water containing system: **a**, phase separation line; **b**, coacervate formation line; [M], miscible region; [E], emulsion formable region; [C], coacervate formable region. Water containing system: **a***, phase separation line of polymer; **b***, water phase separation line; [I], desired polymeric crystallization region.

was decreased (*i.e.*, increasing acetone), coalesced viscous droplets were formed. This phenomenon may be explained by the following: The increase in acetone increased the amount of separated water, which made coacervate droplets more viscous and easily coalesced. It was found that regarding the ζ potential of polymer emulsion droplets under the condition **a***, the maximum ζ potential value ($\geqq +35$ mV) was found at the acetone–ethanol ratio of 1.0. Electrostatic repulsive force might prevent coalescence of the polymer droplets in region [I] (40—60% of acetone–ethanol mixture). However, above 60% of acetone, the ζ potential was drastically reduced, resulting in the coalescence of coacervate droplets. Therefore, the selection of a proper ratio of ethanol and acetone in the good solvent is very important in the preparation of desirable microspheres.

Water was commixed into the good solvent as a bridging liquid to agglomerate the coprecipitated crystals of the drug and the polymer into coacervate droplets. When the good solvent in the emulsion droplets diffused into the poor solvent, drug crystals were precipitated and suspended in the polymer coacervate droplets. With further diffusion of the good solvent from the coacervate droplets, the drug and polymer were further precipitated in the droplet. The remaining water in the droplet might bridge the drug and the polymer in a funicular state, forming a coprecipitated microsphere. To improve the bridging action of water, PEG 6000 was commixed in the drug-polymer solution, because the resultant aqueous PEG 6000 solution was more wettable to both the polymer and the drug than water. However, over loading of PEG 6000 was unfavorable for sustaining drug release, because of its hydrophilic property, thus increasing drug releasing. Furthermore, the addition of a small amount of Carbopol in the system much improved the drug-polymer affinity, possibly due to the electrostatic interaction between the positively charged acrylic polymer ($-N^+(CH_3)_3-$) and the negatively charged Carbopol ($-COO^-$). Introducing

PEG 6000 and Carbopol into the preparation system improved the recovery of microspheres up to 95% or more. Eighty to 90% of the microspheres remained in the sieve fraction of $-20+42$ mesh (840—350 μm) when prepared with agitation at 700—800 rpm and at room temperature.

Powder Coating of Microspheres with Sodium Alginate Powder coating of the microspheres was carried out using the wet spherical agglomeration technique,[1] by which sodium alginate powder was preferentially deposited on the surface of the microspheres with the bridging liquid (*i.e.*, adsorbed water on the microsphere) by a layering agglomeration mechanism. To smoothly accomplish this layering agglomeration, a small amount of surplus water was preliminarily added to the polymeric spherical crystallization system to avoid the cohesion of sodium alginate powder. The close, intra-packing of the microspheres during agitation squeezed the surplus water to the outer surface of the microspheres due to a capillary action. The sodium alginate powder preferentially adhered on the wet surface of the microspheres and was gelatinized with the water, resulting in the uniform coating of the microspheres. Those coating processes are illustrated in Fig. 1.

Micromeritic Properties of Microsphere and Coated Microsphere with Sodium Alginate Powder The mass median diameter and the bulk density of the coated microspheres increased with an increase in the amount of coating material (sodium alginate) formulated, as shown in Table 1, compared with the uncoated microspheres. These findings indicated that the coating materials were closely adhered on the surface of the microspheres. This was confirmed by observing the surface topographies of microspheres and coated microspheres by the scanning electron microscope (Fig. 3).

It was found that the needle-like fine crystals of drug with polymer were closely compacted on the surface of the microspheres as shown in Fig. 3 (A-1, A-2). A cross section of the microspheres revealed that a polymeric

Table 1. Mass Median Diameter and Bulk Density of Microspheres and Coated Microspheres

Microspheres	Alginate Na (g)	D_{50} (μm)	ρ_b (g/ml)
CM	—	606	0.255
C-CM	0.5	736	0.301
C-CM	1.0	767	0.361
C-CM	1.5	820	0.409

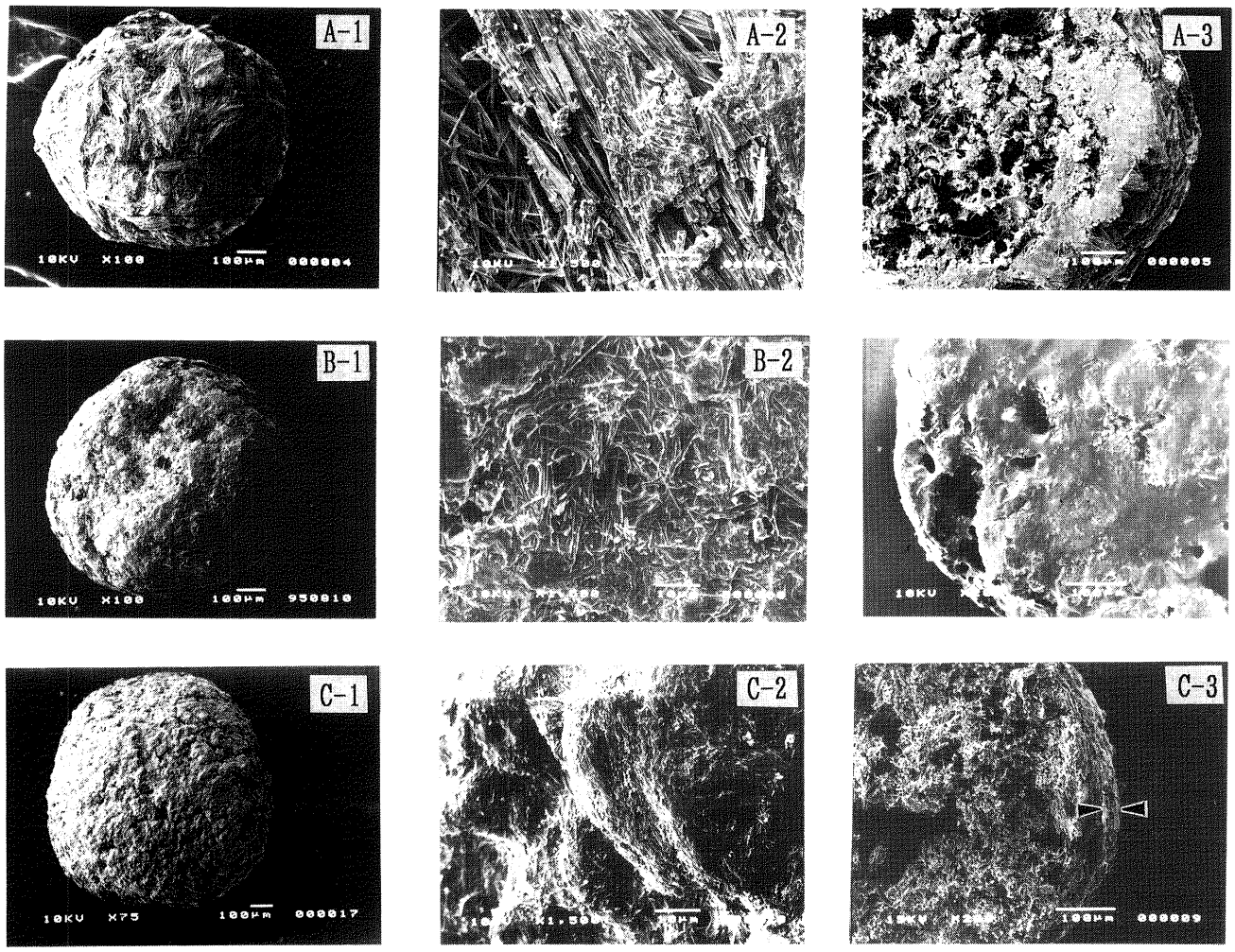

Fig. 3. Scanning Electron Microphotographs of Microspheres

A, coprecipitated microsphere (CM); B, treated microsphere (T-CM); C, coated microsphere (C-CM). A, B, C-1, whole image; A, B, C-2, surface; A, B, C-3, cross section.

matrix structure embedding drug crystals was fabricated in the microsphere (Fig. 3 (A-3)). The surface of the microspheres became smooth, as shown in Fig. 3 (C-1, C-2) following coating with sodium alginate powder, because the needle-like crystals were covered by the coating layer formed on the surface of the microspheres as shown in the cross section of the coated microspheres in Fig. 3 (C-3) (between arrows). When the microspheres were treated with triethyl citrate, the polymeric matrix structure of the microspheres was transformed into a wax-like matrix structure (Fig. 3 (B-3)), which suggested that the triethyl citrate was immersed into the interstices of the microspheres during treatment. This treatment greatly enhanced the plasticity of the polymer, improving the embedding of the drug in the polymer. It was found that the treated microspheres were more plastically deformed by compressing them with fingers, compared with the brittle properties of the untreated microspheres. This finding might be explained by the decrease in glass transition temperature of the treated microspheres. This was speculated by the DSC data showing that the glass transition temperature (37.8 °C) of the mixture of EuRS PM and PEG 6000, coprecipitated in the same preparation system of microsphere without the drug, was lowered to 23.4 °C, when treated with triethyl citrate for 1 h. The drug was removed from the thermocalorimetrical experiments, otherwise the data were too complicated reasonably to analyze. There was a fair decrease (about 8 °C) in the melting point of the original drug (144 °C) in the microsphere by treatment with triethyl citrate, indicating some amorphisms of the drug embedded in the polymer (Fig. 3, B). It was found that the original crystalline form [I][11] of acebutolol hydrochloride remained in all the resultant microspheres according X-ray diffraction analyses.

Drug Releasing Behavior of the Resultant Microspheres The drug release rate of the microspheres (CM) was not significantly retarded compared to that of the spherically agglomerated crystals of drug without polymer (PM), because of the porous matrix structure of the microspheres (Fig. 3 (A-3)) and the high solubility of the drug ($\geqq$1.0 g/ml in water at room temperature). The treatment of microspheres with the plasticizer (T-CM) had little effect on retarding the drug release rate, due to the same reason as the above microspheres and to the excellent wettability of PEG 6000. However, the coat-treated microspheres (CT-CM) significantly prolonged the drug release from the resultant microsphere, which depended on the coating amount used, as shown in Fig. 4. The gel layer formed on the surface of the coated microspheres retarded the diffusion rate of the drug from the microspheres.

Drug Release Behaviors of the Hard Capsules Containing the Coat-Treated Microspheres (CT-CM) When the coated microspheres treated with the plasticizer (CT-CM) were filled in a hard capsule, the drug release rate from the capsule was surprisingly prolonged compared to the dispersed system of the microspheres in Fig. 5. It was found that the coat-treated microspheres coagulated and formed a gelled lump in the hard capsule during the dissolution process. Even after dissolving the hard capsule completely, the gelled microspheres were maintained in coagulated capsule form. This phenomenon might occur

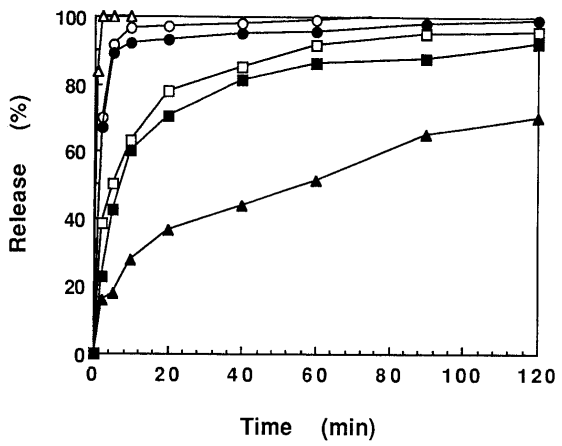

Fig. 4. Drug Release Profiles of Microspheres

△, PM; ○, CM; ●, T-CM; □, CT-CM; ■, CT-CM; ▲, CT-CM. Size fraction of microsphere: △, ○, ●, □, −20+42 mesh; ■, ▲, −16+20 mesh. Amount of sodium alginate for coating: □, ■, 1.0 g; ▲, 1.5 g.

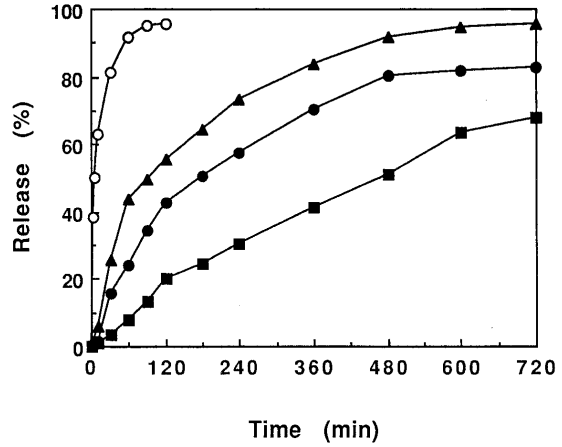

Fig. 5. Drug Release Profiles of Microspheres and Capsules Containing CT-CM

Amount of sodium alginate for coating: ▲, 0.5 g; ○, ●, 1.0 g; ■, 1.5 g. Open symbol, microspheres; solid symbol, capsules.

due to the reduced glass transition temperature of the polymer by treatment with a plasticizer, as found in the previous report,[7] and to the gelatinization of sodium alginate deposited on the microsphere. The drug release rate was significantly retarded by the decreased diffusion rate of drug through this gelled layer. The drug release rate was further reduced when the thickness of gel layer was increased, which depended on the amount of sodium alginate powder formulated for coating.

Drug Release Behaviors of the Tablets with the Microspheres The drug release rate of the tablets of the microspheres (CM) was significantly prolonged compared to that of the physical mixture (PH) of drug and polymer having a corresponding formulation to the microsphere. It was found that the tablets with the microsphere (CM) and coated microsphere (C-CM) gradually reduced in size, along with releasing the discrete microspheres from the outer surface of tablet with some swelling. However, the tablet with the coated microsphere (C-CM) formed a gelled matrix layer, reducing the drug release rate more than that of the uncoated microspheres. The tablets of microspheres treated with the plasticizer (T-CM) were spherically swelled without disintegration during the

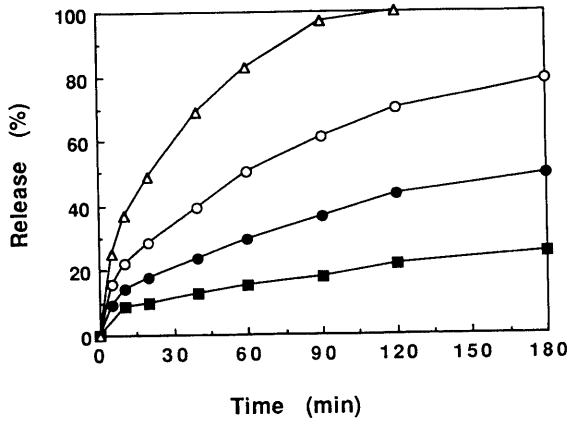

Fig. 6. Drug Release Profiles of Tablets Produced with Microspheres △, PH; ○, CM; ●, T-CM; ■, CT-CM.

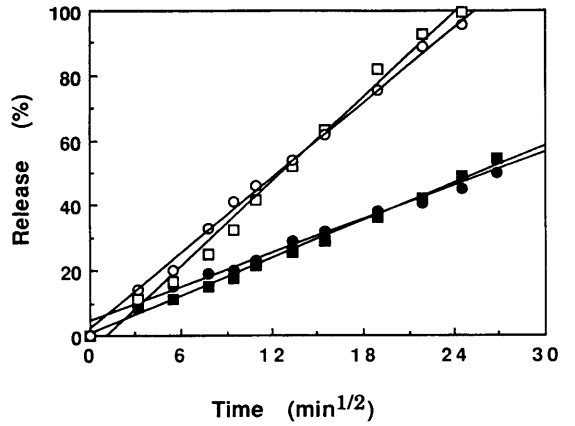

Fig. 7. Drug Release Profiles of Tablets Produced with C-CM, CT-CM Plotted in Square Root Time

Amount of sodium alginate for coating: ○, ●, 1.0 g; □, ■, 1.5 g. Open symbol, C-CM ; solid symbol, CT-CM. Drug release rate constant, K_H and correlation coefficient of the straight line, R (K_H, R): ○, (3.84, 0.996); □, (4.33, 0.992); ●, (1.72, 0.986); ■, (1.94, 0.995).

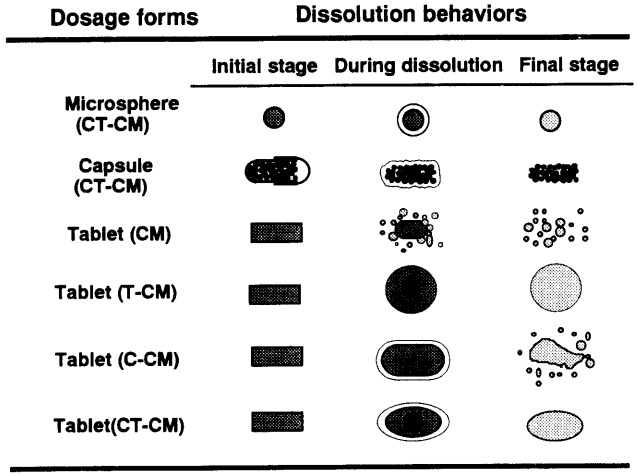

Fig. 8. Drug Release Behaviors of Microspheres (CT-CM), Capsules (CT-CM) and Tablets (CM, T-CM, C-CM, CT-CT)

dissolution process due to the enhanced embedding of the drug in the polymer (Fig. 3 (B-3)). The viscous drug solution pool remained in the center of the tablet, although some swelling occurred, and this pool was shrunk during the dissolution process. The drug release rate from the tablet of coated microspheres treated with triethyl citrate (CT-CM) was much reduced, as shown in Fig. 6, although some erosion of the swelled polymer was observed. The matrix structure with a drug solution pool was also found. It was assumed that the drug release rate was determined by the diffusion of the drug through the gelled matrix layer from a viscous pool saturated with the drug. Fig. 7 shows the drug release profiles of the tablets produced with coated microspheres (C-CM) and coat-treated microspheres (CT-CM), plotted according to the square root model equation (1).[12-14]

$$F_t = K_H \cdot t^{1/2} \quad (1)$$

Where F_t is the percent drug released at time t and K_H is the drug release rate constant. A linear correlation between the percent drug released and the square root of time was found, indicating an apparent diffusion-controlled drug releasing mechanism through the expanding matrix layer. The drug release rate of the tablets was effectively reduced by treatment of the coated microspheres with a plasticizer rather than the coating amount of sodium alginate.

In conclusion, a highly water soluble drug such as acebutolol hydrochloride was successfully entrapped in an acrylic polymer microsphere prepared using the polymeric spherical crystallization technique by improving the embedding of the drug in the polymer in the system. The drug release rate of microspheres was significantly controlled by powder coating with sodium alginate and by plasticizing with triethyl citrate, lowering the glass transition temperature of the polymer, and forming a gel layer on the surface of the microspheres dispersed in water. The drug release rate was further modulated by formulating them into capsules or tablets. Their drug release mechanisms are summarized in Fig. 8.

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