Dissolution Properties of Soybean Lecithin Microcapsules for Short-Term Controlled Release Prepared Using the Wurster Process

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Microcapsules with a soybean lecithin coat as a short-term controlled release dosage form were successfully prepared using the Wurster process. Each of them was composed of a lactose core of 75–106 μm, a drug-layer of carbazochrome sodium sulfonate (CCSS, a model drug), soybean lecithin (SL), cholesterol (CH), stearic acid (SA) and polyvinylpyrrolidone (PVP) and a coat of SL, CH, SA and PVP. Their release properties were evaluated at 37 °C in a 0.9% saline solution by a column method. When the coat lacked either or both CH and SA, the microcapsules showed rapid burst in CCSS release. However, the release of CCSS exhibited a short-term delayed and subsequently prolonged profile when the coat was composed of all of four components; the lag time and the subsequent release rate were sensitive to the composition of coat and the coating level. As a dosage form with a short-term controlled release property, the microcapsules more than 100% coated with a SL–CH–SA mixture of 5:5:2 weight ratio and 42% PVP based on this mixture were found.

Keywords microcapsule; lecithin; controlled release; coating; fluidized bed; delayed release

Various phospholipids have been used for pharmaceutical solid dosage forms, including coprecipitates,[1,2] solid dispersions,[3] suppositories,[4] granules[5] and tablets.[6] Most of them were essentially matrix systems intended to improve the solubility and dissolution rate of poorly water-soluble drugs or to sustain release of water-soluble drugs. In this study, phospholipids were applied as a membrane material of microcapsules, because their sensitive and widely variable response to hydration was expected to especially lead to a variety of short-term controlled release properties in a manner different from the matrix systems. For example, a controlled release system such as a short-term delayed and subsequently prolonged release dosage form would be beneficial for taste-masking, chemoembolization therapy in cancer treatment,[7] neutron-capture therapy of cancer[8] and so on.

The physicochemical processes in liquid phases like the emulsion process and the phase-separation method have been used to prepare microcapsules and microspheres. In spite of their convenience for laboratory-scale production, it was very often difficult even for their fundamental properties, such as particle size, drug content and release rate, to be flexibly adjusted to requirements from preclinical approaches. A method to prepare particulate systems whose properties could be changed over a wide range seemed to be required for more effective therapy.

The fluidized bed processes, including those of tumbling, spiral and centrifugal fluidization, are considered to more flexibly produce particles with various structures and properties than many other microencapsulation methods due to their simple mechanism of film-formation. However, in spite of their many advantages, their applications have long been limited to particles larger than 200—300 μm. The Wurster process,[9] a kind of spouted bed process, has been characterized by fine particle coating; however, comprehensive approaches to fine particle coating technologies have only recently been started by some of the present authors. They reported that even such a fine powder as 12 μm corn starch had been discretely coated as single-core microcapsules by the Wurster process.[10] This seemed to open a new road for broader applications of the Wurster process for particulate drug delivery systems.

There are two ways to seek new coating materials for use in preparing microcapsules with required functions: the first is to synthesize new compounds; the second is to constitute new mixtures by using well-known materials. Since newly synthesized materials must be investigated for their biological toxicity, their practical or clinical use is delayed. In this study, soybean lecithin was used as the main membrane material of microcapsules, because it is nontoxic and its sensitive hydration was expected to lead to some interesting short-term controlled release properties; especially, its bioerodible properties in water were expected to allow broad applications to cancer therapy such as chemoembolization and neutron-capture therapy.

Experimental

Materials Lactose (DMV 200M) sieved to 75—106 μm was used as a core material. Soybean lecithin (SL, CP reagent grade, about 30% phosphatidylcholine, a minimum of 95% phospholipids), cholesterol (CH, SP reagent grade), stearic acid (SA), polyvinylpyrrolidone (PVP, K30, molecular weight (MW) = 45000), methylene chloride and ethanol were used as purchased from Nacalai Tesque Co., Ltd. without purification. Carbazochrome sodium sulfonate (CCSS), a water soluble model drug, was supplied by Kanebo, Ltd. Glass beads (200 μm, GB-02, Top Co., Ltd.) used as a diluent in dissolution tests were washed with ethanol and distilled water.

Coating An NQ-GM spouted bed coater with a draft tube (Fuji

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Paudal Co., Ltd.) was used. A spray nozzle of 0.8 mm diameter and a bag filter with an opening of about 5 μm were employed throughout all experiments.

Particle Size Distribution A sieve analysis was performed using a row-tap shaker (Iida Seisakusho Co., Ltd.). The shaking time was 10 min and the charged weight was 50 g.

Dissolution and Drug Content Dissolution tests were performed by a column method using a high-performance liquid chromatograph (HPLC, Shimadzu LC3A), as previously reported.[8b] The prepared microcapsules were dried in a vacuum at room temperature for 12 h. A constant weight, 5 mg, of microcapsules was mixed with 185 mg of glass beads and poured into a stainless steel column for HPLC; no correction of dissolution data was performed with regard to drug content, since interest in this study was primarily in the dissolution profile. A 0.9 % saline solution was used as a dissolution fluid. The solution eluted from the column was monitored at 330 nm by a spectrophotometric detector (Shimadzu SPD-2A). When microcapsules burst very rapidly and some water-insoluble fragments were generated, increase in absorbance due to turbidity was observed in the dissolution tests with the corresponding placebos. Otherwise, the placebos exhibited no significant level of absorbance.

To determine drug content in the microcapsules, 30 mg of microcapsules was dissolved in a glass tube containing 10 ml of chloroform and 20 ml of distilled water, and then the tube was vortexed and centrifuged (Kubota KN-30F) at 3000 rpm for 10 min. The amount of CCSS in 1 ml aqueous phase was spectrophotometrically determined at 363 nm and used to estimate the CCSS content in microcapsules.

Polarizing Microscopy An Olympus POM polarizing microscope was used with a heating stage (MHS, Union Optical). Microscopic observation was performed on microcapsules immersed in a 0.9% saline solution at 37 °C.

Differential Scanning Calorimetry (DSC) DSC samples were prepared by dissolving 500 mg of membrane materials (each individual component or their mixtures) in 50 ml of methylene chloride–ethanol (1 : 1) with slight heating (below 30 °C), evaporating the solvent by a rotary vacuum evaporator at about 25 °C and subsequently drying in a vacuum overnight at room temperature. A differential scanning calorimeter (Shimadzu, DSC-50), equipped with a thermal analyzer (Shimadzu, TA-50WS) on a computer for process controlling, data collection and evaluation, was used. The onset temperatures, taken as the points of intersections of the tangents to the leading edge of the endotherm and to the baseline, of the heating thermograms were considered the temperatures of the peaks. A powdered sample of 6—7 mg, except for 1.65 mg of SA, was loaded into an aluminum sample pan, crimped and heated at a rate of 5 °C/min under a nitrogen flow of 30 ml/min and a thermogram was recorded over the temperature range of −30 to 110 °C.

X-Ray Diffraction X-Ray diffraction patterns were recorded with a Rigakudenki X-ray diffractometer, Miniflex 2005 (Ni filter, CuK_α, 30 kV, 10 mA; time constant, 1 s; scanning rate, 2 degree/min). Powder samples were prepared in the same manner as those in DSC.

Results

Design and Preparation of Microcapsules As a core material, lactose was chosen. Its high water-solubility was expected to introduce water into the microcapsules and its consequent osmotic pressure to act as a driving force to induce a rapid response to water.

SL was selected as the main component of membrane because of its water-insoluble and amphiphilic properties, which were expected to lead to low permeation of its membrane and/or easy erosion of the coat of microcapsules in aqueous media. However, coating of only such a small molecule as lecithin resulted in very low efficiency in the Wurster process. Therefore, a polymeric binder was required to achieve a sufficient efficiency of spray coating; PVP was used for this.

In a preliminary experiment, microcapsules coated with SL and PVP rapidly burst in a column dissolution test. Therefore, using cholesterol and stearic acid as additives, membrane compositions with short-term controlled release properties were sought.

Details of the cores, the composition of spray solution and the coating conditions are listed in Table I. The drug, 5 g of CCSS, was suspended in 250 ml of the prepared spray solution and sprayed against 25 g cores. The resultant 500 ml of the solution, in which 50 g of SL, CH and SA and 21 or 15 g of PVP were dissolved, was sprayed to coat the cores on which the drug had already been layered. The final coating level was designated 200% in the following. PVP was added by 42% to the total of SL, CH and SA except for the last run where it was reduced to 30% (Table I). The composition is denoted below by the weight ratio of SL, CH and SA and, in parenthesis, percent of PVP based on the total weight of SL, CH and SA, for example, 1 : 1 : 0 (42). The operating conditions were characterized by a very low inlet air temperature due to softening of membrane materials. The high yield of 91—95% indicated high efficiency in the coating with the membrane materials used. The fraction of agglomerates[11] in the product was less than 4% in each case, indicating the membrane materials used here to be very low in binding strength.

The drug content was set in this study at a low level

Table I. Formulation of Spray Solution and Operating Conditions[a)]

		Membrane composition, SL : CH : SA (PVP)[b)]						
		1 : 0 : 0 (42)	1 : 1 : 0 (42)	1 : 2 : 0 (42)	5 : 0 : 2 (42)	5 : 5 : 1 (42)	5 : 5 : 2 (42)	5 : 5 : 2 (30)
Core: 75—106 μm lactose	(g)				25			
Drug: CCSS	(g)				5			
Spray solution								
SL	(g)	75.0	37.5	25.0	53.6	34.1	31.2	31.2
CH	(g)		37.5	50.0		34.1	31.2	31.2
SA	(g)				21.4	6.8	12.6	12.6
PVP	(g)	31.2	31.2	31.2	31.2	31.2	31.2	22.5
Ethanol–CH_2Cl_2 (1 : 1)					added			
Total	(ml)				750			
Yield	(%)	95	95	93	94	94	92	91
Mass median diameter	(μm)	170	181	165	170	164	187	168
Content of CCSS	(%)	2.2	2.2	2.1	2.6	2.7	2.6	3.1

a) Operating conditions: inlet air temperature, 30 °C; outlet air temperature, 22—27 °C; inlet air flow rate, 0.87—0.93 m^3/min; spray pressure, 2.0—2.1 atm; liquid flow rate, 3.6—6.3 ml/min; nozzle diameter, 0.8 mm. *b)* Weight ratio of SL, CH and SA and, in parenthesis, percent of PVP based on the total weight of SL, CH and SA.

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enough to monitor the drug release. For example, 100 mg of microcapsules will be the upper limit of injectable amount in single-dose intraarterial administration to a patient in chemoembolization therapy; therefore, the drug content will be desired to be at least 20—30% for dosing 20—30 mg of a drug. There is no technical difficulty in entrapping 20—30% or more drug in microcapsules by the Wurster process.[8b)]

Factors Affecting Drug Release The release of CCSS from microcapsules by the column method is shown in Fig. 1. Microcapsules containing no CH (1 : 0 : 0 (42) and 5 : 0 : 2 (42)) exhibited a rapid burst. The addition of CH alone to SL (1 : 1 : 0 (42) and 1 : 2 : 0 (42)) led to a slightly delayed release, but it still seemed too fast. On the other hand, the addition of both CH and SA to SL resulted in a delayed and prolonged profile of release. The increase in SA from 5 : 5 : 1 (42) to 5 : 5 : 2 (42) remarkably lengthened the lag time and subsequent release prolongation. The reduction of PVP from 42% to 30% led to a little faster release. These results indicated that only the four component mixtures of SL, CH, SA and PVP brought about a prolonged release with a lag time, and that the lag time and the subsequent release rate could be controlled over a wide range, especially by the content of SA.

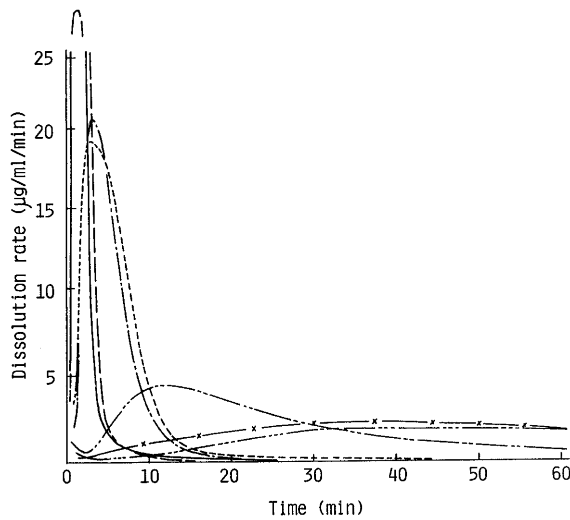

Fig. 1. Effect of the Membrane Composition on Release of CCSS from Microcapsules 200% Coated

Dissolution temperature: 37 °C. Dissolution medium: 0.9% saline solution. Weight ratio of SL, CH and SA (% of PVP): ——, 1 : 0 : 0 (42); ------, 1 : 1 : 0 (42); —-—, 1 : 2 : 0 (42); ----, 5 : 0 : 2 (42); —-—, 5 : 5 : 1 (42); ———, 5 : 5 : 2 (42); —×—, 5 : 5 : 2 (30).

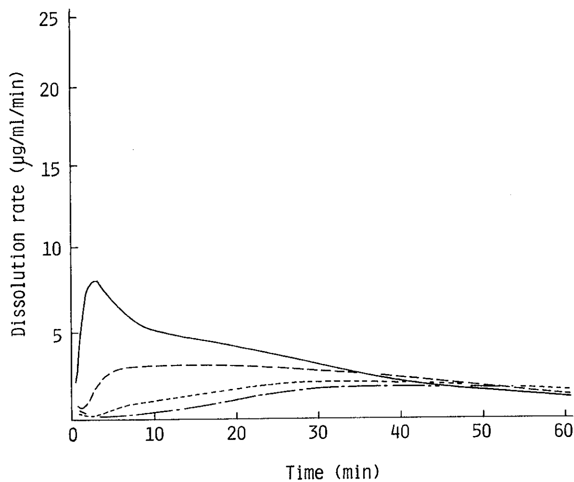

Fig. 2. Release of CCSS from 5 : 5 : 2 (42) Microcapsules Coated at Different Levels

Dissolution temperature: 37 °C. Dissolution medium: 0.9% saline solution. Coating level (%): ——, 50; ----, 100; ------, 150; —-—, 200.

The effect of coating level on the release profile is shown in Fig. 2 for 5 : 5 : 2 (42) microcapsules. The coating level of 50% was insufficient, since a significant amount of drug burst at the early stage of dissolution. At the 100% coating level, the release profile had a short lag time, and after the release rate reached maximum, an almost constant rate of release was observed. By coating above the 100% level, the lag time was prolonged, corresponding to the coating level. After 40 min, the release rate was almost stable regardless of coating level.

The analytical procedure of dissolution data is shown in Fig. 3, as an example, using those at the 200 % coating level (Fig. 2). The leading edge of dissolution rate peak was most simply approximated by a straight line (Eq. 1).

$$R = R_{max}(t - T_0)/(T_m - T_0) \quad (1)$$

where t is time, R dissolution rate, R_{max} the maximum dissolution rate observed and T_m, T_{half} and T_0 the times at $R/R_{max} = 1$, 1/2, 0 (Fig. 3A). The linear regression line obtained by the least squares method using the data of five points around $(t, R) = (T_{half}, R_{max}/2)$ is shown in Fig. 3A. On the other hand, the cumulative amount of drug released, Q, is plotted in Fig. 3B. The integration of

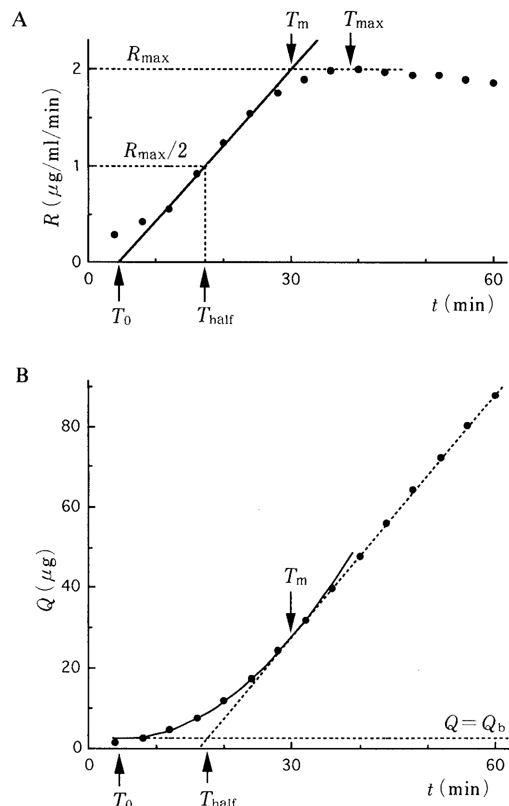

Fig. 3. Analytical Procedure of Dissolution Data

Data: for 5 : 5 : 2 (42) microcapsules 200% coated. A: time course of release rate, R. B: time course of cumulative amount of drug released, Q.

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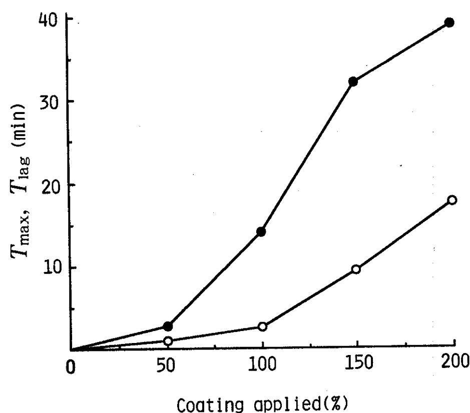

Fig. 4. Parameters of CCSS Release from 5:5:2 (42) Microcapsules Plotted against Coating Level

○, T_{lag}; ●, T_{max}.

Eq. 1 gave Eq. 2:

$$Q = R_{max}(t - T_0)^2/\{2(T_m - T_0)\} + Q_b \quad (2)$$

where Q_b is the amount of drug released until $t = T_0$, which can be estimated by the least squares method using the five data around T_{half}. The regression curve is shown in Fig. 3B. It can easily be shown that the tangent to the regression curve at $t = T_m$ passes through the point of $(t, R) = (T_{half}, Q_b)$. Figure 3B shows that the data after T_m are well fitted to this tangent and, consequently, T_{half} defined as the time at $R = R_{max}/2$ in Fig. 3A is a reliable estimate of the lag time of dissolution, T_{lag}.

Thus, T_{lag} was conveniently obtained from the time when the dissolution rate reached half the maximum. The obtained T_{lag} is plotted in Fig. 4 against the coating level, together with the time at the maximum dissolution rate observed, T_{max}; in contrast to T_{lag}, it was often difficult to correctly determine T_{max} when the dissolution rate peak was flat. T_{lag} increased with coating level and reached 20 min at the 200% level (Fig. 4); for example, if a minimal lag time of 2 min were required to prepare a microcapsule suspension and embolize blood vessels by intraarterial injection, the required coating level would be 100%.

Phase Separation in SL–CH–SA–PVP Mixtures DSC thermograms of the powders of membrane components and their mixtures are shown in Fig. 5. In the range of temperature studied here, SL and the mixtures containing SL exhibited no clear peak arising from the transition to a liquid crystalline phase. The endotherm at 40 °C with CH was due to a polymorphic change in the structure of CH.[2a)] This endotherm was also detectable in the thermograms of 1:1:0 (42) and 1:2:0 (42) mixtures. The X-ray diffraction patterns shown in Fig. 6 indicated that CH crystals were separated in the mixtures. With 5:0:2 (42), an endotherm was also observed at 55—60 °C (Fig. 5h). It was clear from the corresponding X-ray diffraction pattern (Fig. 6h) that SA was separated in the membrane. The thermogram with 5:5:1 (42) exhibited no clear endotherms in Fig. 5i, but a small endotherm was detectable at 40 °C when scanned at a higher sensitivity. Its X-ray diffraction pattern also indicated the separation of CH (Fig. 6i). With 5:5:2 (42) and 5:5:2 (30) which had been increased in SA content, SA was also separated in addition to CH, which was clear from DSC thermograms (Figs. 5j and k) and X-ray diffraction patterns (Figs. 6j and k). Consequently, the separated CH and/or SA crystalline particles were observed on the surfaces of the

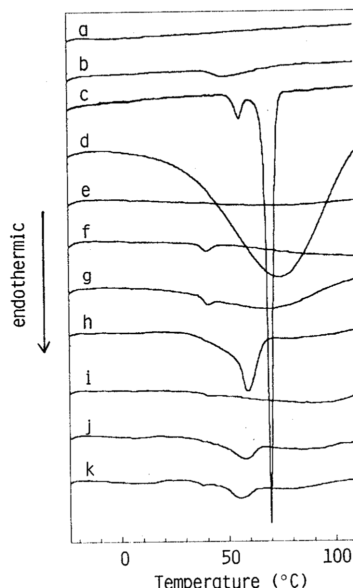

Fig. 5. DSC Thermograms of Components of Microcapsule Membranes and Their Mixtures

Sample weight (mg): 6—7, but 1.65 for SA. Component: a, SL; b, CH; c, SA; d, PVP. Mixture (weight ratio (addition of PVP, %)): e, SL:CH:SA = 1:0:0 (42); f, SL:CH:SA = 1:1:0 (42); g, SL:CH:SA = 1:2:0 (42); h, SL:CH:SA = 5:0:2 (42); i, SL:CH:SA = 5:5:1 (42); j, SL:CH:SA = 5:5:2 (42); k, SL:CH:SA = 5:5:2 (30).

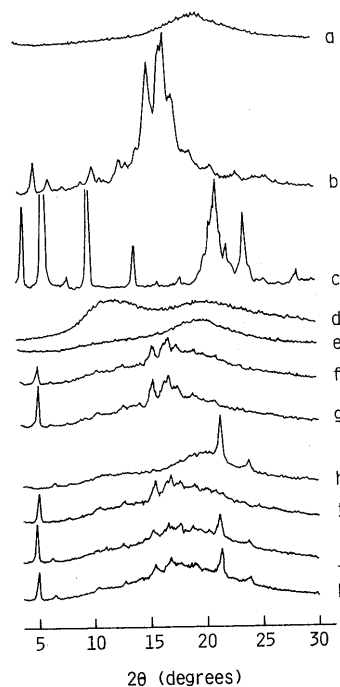

Fig. 6. X-Ray Diffraction Patterns of Components of Microcapsule Membranes and Their Mixtures

Component: a, SL; b, CH; c, SA; d, PVP. Mixture (weight ratio (addition of PVP, %)): e, SL:CH:SA = 1:0:0 (42); f, SL:CH:SA = 1:1:0 (42); g, SL:CH:SA = 1:2:0 (42); h, SL:CH:SA = 5:0:2 (42); i, SL:CH:SA = 5:5:1 (42); j, SL:CH:SA = 5:5:2 (42); k, SL:CH:SA = 5:5:2 (30).

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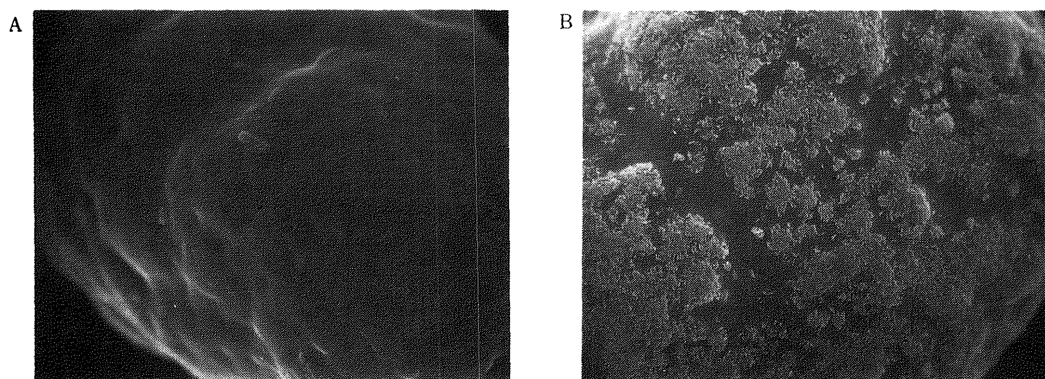

Fig. 7. Scanning Electron Micrograms of Surfaces of Microcapsules
Magnification: ×800. A, 1:0:0 (42); B, 5:5:2 (42).

corresponding microcapsules, as shown in Fig. 7 for 5:5:2 (42) microcapsules; the separation of crystals in the membrane should contribute to suppression of agglomeration in the Wurster process.[12]

When 5 g of CCSS powder was dispersed in 250 ml of the spray solutions dissolving the membrane materials shown in Table I, only 0.16% or less of it was dissolved. This meant that the content of CCSS incorporated in the membrane materials was only 0.023% at the maximum and the remainder was separated as easily water-soluble crystals. In fact, the dry substances prepared from CCSS dispersions in the spray solutions exhibited no significant difference from those containing no CCSS on the DSC thermograms.

Observation of Microcapsules in Aqueous Medium Microcapsules were immersed in a 0.9% saline solution of 37 °C and observed at 100× magnification under a polarizing microscope with a heating stage which kept the temperature constant. All kinds of microcapsules prepared in this study were swollen and enlarged in size over 60 min. The 1:0:0 (42) microcapsules expanded most rapidly (Fig. 8A). Some materials like droplets spouted out from microcapsules coated with the mixtures of the three components of SL, either CH or SA, and PVP (Figs. 8B—D). These clearly corresponded to the burst in drug release shown in Fig. 1. The addition of a small amount of SA (5:5:1 (42) microcapsules) resulted in a drastic change; nothing was seen spouting out and the membrane became very swollen (Figs. 9A—C). The membrane seemed to work as a diffusion barrier when compared with the dissolution profile (Fig. 1). When more SA was added (Figs. 9D—F), the membrane (5:5:2 (42)) seemed to be less swollen (Figs. 9D and E), leading to more delayed and prolonged release (Fig. 1).

Discussion

Most pharmaceutical solid dosage forms prepared to date using phospholipids have essentially been matrix systems. It was easy to prepare the particulate system as a matrix by the Wurster process, but it seemed clear that fast release from the matrix at the early stage of dissolution, resulting from the rapid release of drug near the surfaces of the fine matrix particles,[1e] and easy wetting of lecithin in aqueous media would make it impossible to suppress the burst from the matrix. Thus, phospholipids were used as the membrane material of microcapsules in this study.

Nishihata *et al.* reported that the release of sodium diclofenac from triglyceride based suppositories was sustained by the addition of lecithin, due to the formation of lecithin micella entrapping the drug in the hydrophobic base.[4a] This suggested that triglycerides might be a favorable candidate as membrane material. However, in this study, lecithin was selected as a main component of membrane because its sensitive interaction with water was expected to lead to more widely variable functions of microcapsules.

As is well known, phospholipids in the liquid crystalline phase have a high ability to hydrate in the presence of water.[13,14] Bourges *et al.* demonstrated that the lecithin containing unsaturated acyl chains of 55.1%, whose gel to liquid crystalline phase transition temperature would be far below 37 °C, formed a hydrated lamellar phase in the range of 12—45% of water content, and this lamellar phase could be dispersed in excess of water as small particles composed of 55% lecithin and 45% water.[13,15] Venkataram and Rogers reported that the spontaneous dispersion of phospholipids upon contact with aqueous solution contributed to solubilization of poorly water-soluble griseofulvin from its coprecipitates with phospholipids,[1b,c] and the solubilization was more enhanced by phospholipid exhibiting lower gel-liquid crystalline transition temperature.[1c] Thus, since SL used in this study was in the liquid crystalline phase at 37 °C (Fig. 5), its high hydration ability was expected to lead to swelling-controlled release and spontaneous bioerosion. In fact, a transparent phase was expanded from the 1:0:0 (42) microcapsules as soon as they came in contact with a 0.9% saline solution at 37 °C (Fig. 8A), followed by rapid release of CCSS (Fig. 1). This transparent phase was gradually expanded until it fused with those from other microcapsules. Since it remained water-insoluble during observation over 60 min and SL was the only water-insoluble component of the microcapsules, it was suggested that the hydration of SL accounted for the appearance of this transparent phase.

The addition of CH to SL (1:1:0 (42) and 1:2:0 (42) microcapsules) seemed to reduce the swelling, and droplets colored by yellow CCSS were observed to spout out from

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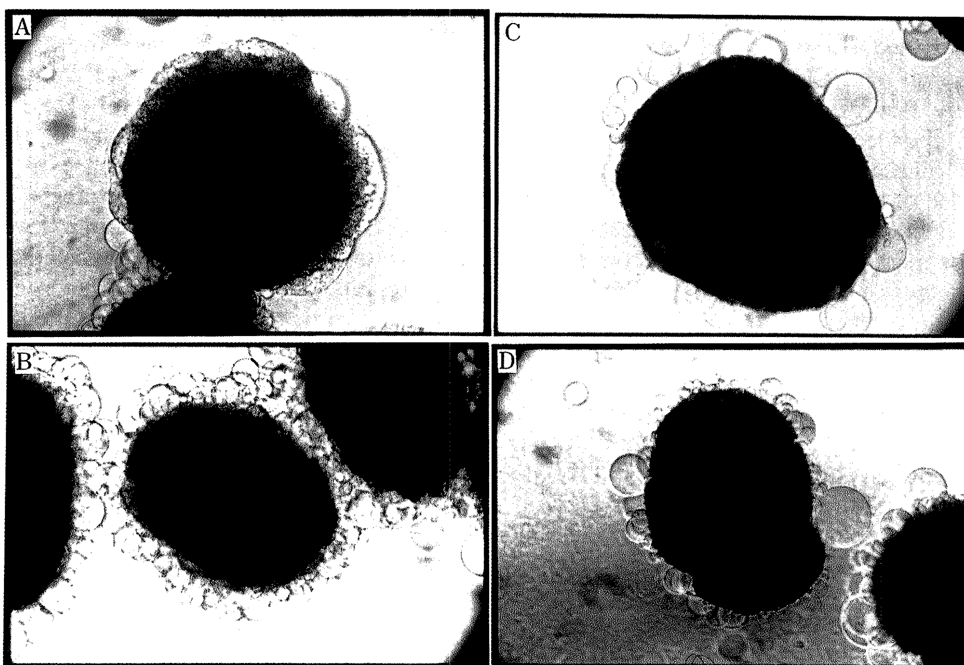

Fig. 8. Microcapsules Immersed in a 0.9% Saline Solution at 37 °C

Magnification: × 100. Coating level: 200%. Time after initial immersion: 3 min. Membrane composition (SL : CH : SA (PVP, %)): A, 1 : 0 : 0 (42); B, 1 : 1 : 0 (42); C, 1 : 2 : 0 (42); D, 5 : 0 : 2 (42).

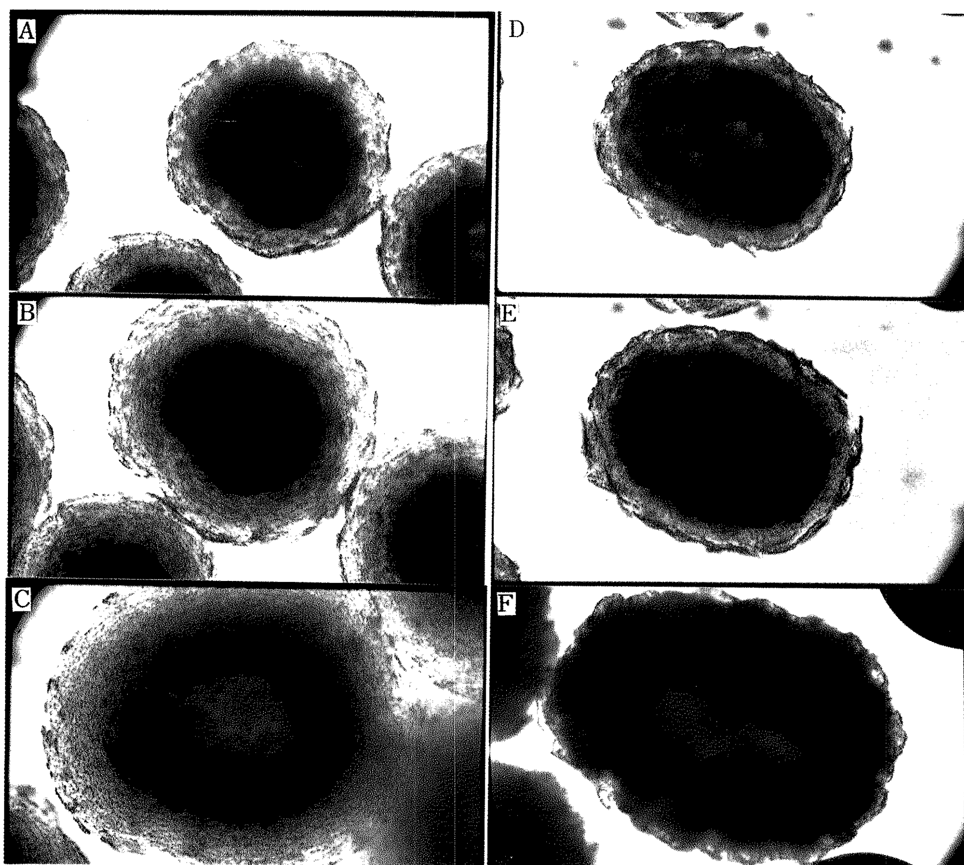

Fig. 9. Microcapsules with Different Content of SA Immersed in a 0.9% Saline Solution at 37 °C

Magnification: × 100. Coating level: 200%. Membrane composition [time (min) after initial immersion]: A, 5 : 5 : 1 (42) [3]; B, 5 : 5 : 1 (42) [10]; C, 5 : 5 : 1 (42) [60]; D, 5 : 5 : 2 (42) [3]; E, 5 : 5 : 2 (42) [10]; F, 5 : 5 : 2 (42) [60].

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the surfaces of microcapsules (Figs. 8B and C). This change of membrane property led to a slightly delayed release (Fig. 1). The phase diagram of the lecithin–CH–water ternary system reported by Bourges *et al.*[13] indicated that in excess of water the lecithin–CH–water system was separated into two phases: water and the lamellar phase which was composed of lecithin, CH and water. Then, the proportion of water in the lamellar phase decreased from 45 % to 35% with increase in that of CH from 0% to 21%, which was the maximum amount of CH the lamellar phase could incorporate; then, the corresponding lecithin content changed from 55% to 44%, which meant that the lecithin–CH had an equimolar ratio (about 2 : 1 weight ratio) in the hydrated lamellar phase. This indicated that CH reduced water intake in the CH–lecithin mixture, in agreement with our observation. Venkataram and Rogers also reported that the addition of CH to coprecipitates of griseofulvin with L-α-dimyristoylphosphatidylcholine (DMPC) whose phase transition temperature was 23 °C in excess water[16] led to a decrease in the release rate at the early stage of dissolution at 37 °C, though the amount of drug released after 60 min increased.[1c] Their observation also seemed to suggest that water intake of the phospholipid might be suppressed by CH, since the hydration of the lecithin–CH mixture would occur at the early stage after contact of the mixture with water.

The phase diagram reported by Bourges *et al.* showed that an excessive CH added to the lecithin at CH content beyond 18 % was separated as pure crystals in anhydrous state, though the lecithin could incorporate CH at equimolar ratio (67% lecithin, 33% CH) in excess of water.[13] The separation of CH was also observed on X-ray diffraction patterns (Fig. 6) of 1 : 1 : 0 (42) and 1 : 2 : 0 (42) mixtures studied here. With regard to the maximum amount of CH that phospholipids can incorporate into the CH–lecithin bilayers, there is disagreement; the maximum lecithin–CH molar ratio reported so far varies in the range from 4 : 1 to 1 : 2.[2a,13] Figures 5 and 6 indicated that the weight ratio of SL to CH incorporated in the present systems was larger than 1 : 1, which would correspond to the molar ratio of about 1 : 2.

The addition of SA to the SL–CH–PVP mixture induced a drastic change of membrane properties. The 5 : 5 : 1 (42) membrane no longer appeared to burst, but gradually swelled and acted as a diffusion barrier (Figs. 9A—C). The addition of more SA (5 : 5 : 2 (42)), which led to separation of SA crystals in the anhydrous mixture, seemed to suppress the swelling (Figs. 9D—F). Schullery *et al.*[17] reported that the fatty acids such as palmitic, stearic and myristic acids added to dipalmitoylphosphatidylcholine (DPPC, phase transition temperature: 41.5 °C) raised the liquid-crystalline phase transition temperature and formed sharply melting (66 °C for stearic acid) complexes in excess water, with 1 : 2 DPPC–fatty acid stoichiometry (1 : 0.77 weight ratio for stearic acid) observed for palmitic and stearic acids and suggested for myristic acid. Then, at mole fractions of stearic acid between 0.28 (0.24 for palmitic acid) and 0.66, the mixture formed a gel solid solution of DPPC in a 1 : 2 complex of DPPC–fatty acid in excess water; this might also be the case in the present systems. These suggested that in excess water the 5 : 5 : 2 (42) mixture might form a SA-rich phase mixed with a more swellable, SL-rich phase, though SA seemed to be dissolved in anhydrous 5 : 5 : 1 (42) mixture (Figs. 5 and 6). Further, increase in SA content beyond 5 : 5 : 2 (42) might lead to increase in SA-rich phase; consequently, this possibly structured SA-rich phase might suppress the swelling of microcapsule membrane (Figs. 9D—F) and the CCSS release (Fig. 1). Although it was not easy to explain with certainty how SA affected the properties of the present systems containing heterogeneous phospholipids, CH and PVP, SA contributed to formation of low-permeable membrane; the release observed with the 5 : 5 : 1 (42), 5 : 5 : 2 (42) or 5 : 5 : 2 (30) microcapsules had a desired short-term prolonged profile.

The effect of the addition of PVP to fludrocortisone–DMPC coprecipitates on the dissolution behaviors was studied by Vudathala and Rogers.[1d] The addition of PVP 40 (MW = 40000), comparable to PVP K30 used in our study, up to 6% (w/w) of the lipid rapidly reduced the dissolution efficiency,[18] defined as the area under the dissolution curve up to 90 min, and the efficiency was almost level in the range from 6% to at least 59%. This tendency of PVP to reduce the dissolution rate was qualitatively in agreement with our results (Fig. 1). Vudathala and Rogers demonstrated that dextran (MW = 2 million) and poly(L-lactic acid) (MW = 24000) also caused a decrease in dissolution, along with a decrease in the heat of fusion of the drug in the coprecipitates.[1d] Although it was suggested that these two polymers reduced the interaction of the lipid in the coprecipitates, the mechanisms, including the case of PVP, were unclear.

It was demonstrated in this study that the release properties of SL microcapsules changed according to the contents of CH, SA and PVP and the coating level. In addition to these formulation factors, the solubility of core material would be a factor controlling the release and erosion, though water-soluble lactose was used in the present study. These wide variations in formulation are essential for development of drug delivery systems whose properties must be optimized according to drugs and therapeutic strategies to be used.

Conclusion

Soybean lecithin was used as a membrane material of microcapsules to utilize its sensitive response to water for short-term controlled release dosage forms. The release of drug (CCSS) from microcapsules whose membranes were composed of lecithin and PVP, a binder, could not be controlled due to very rapid swelling and consequent burst. The very fast release of drug was only insufficiently suppressed, even when CH or SA was added to the membrane. However, the release of CCSS exhibited a short-term delayed and subsequently prolonged profile when the coat was composed of all of four components, SL, CH, SA and PVP; the lag time and the subsequent release rate were sensitive to the composition of coat and the coating level. As a dosage form with a useful short-term controlled release property, the microcapsules more than 100% coated with a SL–CH–SA mixture of 5 : 5 : 2 weight ratio and 42% PVP based on this mixture were found.

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