[Chem. Pharm. Bull.]
30(6)2189-2195(1982)

Mechanical Properties, Dissolution Behavior and Stability to Oxidation of L-Ascorbylmonostearate Microcapsules prepared by a Spray-Drying Polycondensation Technique¹⁾

HIDEO TAKENAKA,^a YOSHIKI KAWASHIMA*,^a YOSHIHIRO CHIKAMATSU^b
and YUTAKA ANDO^b

Gifu College of Pharmacy,^a Mitahora, Gifu, 502, Japan and Ichimaru Co., Ltd.,^b Matsuhora, Takatomi, Gifu, 502-21, Japan

(Received November 26, 1981)

L-Ascorbylmonostearate was microencapsulated by a spray-drying polycondensation method with polymers such as polyvinyl alcohol, carboxymethylcellulose and polyvinylpyrrolidone, and polycondensed trimethylolmelamin trimethylether at 140 °C. The particle size (1 to 10 μm) and the density (1.18 to 1.34 g/cm³) of the microcapsules increased with increasing trimethylolmelamin trimethylether content in the formulations for spray drying. The flow curve of the ointment compounded with the microcapsules under the influence of shear exhibited a thixotropic curve with a spar. The spar value and the hysteresis loop area of the curve increased with the trimethylolmelamin trimethylether content. The amount (percent) of L-ascorbylmonostearate released from the microcapsules subjected to shear stress decreased with increasing content of trimethylolmelamin trimethylether, which might strengthen the microcapsule wall. Addition of a small amount of trimethylolmelamin trimethylether to the microcapsules imparted plastic properties to them, while the addition of an excess made the microcapsules brittle. The L-ascorbylmonostearate release rate from the microcapsules decreased with increasing trimethylolmelamin trimethylether content in the microcapsules. The drug release rates were correlated linearly with the solubilities of the polymer films prepared on a glass plate from the same formulations as used for spray drying. Polyvinyl alcohol significantly decreased the release rate. The decomposition process of L-ascorbylmonostearate in the microcapsules dispersed in water by air-oxidation followed first-order kinetics. The decomposition rate decreased with increasing trimethylolmelamin trimethylether content in the microcapsules.

Keywords—spray-drying polycondensation; microcapsule; L-ascorbylmonostearate; ointment, mechanical properties under shear force; dissolution behavior; stability to oxidation

Introduction

The spray-drying technique is an attractive method for the preparation of microcapsules and agglomerates of drugs, because they are prepared directly from droplets in a single process. To coat the products, usually film-forming polymers or reactive monomers are compounded in the formulations for spray drying. Kawashima and coworkers^{2,3)} produced microcapsules of drugs with sustained release or enteric actions for tableting from aqueous drug suspensions containing coating polymers. Speiser *et al.*^{4,5)} produced microcapsules of barbituric acid and phenobarbital employing a spray polycondensation method with monomers and precondensates.

Drug release from microcapsules may be accomplished by rupture of the microcapsule or by drug diffusion through the microcapsule wall and texture. However it is difficult to describe quantitatively the relationship between drug release behavior and such a mechanism, because it is hard to evaluate the mechanical properties of microcapsules.

In the present paper, a method to relate the mechanical strength of L-ascorbylmonostearate microcapsules, prepared by a spray-drying polycondensation technique, to the shear force applied is proposed. The drug release behavior from the microcapsules is described quantita-

tively in terms of the dissolution and the rupture of the microcapsule wall under the influence of shear force. The effect of the formulation for spray drying on the properties of the resultant microcapsules, such as mechanical strength, dissolution behavior and stability to air oxidation, was also investigated.

Experimental

Materials—L-Ascorbylmonostearate (Kishida Chemical Co.) was used as a model drug or cosmetic. As a film-forming polymer, polyvinyl alcohol ($(\text{CH}_2=\text{CHOH})_n$, $n=500$, Kishida Chemical Co.) carboxymethylcellulose (Kishida Chemical Co.) or polyvinylpyrrolidone (K-30, Kishida Chemical Co.) was used. Trimethylolmelamin trimethylether (Mitsui Toatsu Chemical Co.) and glutaraldehyde (Kishida Chemical Co.) were used as a reactive monomer and a hardening agent, respectively. An organic amine salt (Cat-O, Mitsui Toatsu Chemical Co.) was used as a catalyst for enhancing the polymerization of trimethylolmelamin trimethylether. The formulation details for spray drying are listed in Table I.

Spray-drying Technique—The polymer (10 g), trimethylolmelamin trimethylether (0–10 g), 50% glutaraldehyde (1 ml) and the organic amine salt (0–1 ml) were dissolved in 500 ml of water, and 10 g of L-ascorbylmonostearate was dispersed in the resultant aqueous solution. The aqueous suspensions were sprayed into a drying chamber (Yamato Mini Spray, Yamato Kikai Co.) at 140°C using a two-fluid type nozzle.

Measurement of Properties of Microcapsules—L-Ascorbylmonostearate content in the microcapsules was determined by a modified 2-nitro-4-methoxyaniline method.⁶⁾ Diazonium pigment produced by this method was measured spectrophotometrically at 570 nm (Model 100-60 spectrophotometer, Hitachi Manufacturing Co.).

Particle sizes and particle densities of the products were measured by a photographic counting method (TGZ-3, Karl-Zeiss, West Germany) and with a helium-air comparison pycnometer (Model 1302, Micromeritics Instrument Co., U.S.A.), respectively. Surface topography of the products was investigated with a scanning electron microscope (Nihon Denshi JMS-SI, Nihon Denshi Co.).

A flow curve of the ointment base (Composition (%); liquid paraffin (60), isopropylmyristate (36), cetyl alcohol (2), L-glycerylmonostearate (1), and polyoxylstearic acid (1)) compounded with the microcapsules (10.5%) was obtained with a cone and plate viscometer (Ferranti-Shirley Viscometer, Ferranti-Shirley Co., England) to investigate its rheological properties.

The mechanical strength of the microcapsules under the influence of shear was investigated by using the cone and plate viscometer. Three milliliters of liquid paraffin was placed on a plate and 50 mg of the microcapsules was dispersed well in the paraffin on the plate. After shearing the microcapsules dispersed in the paraffin at a constant shear rate, *i.e.* 100 rpm, for various residence times, the amounts of L-ascorbylmonostearate released in the paraffin were measured. The released amount was taken as a measure of the mechanical strength of the microcapsules, since the L-ascorbylmonostearate release from the microcapsules was brought about only by collapse of the microcapsules.

The release of L-ascorbylmonostearate from the microcapsules was determined by a modified U.S.P. method. The rotating speed of the basket was set at 400 rpm. The dissolution media used were a mixture of ethanol and propyleneglycol (mixing ratio; 4:1), buffer solution (pH=7.0) and acidic solution (pH=4.0), which were thermally controlled at 50 or 37°C.

To predict the solubility of the microcapsule wall, a dissolution test of a film prepared from the same formulation as employed for preparation of the microcapsules was undertaken. Aqueous solutions of polymers for spray drying without drugs were spread over a glass plate, and dried at ambient temperature. A square film (3×3 cm) 0.3–0.5 mm in thickness was dissolved in 100 ml of each dissolution medium, and the solution was shaken at 100 rpm. The other experimental conditions were the same as those of the dissolution test for microcapsules.

The stability of the microcapsules to air-oxidation was tested by introducing air at 5 l/min into an aqueous suspension of the microcapsules. The microcapsules (2 g) were dispersed in 200 ml of water containing a small amount of polyoxyethylene sorbitan monooleate (Tween 80, Kao Soap Co.) as a dispersing agent.

Results and Discussion

Micromeritic Properties of the Microcapsules

The surface topography of the microcapsules is shown in Fig. 1. The surfaces of the microcapsules were almost smooth without holes and gaps. This finding confirmed that the microencapsulations in this study were successful. The sizes of the microcapsules varied from 1 to 10 μm and their distributions followed a log-normal form. The geometric mean diameters of the microcapsules were 2 to 5 μm . The average sizes increased and the drug contents in the microcapsules decreased with increasing amount of trimethylolmelamin

trimethylether contained in the formulations. It was assumed that the microcapsule size was related to the viscosity of the feeding liquid for spray drying, as suggested by the previous study.⁷⁾ However, no variation in the viscosity was found among the formulations, as can be seen in Table I. Therefore the microcapsule size mainly depended on the polymerizing ability of trimethylolmelamin trimethylether. The decrease in the drug contents could also be explained in terms of enhanced polymerizations forming a wall-thickened microcapsule. A similar trend was observed in the particle densities (1.18 to 1.34 g/cm³) of the microcapsules. The variations of the micromeritic properties and L-ascorbylmonostearate contents in the microcapsules with the formulations for spray drying are listed in Table I.

Flow Properties of Ointment Base compounded with the Microcapsules and the Mechanical Strength of the Microcapsules

The flow curves of the ointment base compounded with the microcapsules at 0.5% content under the influence of shear force are shown in Fig. 2. The ointment base containing the original ascorbylmonostearate powder and the microcapsules both exhibited a thixotropic property. On compounding the microcapsules, the hysteresis loop area of the flow curve increased and a marked spar appeared on the flow curve. Before the microcapsules in the ointment moved under the external force applied, they changed position and some of them deformed or collapsed, which brought about the large shear stress. Once the microcapsules moved, the shear stress fell rapidly. This change in the shear stress before and after the movement produced the spar, which increased with increasing trimethylolmelamin trimethylether content in the microcapsules.

After applying a constant shear to liquid paraffin compounded with the microcapsules for various residence times the amount of L-ascorbylmonostearate released from the microcapsules into the liquid paraffin was determined. The amount (percent) of L-ascorbylmono-

TABLE I. Formulations for Spray Drying and Micromeritic Properties of Spray-Dried Microcapsules

Formulation for spray drying	Formulation # No.					
	1	2	3	4	5	6
AsA-MS (g)	10	10	10	10	10	10
Polymer (g)	10	10	10	10	10	10
TMMTE (g)		1	2.5	5	7.5	10
Cat-O (ml)		0.1	0.25	0.5	0.75	1
Gultaraldehyde (50%) 1 ml						
Water (ml)	500	500	500	500	500	500

Key: AsA-MS, L-ascorbylmonostearate,
Polymer, polyvinyl alcohol, carboxymethylcellulose and polyvinylpyrrolidone,
TMMTE, trimethylolmelamin trimethylether,
Cat-O, organic amine salt.

Micromeritic properties of microcapsules

Formulation	Dg (μ)	ρ (g/cm)	AsA-MS contents (%)	Viscosity of feeding liquid for spray drying (cp) at 20°C
1	1.95	1.23	47.5	2.5
2	1.68	1.26	47.6	2.6
3	3.57	1.18	42.8	2.4
4	3.24	1.28	39.1	2.6
5	3.62	1.28	32.4	2.6
6	4.59	1.34	30.5	2.7

Key: Dg, geometric mean diameter,
 ρ , particle density.
Viscosity was measured with a rotating viscometer (B type, Tokyo Seiki Co.).

Fig. 1. Scanning Electron Microscopic Photographs of the Original and Microencapsulated L-Ascorbylmonostearate by Spray Drying

(A), original.

(B), microcapsules from formulation No. #6.

Fig. 2. Flow Curves of Ointment Base compounded with the Original and Microencapsulated L-Ascorbylmonostearate

Formulation #No: (1) original; (2) 1; (3) 2.

Fig. 3. Release of L-Ascorbylmonostearate as a Function of Shear Energy

Formulation #No: ○, 1; ●, 2; △, 6.

stearate released is plotted against the shear energy applied to the system defined in terms of the product of shear stress ($\text{g} \cdot \text{cm}$) and shear time (minute) as shown in Fig. 3. In the case of the microcapsules without trimethylolmelamin trimethylether, the release percent increased exponentially in the range above $17 \text{ g} \cdot \text{cm} \cdot \text{min}$ shear energy. When larger shear energies than $50 \text{ g} \cdot \text{cm} \cdot \text{min}$ were applied to the system, the release reached almost 100%, which indicated that almost all the microcapsules had collapsed. When trimethylolmelamin trimethylether was introduced into the formulation, the shear energy required for collapsing the microcapsules became larger than that for microcapsules without trimethylolmelamin trimethylether. When the amount of trimethylolmelamin trimethylether in the formulations was increased, the release from the microcapsules became proportional to the shear energy applied and the proportionality constant decreased with the trimethylolmelamin trimethylether content. This finding indicated that the mechanical strength of microcapsules increased with increasing amount of trimethylolmelamin trimethylether contained in the microcapsules. In addition, a plastic property was imparted to the microcapsules up to a certain content of trimethylolmelamin trimethylether in the microcapsules. However, at higher contents, the microcapsules lost this property and became brittle.

Drug Release Behavior of the Microcapsules

The release profiles of the microcapsules in ethanol-propylene glycol mixture, alkaline and acidic medium are shown in Fig. 4(a), (b) and (c), respectively. Irrespective of the type of dissolution medium used, it was found that the drug release rates from the microcapsules were much slower than that of the original powder. The drug release rate of the microcapsules decreased with increasing trimethylolmelamin trimethylether content in the microcapsules. This rank order was the same in all the media, but the release patterns varied with the type of medium used. In ethanol-propylene glycol, the release patterns were convex curves whose curvature decreased with increasing trimethylolmelamin trimethylether content in the microcapsules. In the alkaline medium, the release patterns were linear except at the initial and final stages of release. The drug release rates in the alkaline medium were faster than those in the acidic medium. The release patterns in the acidic medium followed sigmoid curves except for the microcapsules without trimethylolmelamin trimethylether. In all the media, an increased release rate was observed at the initial stage because of the rapid dissolution of minute microcapsules (Fig. 1).

Fig. 4. Dissolution Profiles of Microcapsules

- (a) In ethanol-propylene glycol at 50°C, formulations; ○, original; □, #1; △, #2; ●, #3 and ▲, #4.
 (b) In alkaline solution at 37°C, formulations; □, #1; △, #2; ○, #3.
 (c) In acidic solution at 37°C, formulations; □, #1; △, #2; ○, #3.

It was assumed that the drug release behavior of the microcapsules depended on the solubility of the microcapsule wall. The times required for 50 or 30 percent drug release from the microcapsules, *i.e.* T_{50} or T_{30} , are plotted against the solubilities of films prepared from the same formulations as used for the microcapsules in Fig. 5. T_{50} in the acidic and alkaline media and T_{30} in ethanol-propylene glycol decreased linearly with the solubility of the film in the same medium. This finding suggested that drug release from the microcapsules was controlled by dissolution of the microcapsule wall as well as by diffusion of the drug through the microcapsule wall.

The effects of the wall materials of the microcapsules on the drug release behavior are illustrated in Fig. 6. In ethanol-propylene glycol, no difference in drug release behavior

Fig. 5. T_{50} or T_{30} of Microcapsules as a Function of Solubility of Microcapsule Film

- Dissolution medium: ●, (T_{30}) ethanol-propylene glycol;
 ○, alkaline solution;
 △, acidic solution.

was found between the microcapsules with carboxymethylcellulose and with polyvinylpyrrolidone. Polyvinyl alcohol was the most effective for delaying the drug release from the microcapsules. Significant differences in the drug release pattern of the microcapsules with polyvinyl alcohol as compared with those formed from the other wall materials were observed, as shown in Fig. 6(a). In the acidic medium, the effects of wall material on the drug release rate were significant, as can be seen in Fig. 6(b), compared with the effects in ethanol-propylene glycol. The prolonged release effect of polyvinyl alcohol was the greatest among three materials. Polyvinylpyrrolidone moderately retarded the drug release. In the alkaline medium the same rank order for delay of drug release rate was obtained as in the acidic medium.

Fig. 6. Dissolution Profiles of Microcapsules with Various Polymers

(a) In ethanol-propylene glycol at 50°C,
polymers; ○, polyvinyl alcohol;
△, carboxymethylcellulose;
□, polyvinylpyrrolidone.

(b) In acidic solution at 37°C,
polymers; ○, polyvinyl alcohol;
△, carboxymethylcellulose;
□, polyvinylpyrrolidone.

Stability of the Microcapsules to Air Oxidation

The amount of ascorbylmonostearate retained in the microcapsules after air oxidation conducted in an aqueous suspension is plotted against the air-exposure time on a semilogarithmic scale in Fig. 7. A linear relationship was obtained between $\ln(C/C_0)$ and the air-exposure time, which suggested that the degradation of L-ascorbylmonostearate in the microcapsules followed first-order kinetics;

$$\ln(C/C_0) = -kt$$

Fig. 7. First Order Kinetic Plots for the Oxidation of Microencapsulated L-Ascorbylmonostearate

Formulations and oxidation rate constant (d^{-1}):
○, original, 1.70×10^{-1} ;
●, #4, 1.18×10^{-2} ;
△, #5, 4.26×10^{-3} ;
□, #6, 2.18×10^{-4} .

where C and C_0 are the L-ascorbylmonostearate concentrations in the microcapsules at time t and initially, respectively, k is the apparent oxidation rate constant and t is the air-exposure time. The apparent oxidation rate constants were obtained from the slopes of the straight lines in Fig. 7. The apparent oxidation rate of the original L-ascorbylmonostearate powder was greater than that of the microcapsules. The apparent oxidation rate constants for the microcapsules decreased with increasing trimethylolmelamin trimethylether content. The finding can be interpreted in part in terms of the decreased specific surface area of the microcapsules, as shown in Table I. The main factor, however, is that the diffusion rate of water through the microcapsule

wall for reaction was depressed by increasing trimethylolmelamin trimethylether content in the formulations. It was proved that the stability of L-ascorbylmonostearate to oxidation was enhanced by microencapsulation with a large amount of trimethylolmelamin trimethylether.

References and Notes

- 1) This paper is Part XII of studies on "Spray-Drying Agglomeration." Part XI was accepted for publication in *J. Pharm. Sci.*, **71**, in press (1982).
- 2) Y. Kawashima and H. Takenaka, *J. Pharm. Sci.*, **63**, 1546 (1974).
- 3) H. Takenaka, Y. Kawashima and S.Y. Lin, *J. Pharm. Sci.*, **69**, 1388 (1980).
- 4) P. Speiser, H.P. Merkle and L. Schibler, Ger. Offen., 2233428 (1973).
- 5) C. Voellmy, P. Speiser and M. Soliva, *J. Pharm. Sci.*, **66**, 631 (1977).
- 6) T. Adachi, Y. Nakaji, K. Sato and H. Ota, *Vitamins* (Japan), **34**, 188 (1966).
- 7) H. Takenaka, Y. Kawashima, T. Yoneyama and K. Matsuda, *Chem. Pharm. Bull.*, **19**, 1234 (1971).