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Research Article

Preparation of Agglomerated Crystals for Direct Tabletting and Microencapsulation by the Spherical Crystallization Technique with a Continuous System

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Adhesive and cohesive properties of chlorpromazine hydrochloride (CP) crystals were modified to improve their powder processing, e.g., direct tabletting and microencapsulation, by agglomeration. Moreover, sustained-released gelling microcapsules of CP were devised to prolong the pharmacological effect. The spherical crystallization technique was applied to prepare agglomerates for direct tabletting and microencapsulation to use them as core materials. The ethanolic solution dissolving CP was poured into a stirred cyclohexane, yielding spherically agglomerated crystals. The resultant agglomerates were free-flowing and easily packable spheres with average diameters of 200 to 1000 μm. The agglomerates reserved the high compressibility of the original powder having a small particle size (14 μm). The compression behavior represented by Heckel's equation suggested that the agglomerates were disintegrated to individual primary crystals at low compression pressures, and then they were closely repacked and plastically deformed at higher pressures. After agglomeration, microencapsulation was continuously performed in the same batch by a phase separation method. Coacervate droplets produced by pouring cyclohexane into a dichloromethane solution, dissolving polyvinyl acetate as a coating polymer, were added to the crystallization system under stirring, to prepare the microcapsules. By filling the microcapsules in gelatin hard capsules or tabletting them, their drug release rates became retarded compared with the physical mixture treated in the same way, having the same formulation as the microcapsules. This phenomenon was due to the gelation of polyvinyl acetate of the microcapsules in the dissolution medium, whose glass transition temperature is very low. This novel sustained-release dosage form is termed "gelled microcapsules."

KEY WORDS: spherical crystallization; direct tabletting; phase separation; microencapsulation; gelation; chlorpromazine hydrochloride.

INTRODUCTION

Modification and design of micromeritic properties of pharmaceutical powders, such as flowability, packability, and solubility, are necessary to guarantee stable and reliable powder processing (mixing, granulation, tabletting, coating; etc.) and to improve the bioavailability of the products. Pharmaceutical powders are often spherically agglomerated by the extrusion and spheronization method (1) or by fixing fine drugs on spherically agglomerated excipients, because the spherical shape has several advantages: (i) Spherical granules have the free flowability and uniform packability required for pharmaceutical processing; and (ii) they are suitable for coating granules since spherical core materials can be uniformly coated with a relatively small amount of polymer.

Development of a novel technique to prepare spherical granules by a unit and simple operation has long been desired. The present authors have developed the spherical crystallization (SC) technique, by which pharmaceutical powders are simultaneously crystallized and agglomerated in one step (2). The products are spherically agglomerated crystals, which are advantageous for improving their micromeritic properties (3,4). This technique can be applied to design novel drug delivery devices, e.g., microsponges (5) or microballoons (6).

In this study, chlorpromazine hydrochloride (CP) was selected as a model drug. The crystal modification of this drug is required to improve the powder processing because of its adhesive and cohesive property. Moreover, a sustained-release dosage form of CP is desirable to prolong its pharmacological effect, because CP is a highly water-soluble drug. In the present study, the SC technique was applied to prepare the agglomerates for direct tabletting. Further, a new process, microencapsulating the resultant agglomerated

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crystals, was continuously performed by using the phase separation method in the same batch after the SC process with cyclohexane as a nonsolvent. In the present report, the micromeritic properties and the compression behavior of the agglomerated crystals for direct tabletting were investigated. Further, the characteristics of the resultant microcapsules (gelled microcapsules) were clarified to develop a novel sustained-release dosage form.

EXPERIMENTAL

Materials

Chlorpromazine hydrochloride (CP) was supplied by Rhône-Poulenc Rorer Co., Ltd. (France). The polymers used in the study were polyvinyl acetate (degree of polymerization, 500; Kishida Chemical Co., Ltd., Japan) as a coating material and ethylcellulose (viscosity, 45 cp; Wako Pure Chemical, Ltd., Japan) as an antiaggregation component.

Preparation of Spherical CP Agglomerates

The procedure for the preparation of agglomerates was outlined previously (5). CP (15 g) was dissolved in ethanol (12.6 mL), which was thermally controlled at 65°C. This ethanolic solution was poured into cyclohexane (200 mL) thermally controlled at 20°C under stirring at 600 rpm. After agitating the system for 5 min, the spherically agglomerated crystals were filtered and dried at 80°C for 3 hr in an oven. The coarse unagglomerated crystals were prepared by recrystallizing CP in an ethanol/diethyl ether system.

Measurement of Micromeritic Properties

The shape and surface topographies of the modified crystals were observed with a scanning electron microscope (JSM-T330, Nihon Denshi, Japan). The particle sizes and their distributions were measured by sieve analysis. The flow property was investigated by measuring the angle of repose ($n = 10$). The packability was evaluated by measuring the tapped density according to Kawakita's (1) and Kuno's (2) equations as follows.

$$(n/C) = (1/ab) + (n/a), \qquad C = (V_o - V_n)/V_o \tag{1}$$

$$\rho_f - \rho_n = (\rho_f - \rho_o)\exp(-kn) \tag{2}$$

where n is the tapped number, V_o and V_n are the powder bed volumes in the initial and nth tapped state, respectively, and ρ_f, ρ_n, and ρ_o are the apparent densities in the equilibrium, nth tapped, and initial state, respectively.

Measurement of Compressibility

The compressibilities of original and agglomerated crystals were evaluated by the tensile strength required for crushing the tablets prepared by compressing them without excipients. The tablets were prepared using a compaction test apparatus (Autograph 5000D, Shimadzu, Japan) with a die with an 8-mm internal diameter and flat-faced punches. The agglomerates fractionated to 350–500 μm and the original (average diameter, 14 μm) and the recrystallized (average diameter, 310 μm) crystals were used for tabletting. Two hundred milligrams of the crystals was compressed with the upper punch moving down at 2 mm/min and releasing at 2 mm/min, then the tablet was ejected with the lower punch moving up at 100 mm/min. The apparent volume of the compact was determined from the stroke distance of the upper punch to calculate the porosity (ϵ) of the compact during compression. Data were analyzed by the following Heckel equation to evaluate the densification process of the powder bed:

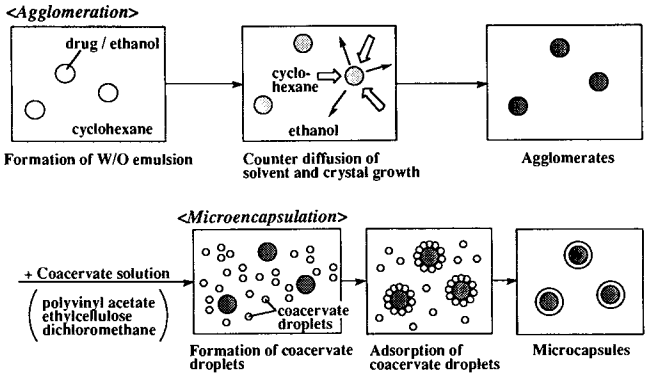
$$\ln(1/\epsilon) = kP + A \tag{3}$$

where ϵ is the porosity at an applied pressure P, and k and A are constants. The yield pressure, from the reciprocal of k, was obtained by regression analysis of the linear portion of the plots. The diameter (D) and thickness (T) of the tablet were measured with a dial-gauge. The tablet was compressed diametrically at 0.5 mm/min using an Autograph, and the force (F) fracturing the tablet was measured to calculate the tensile strength by Eq. (4). The data are expressed as the mean value of triplicate measurements.

$$\text{Tensile strength} = 2F/\pi DT \tag{4}$$

Microencapsulation

After preparing the agglomerates (drug loading, 4 g), the microencapsulation process was continuously applied in the same batch by a phase separation method at room temperature. A flowchart of the procedure is shown in Scheme I. Coacervate droplets were produced by pouring cyclohexane (60 mL) into a dichloromethane solution (30 mL) of polyvinyl acetate (0.57 g) as a coating polymer, where ethylcellulose (0.9 g) was codissolved to prevent coacervate droplets from aggregating. A sample withdrawn was observed under an optical microscope. The phase diagram was constructed to find the phase separation region to prepare stable coacervates. Then the coacervate dispersions were added to the agglomerates remaining in the system after removing the crystallization solvent by decantation. The system was subsequently agitated for 30 min to allow further generation of coacervate droplets. Then 170 mL of a nonsolvent (mixture of pure cyclohexane and the crystallization solvent removed) was added to the system under agitation to harden the coacervate film, leading to the formation of microcapsules. The resultant encapsulated particles (microcapsules) were sepa-



Scheme I. Scheme of sequential process for agglomeration and microencapsulation.

rated and dried at room temperature in a desiccator on silica gel for more than 1 day.

Release Test of CP from Microcapsules

The microcapsules fractionated to 500–1000 μm were compressed into a tablet or packed in a gelatin hard capsule (No. 3) to characterize the release behavior. The drug release tests of the resultant tablet or capsule were carried out by the paddle method specified in the Japanese Pharmacopeia XII (JPXII). The sample placed in a sinker was rotated at 100 rpm in distilled water (900 mL) thermally controlled at 37°C. The sample solution was withdrawn at suitable intervals from the dissolution vessel and assayed spectrophotometrically at 263 nm (UV-160A, Shimadzu Co., Ltd., Japan).

Penetration Rate of Water Through a Powder Bed of Polymer

One hundred milligrams of polyvinyl acetate powder was manually packed in a glass tube (inside diameter, 3.5 mm) and tapped until the length of the powder bed reached 3 cm (porosity, 35%). The front opening of this tube was covered with filter paper, then the tube was horizontally placed in a water bath thermally controlled at 20 or 37°C, at 1 cm below the water surface. To prevent water from flowing into the opposite opening of the glass tube, the opening of the glass tube was connected to a rubber tube opened to the air. The distance of water penetration into the powder bed was measured directly with a scale.

RESULTS AND DISCUSSION

Preparation Process and Micromeritic Properties of Agglomerates

When the ethanolic solution of the drug was poured into cyclohexane, finely dispersed ethanol droplets were formed immediately, because of the delayed diffusion of ethanol interacted with the drug diffusion into cyclohexane. The ethanol and cyclohexane counterdiffused out of and into the droplet of ethanol, respectively, inducing the crystallization of CP in the droplets. Finally, spherical crystals of CP were produced, which preserved the original shape of the emulsion droplets initially formed as shown in Scheme I.

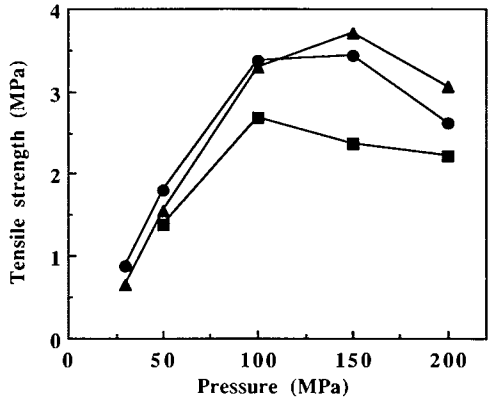


Fig. 1. Compressibility of agglomerates and original powders. (●) Agglomerates; (▲) original powders; (■) recrystallized powders.

It was found that the agglomerated CP preserved its original physicochemical properties, such as crystalline form and crystallinity, which were proved by thermal analysis with a differential scanning calorimeter (DSC Model CN808521, Rigaku, Japan) and powder X-ray analysis with a diffractometer (RAD-IC, Rigaku, Japan).

The micromeritic properties of the agglomerates fractionated by standard sieves are shown in Table I, including those of the original powders as a reference. The flowability, represented in terms of the angle of repose of the agglomerates, was much improved compared to those of the original powders, which were fine plate- or rod-like crystals. The agglomerates were easily packed by tapping, the process of which was described by Kawakita's and Kuno's equations (7,8). The smaller values of parameter *a* in Kawakita's equation for the agglomerates indicated their higher packabilities than the original powders'. The larger values of parameter *k* in Kuno's equation for the agglomerates indicated that the rate of their packing process was much higher than that of the original crystals. The excellent flowability and packability of the agglomerates were attributed to the increase in particle size. Further, the spherical shape was also a factor of improvement in the micromeritic properties, because the ag-

Table I. Micromeritic Properties of Original Powders and Agglomerates

Sample (average size)	Parameter in Kawakita's equation *a*	*b*	Parameter in Kuno's equation *k*	Angle of repose (°)
Original powders (14 μm)	0.437	0.030	0.021	56.7
Recrystallized powders (310 μm)	0.544	0.031	0.014	58.9
Agglomerates				
214 μm	0.230	0.188	0.087	44.2
300 μm	0.152	0.196	0.096	40.0
425 μm	0.103	0.201	0.112	37.8

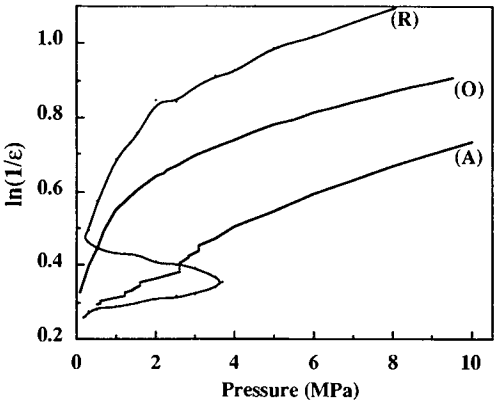


Fig. 2. Heckel plots of agglomerates and original powders at lower compression pressure. (A) Agglomerates; (O) original powders; (R) recrystallized powders.

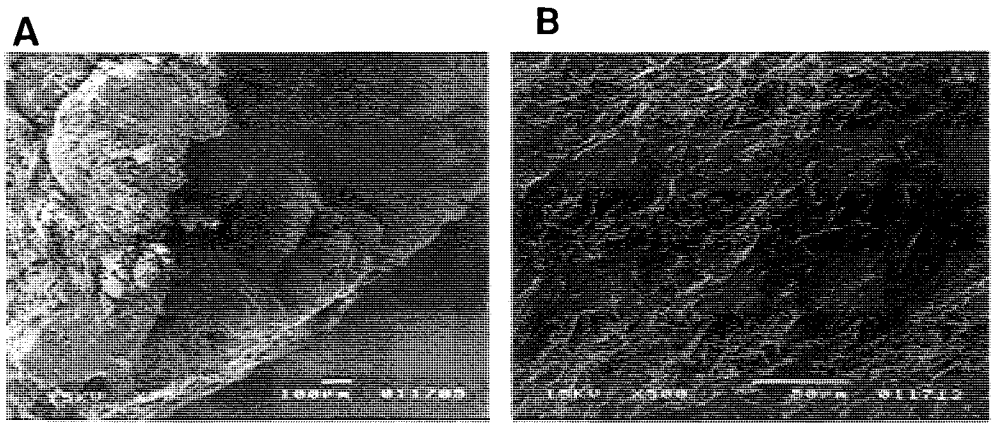


Fig. 3. Scanning electron microphotographs of a cross section of a tablet prepared with agglomerates at (A) 10 MPa and (B) 100 MPa.

glomerates still had properties superior to those of the recrystallized powders, with a 310-μm size and a needle-like shape. Improvements in flowability and packability of the agglomerates might be satisfactory for direct tabletting due to their smooth flowing and packing into the die cavity of the tablet machine.

Compressibility of Agglomerates

The compressibility of the agglomerates was evaluated by the tensile strength required for destructing a tablet prepared by direct compression (9). Figure 1 shows the tensile strength of the tablet compressed at various compression pressures. The higher tensile strengths for the original powders of CP indicated their high compressibility due to their small particle size (14 μm). However, the unagglomerated recrystallized powders of a larger size (average diameter, 310 μm) showed a poorer compressibility than the original powders. In particular, the recrystallized powders could not be transformed to tablets by compressing at 30 MPa due to their low compressibility. Therefore, the high compressibility of the original powders was assumed to be due to their small size. On the other hand, the agglomerates retained the excellent compressibility of the original powders irrespective of their "agglomerated" form. The tensile strengths of all samples decreased at higher compression pressures because some cappings occurred.

To clarify the cause of this phenomenon, the compression process represented by the relationship between compression pressure and porosity of the powder bed was analyzed by means of the Heckel equation (10,11), which is widely applied to elucidate the compression mechanism of powders. The Heckel plots obtained during compression of powders or agglomerates at pressures below 10 MPa are illustrated in Fig. 2. The original powders exhibited a smooth curve over the entire pressure range, which was attributed to densification of the powder bed occurring by particle movement and rearrangement (10,11). During the compression of the recrystallized powders, a large stress relaxation was observed at 4 MPa. This phenomenon was derived from the destruction of the scaffolding structure built of large-sized needle crystals. The agglomerates also showed a noncontinuous stress curve around 0.5–3 MPa of compression pressure, indicating the deformation or the crushing of the "ag-

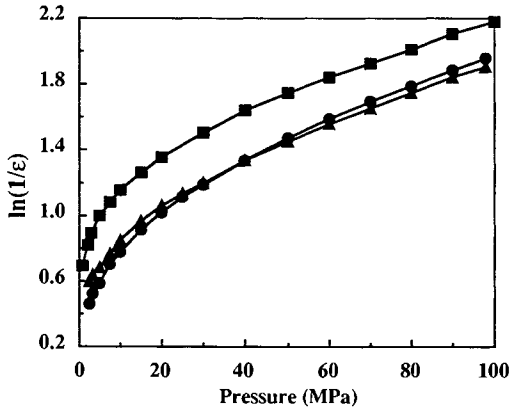


Fig. 4. Heckel plots of agglomerates and original powders at higher compression pressures. Sample, yield pressure (MPa): (●) agglomerates, 94.6; (▲) original powders, 102.2; (■) recrystallized powders, 112.1.

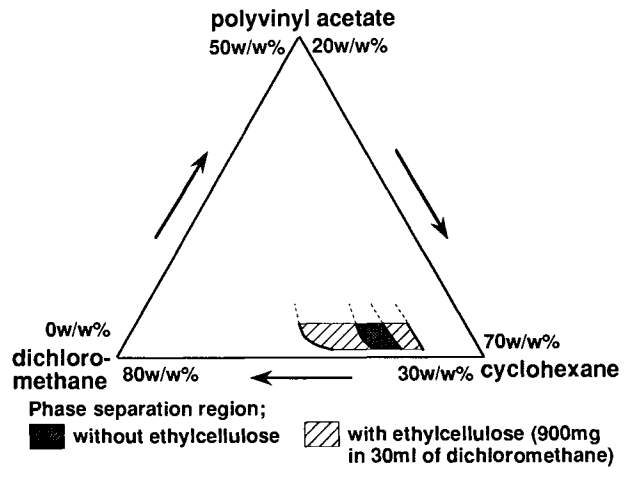


Fig. 5. Triangular phase separation diagram of polyvinyl acetate in the dichloromethane–cyclohexane system. The net and oblique zones show the stable coacervation regions in the absence and presence of ethylcellulose (900 mg) in the system, respectively, as discussed under Experimental.

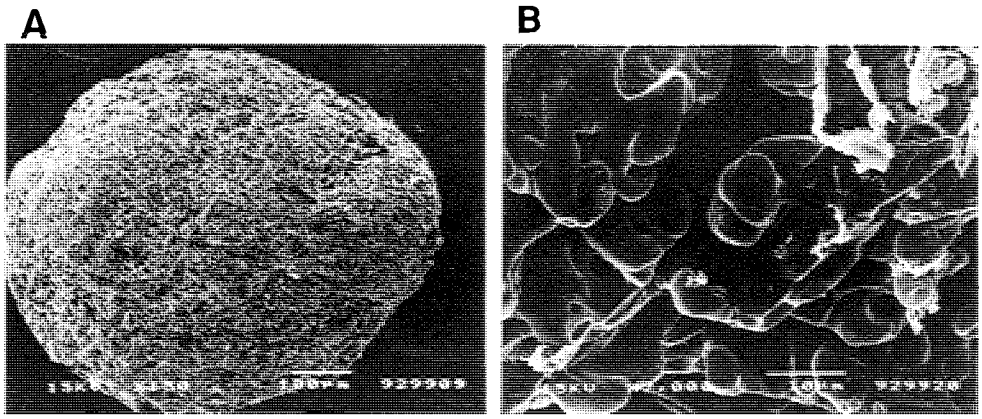


Fig. 6. Scanning electron microphotographs of a microcapsule. (A) Appearance of the microcapsule; (B) magnified inner surface of the microcapsule after drug release at 20°C.

glomerated" structure, causing the relaxation of stress. A scanning electron microphotograph of a cross section of the tablet showed that the "agglomerated" structure partially remained in the tablet compressed at 10 MPa (Fig. 3A), suggesting that the densification process of the agglomerates at lower pressure was due to both the disintegration to primary crystals and the plastic deformation of the agglomerates.

The compression behaviors expressed by the Heckel plot at higher pressures, up to 100 MPa, are shown in Fig. 4. At compression pressures above 25 MPa, the plot obtained with the agglomerates was almost superimposed on that of the original powders. It was also found by SEM that the "agglomerated" structure disappeared and fine crystals were closely packed in the cross section of the tablet compressed at 100 MPa (Fig. 3B). These results suggested that the agglomerates disintegrated into the individual primary crystals composed of them at compression pressures lower than 25 MPa, and then each crystal rearranged and plastically deformed at higher compression pressure. The data obtained over the range of compression pressures 40–100 MPa were analyzed by applying the Heckel equation, and then the yield pressure was calculated from the reciprocal of the slope, k, of the regression line (Fig. 4). Heckel reported that the linear portion of the plot represented the densification process by particle deformation after interparticle bonding and that soft, ductile powders have lower yield pressure values (11). The agglomerates which had the lowest value could be very plastically deformed as a result of the rebonding of smaller primary crystals than those of the original powders. Therefore, the agglomerates behaved like assembled secondary particles without compression and primary particles after compression, resulting in their excellent flowability, packability, and compressibility.

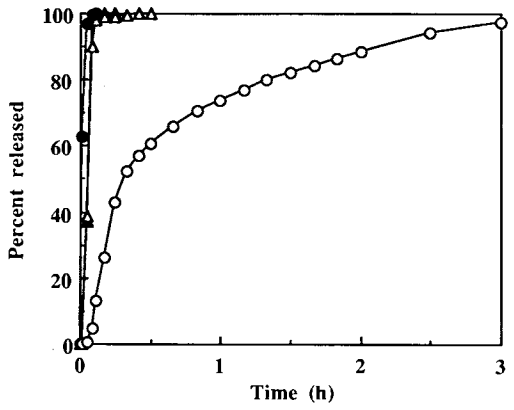


Fig. 7. Release profiles of chlorpromazine hydrochloride from microcapsules and physical mixtures packed in a hard capsule. (●) Unpacked microencapsulated agglomerates of CP; (○) microencapsulated agglomerates packed in a hard capsule; physical mixtures of CP and P-VA containing 84.6% (▲) and 33.3% (△) CP packed in a hard capsule.

Microencapsulation of Agglomerates and Drug Release Behavior from the Gelled Microcapsules

The resultant spherical agglomerates prepared by the SC method were continuously coated with a polymer in the same batch (in cyclohexane) by a phase separation method. Polyvinyl acetate (P-VA) was selected as the wall material because this polymer forms coacervate droplets in the cyclohexane–dichloromethane system according to a previous report (12). Cyclohexane was added to the dichloromethane phase, dissolving P-VA to induce the coacervation. Figure 5 shows the phase diagram of P-VA in the dichloromethane–cyclohexane mixture containing no core materials. The region for generating stable coacervate droplets 5–70 μm in size was obviously expanded by coadmixing ethylcellulose in the system, which played two roles in the coacervation of P-VA. First, it worked as a coacervation inducing agent; that is, the coacervation was generated by smaller amounts of cyclohexane poured into the system with ethylcellulose than without it. Second, it worked as a protective colloid effectively to prevent coacervates from aggregating. The resultant coacervate droplets of P-VA deposited preferentially onto the surface of the agglomerates, satisfactorily producing the microcapsules. In the presence of ethylcellulose, the aggregation of each microcapsule also could be effectively avoided and the particle sizes of the resultant microcapsules were similar to those of the agglomerates. In other words, the size of the microcapsule could be easily controlled by changing the size of the agglomerate, which was determined

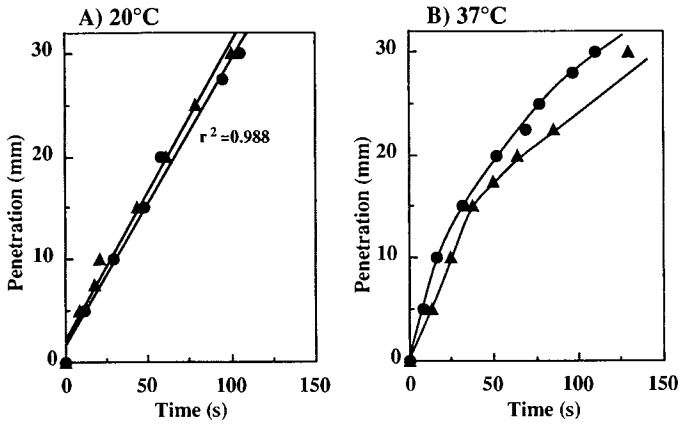


Fig. 8. Water penetration behavior into a polyvinyl acetate powder bed at (A) 20°C and (B) 37°C. (● and ▲) Runs 1 and 2.

by changing the agitation speed in the system during the crystallization process. Due to the spherical shape of the agglomerates, microencapsulation could also be conducted successfully with little aggregation. It was found that over 90% of the core agglomerates could be recovered as microcapsules, and the polymer content in microcapsules (500–1000 μm in diameter) was 13–17%. Ethylcellulose was not contained in the microcapsules according to the FT-IR assay (1720X, Perkin, Elmer, U.S.A.).

Figure 6A shows the scanning electron microphotographs of microcapsules obtained by the present continuous technique. Although the agglomerates retained their spherical shapes without disintegration and aggregation, the shell-type coating layer was not observed on the surface of the microcapsule. The SEM of the microcapsule after drug release (Fig. 6B) revealed that the microcapsule had a porous matrix structure rather than a reservoir structure, whose primary crystals were coated with polymer. The coacervate droplets of 10 μm in size, which were much smaller than the size of the agglomerates (500–1000 μm), deposited in the interstices of the agglomerates, resulting in the microcapsules having a unique structure.

Since CP is a significantly water-soluble drug, the microcapsules prepared did not have acceptable sustained-release properties as shown in Fig. 7 (T_{50} < 1 min). However, when the microencapsulated agglomerates were packed in a gelatin hard capsule, their release behavior was considerably retarded compared with the physical mixture having the same or a higher polymer content in the microcapsules. This phenomenon might be due to the gelation of P-VA in the dissolution medium at 37°C because the glass transition temperature (T_g) of this polymer was low (about 27°C) as determined with a differential scanning calorimeter (DSC 220C, Seiko Instruments Co., Ltd., Japan). Therefore, it was assumed that P-VA distributed evenly inside and outside of microcapsules, formed a gelatinous film, coalescing the microencapsulated particles into a single unit in the gelatin hard capsule by heat. However, the microencapsulated agglomerates unpacked in the gelatin capsule did not show such sustained-release behavior even after preheating at 37°C.

To clarify this phenomenon, the water penetration behaviors into a P-VA powder bed packed in a glass tube were investigated at various temperatures. Below the T_g (at 20°C) the water penetration rate into the polymer bed, which was represented by the slope of the regression line of the penetration distance vs time, was constant during the test (Fig. 8A). On the other hand, above the T_g (at 37°C) the penetration rate decreased remarkably with time because the gelation and fusion of the P-VA powder caused by the water penetration formed a barrier layer against further water uptake (Fig. 8B). The gelation of the microcapsules caused a decrease in the specific surface area and the elongation of the diffusive path in the microcapsule led to the retardation of drug release. Due to the characteristic structure as observed by SEM (Fig. 6B), P-VA was homogeneously distributed in the present microcapsules and had a large effective surface area, resulting in rapid gelation and interfusion of individual microencapsulated agglomerates. This novel sustained-release dosage form was termed "gelled microcapsules." The physical mixture of CP ad P-VA packed in the capsule did not exhibit such a sustained-release property.

To develop another sustained-release dosage form, the

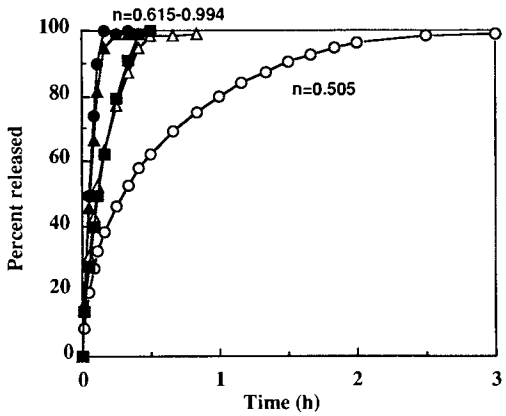


Fig. 9. Release profiles of chlorpromazine hydrochloride from tablets compressed at 100 MPa. Tablets of (●) CP crystals, (○) microencapsulated agglomerates, and physical mixtures of CP and P-VA containing 84.6% (▲), 50% (Δ), and 33.3% (■) CP. Peppas' equation, $M_t/M_\infty = k \cdot t^n$:$M_t/M_\infty$, the fraction of drug release at time t; k, dissolution rate constant; and n, release exponent.

microencapsulated agglomerates were tabletted directly, without any additives. The tablets compressed at 100 MPa were used for the release test because of their acceptable tensile strength (about 2 MPa). Although the tablets which were prepared by compressing the drug crystals alone or the physical mixture having the same or a higher polymer content of the microcapsules showed rapid release profiles, drug release from the microcapsule-tablets was considerably retarded (Fig. 9). During the release test the physical mixture-tablets were quickly disintegrated but the microcapsule-tablets retained their original shape until CP release was completed. To explain the release mechanism of CP, the dissolution data were analyzed using the model introduced by Peppas (13), which has been used to describe drug release from swelling-controlled systems. The release exponent in Peppas' equation for the microcapsule-tablets was about 0.5, suggesting that the drug was released by diffusion through the polymeric matrix. This result was explained by the fact that the P-VA in the microcapsules rapidly gelled and the matrix structure was built in the tablet in the early stage of the release test.

The drug release behaviors of the microcapsules packed in a hard capsule and the microcapsule-tablets were similar, with porosities of 78 and 12%, respectively, indicating that the sustained-release property of the gelled microcapsules was independent of their compactness in the device (i.e., porosity). This property was attained if the individual microcapsules remained assembled at least until starting the gelation of the polymer.

In conclusion, the preparation of the agglomerates for direct compression and the continuous microencapsulation process in the same batch were successfully achieved by combining the SC technique and the phase separation method. The agglomerates had excellent flowability, packability, and compressibility. Sustained release of a highly water-soluble drug was achieved by compressing the microcapsules into tablets or packing them in gelatin hard capsules, respectively.

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