Effect of Additives on Physical Properties of Fine Ethyl Cellulose Microcapsules Prepared by the Wurster Process

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Ethyl cellulose (EC) microcapsules with fine calcium carbonate cores (32–44 μm) and drug layers were prepared. The effect of additives on the particle size distribution, the variation in drug content with particle size and the dissolution properties of the products were evaluated.

Among eight additives used, cholesterol (CH) most restrained the release of phenacetin, a model drug, which resulted in a saving of coating material and time. For sustained release of phenacetin, only 6.25% or less coating material relative to core material was sufficient. In addition, CH remarkably reduced particle agglomeration. The mean particle size of a product 25% coated with EC: CH = 2:1 mixture was 58 μm. However, the drug content and the phenacetin release were strongly dependent on the particle size of the product. This was the result of retardation of particle recycling in the Wurster chamber due to its adhesion to the wall by electrostatic charge. Stearyltrimethylammonium chloride, a cationic surfactant, reduced the particle adhesion when it was added to EC–CH (2:1) in a 1% amount on a dry basis. As a result, the particle size distribution became sharper, and there was higher homogeneity of the physical properties.

This effect was not observed with polysorbate 80, a nonionic surfactant.

Keywords coating; calcium carbonate; ethyl cellulose; cholesterol; stearyltrimethylammonium chloride; microcapsule; Wurster process; fluidized bed; powder

The Wurster process is a method applicable for the industrial production of microencapsulated pharmaceuticals. It can be characterized by fine powder operation. However, some techniques by which the size of the successfully processed particles can be reduced are needed. Difficulties encountered in the coating of fine particles result from particle agglomeration and adhesion to the chamber walls and filters due to remaining solvent or electrostatic charge. The inertia of particles larger than 100 μm is high enough to overcome this cohesion and adhesion; however, with finer particle size the surface properties dominate over the inertia. This causes the production of largely agglomerated particles or imperfectly coated fine particles.

The purpose of this study was to develop a membrane formulation for the preparation of fine microcapsules. Desirable characteristics of the membrane material were as follows: (1) a low agglomeration tendency, (2) a low electrostatic charging and (3) a low membrane permeability for drugs. The third item was necessary to complete coating at a small amount of membrane material. This is of special importance in practice because fine powder has a large specific surface area.

Experimental

Materials As a core material, calcium carbonate (08 Jyutan, Maruo Calcium Co., Ltd.) was used. Ethyl cellulose (EC, 30–50 cps), cholesterol (CH, SP reagent grade), polyethylene glycol 4000 (PEG), propylene glycol (PG), palmitic acid (PA), lauric acid (LA), triacetin (TA), polysorbate 80 (PS 80) and stearyltrimethylammonium chloride (STAC) were used as purchased from Nagalai Tesque Co., Ltd. Triethyl citrate (TEC, Citrolex 2, Pfzer) and acetylated monoglyceride (AMG, Myverject 9-40T, Koyo Mercantile Co., Ltd.) were also used as purchased. Phenacetin (Kawasaki Kagakukogyo Co., Ltd.) was used as a model drug.

Coating A Glatt GPCG-I Wurster was used. A bottom ring such as that shown in Fig. 1 was used to process a small amount of powder (calcium carbonate of 100 g).

Preparation of Microcapsules Details of the cores, the composition of spray solution and the coating conditions are listed in Table 1. The coating conditions were almost similar throughout this study. Calcium carbonate was selected as a model core because of its high density (2.93 g/cm³). Particle agglomeration of high density particles in the Wurster process was presumed to be reduced because of their high inertia. The concentration of dry lacquer (EC plus additive) in spray solution was 2.75% (w/v); EC concentration was 2.5% (w/v). Cores of 100 g were first undercoated with 100 ml of spray solution. Thereafter, 16.7 g of phenacetin (a model

Fig. 1. Bottom Ring for Processing a Small Amount of Powder

| a, chamber; b, partition; c, air distributor; d, spray gun; e, bottom ring. |

TABLE 1. Operating Conditions in the Preparation of EC Microcapsules

| Core material | Calcium carbonate 32–44 μm | 100 g |
| Spray solution | EC | 32.5 g |
| | Additive | 3.25 g |
| | Ethanol | added |
| | Total | 1300 ml |
| Undercoating | Spray solution | 100 ml |
| Fixing of drug | Phenacetin | 16.7 g |
| | Spray solution | 200 ml |
| Coating | Spray solution | 1000 ml |
| Coating conditions | Inlet air temperature (°C) | 40 |
| | Outlet air temperature (°C) | 30–33 |
| | Inlet air rate (m³/min) | 0.7–0.8 |
| | Spray rate (m³/min) | 4.2–4.8 |
| | Spray pressure (atm) | 2.3 |
| | Diameter of spray nozzle (mm) | 0.8 |

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drug), dissolved in a spray solution of 200 ml, was sprayed on the undercoated cores. Finally, 1000 ml of a spray solution was applied to overcoat 25 g of EC (25% coating level).

**Particle Size Distribution** A sieve analysis was performed in the range of 32–63 μm using an Alpine 200LS air jet sieve at a charged weight of 50 or 20 g and a sieving time of 5 min. Above 63 μm, a row-tap shaker (Iida Seisakusho Co., Ltd.) was used. The shaking time was 10 min and the charged weight was 50 or 20 g. A mass median diameter was used as a mean particle size.

**Dissolution and Drug Content** Dissolution tests were performed as previously reported. JP XI disintegration 2nd fluid (pH 6.8) was used as a dissolution fluid. The prepared microcapsules were dried in vacuum at room temperature for 12 h. The sample containing 150 mg of phenacetin was tested, and concentration of the drug was spectrophotometrically determined at 245 nm. Drug content in the microcapsules was similarly determined by dissolving them in ethanol; it was also used to estimate the value of 100% release (Cₐ) in dissolution tests.

As a parameter of dissolution, the constant K (apparent dissolution rate constant) defined by the following equation was determined by the least squares method.¹¹

\[ \ln(1 - C/Cₐ) = -Kt \]

where C was the concentration when the dissolution time was t.

**Thermal Analysis** The measurements of softening temperature of EC films were performed as previously reported; only the heating rate was changed to 2 °C/min in this study. The test film was usually prepared by heating 5 g of ethanol solution containing 0.75 g EC and 0.075 g (10%) or 0.15 g (20%) additive on a Teflon-coated glass dish of 80 mm diameter at 60 °C for 12 h. The formed film was again dried in vacuum at room temperature for 12 h. The EC film containing CH was prepared using 3 g of ethanol solution containing 0.225 g EC and 0.0225 g CH.

EC films containing 20% or more CH did not have even surfaces; therefore, fragments of the EC–CH films were analyzed by differential scanning calorimetry (DSC). The DSC thermograms were recorded on a Shimadzu SC-30 thermal analyzer at a heating rate of 5 °C/min under a dry nitrogen flow of 30 ml/min. Samples, 8–11 mg, were crimped into aluminum cells.

**Scanning Electron Microscopy (SEM)** SEM was performed on a Hitachi S430.

**Polarizing Microscopy** An Olympus POM polarizing microscope was used with a heating stage (MHS, Union Optical Co., Ltd.).

**Results and Discussion**

**Effect of Additives** Coating was performed under the conditions shown in Table I. The additives used and the characteristics of the products are shown in Table II. An additive of 10% relative to EC was used in each case (Table

![Fig. 2. Effects of Additives on Softening Temperature of EC Films](image)

**Fig. 2. Effects of Additives on Softening Temperature of EC Films**

Additives: ○, TA; ●, PG; △, TEC; ▲, PEG; ▼, CH; ▽, AMG; □, LA; ■, PA.

**Table II. Characteristics of EC Microcapsules Prepared by the Wurster Process**

<table>
<thead>
<tr>
<th>Additives</th>
<th>None</th>
<th>TA</th>
<th>PG</th>
<th>TEC</th>
<th>PEG</th>
<th>CH</th>
<th>AMG</th>
<th>LA</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (%)</td>
<td>89</td>
<td>89</td>
<td>87</td>
<td>92</td>
<td>91</td>
<td>89</td>
<td>90</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>Mean particle size (μm)</td>
<td>89</td>
<td>70</td>
<td>71</td>
<td>77</td>
<td>80</td>
<td>81</td>
<td>85</td>
<td>94</td>
<td>108</td>
</tr>
<tr>
<td>Drug content (%) ‡</td>
<td>12.2</td>
<td>11.9</td>
<td>11.8</td>
<td>11.5</td>
<td>11.7</td>
<td>12.2</td>
<td>11.9</td>
<td>11.8</td>
<td>11.7</td>
</tr>
<tr>
<td>Softening temperature (°C)</td>
<td>144</td>
<td>115</td>
<td>126</td>
<td>101</td>
<td>143</td>
<td>122</td>
<td>112</td>
<td>98</td>
<td>102</td>
</tr>
</tbody>
</table>

a) Theoretical value: 11.2% in the case of nonadditive, 11.0% in the others.

![Fig. 3. Typical Particle Size Distributions of EC-Additive (10:1) Microcapsules and Variation of Phenacetin Content and 5 h Release with Particle Size Fractions](image)

**Fig. 3. Typical Particle Size Distributions of EC-Additive (10:1) Microcapsules and Variation of Phenacetin Content and 5 h Release with Particle Size Fractions**

Additives: a, none; b, TA; c, CH; d, PA. The one-dot chain line shows the theoretical value of phenacetin content.
The yield was around 90%. The mean particle size of EC microcapsules without additives was 89 μm. The larger size implies more agglomeration. When compared with EC microcapsules without additives, PA and LA enhance the agglomeration, but AMG, CH, PEG, TEC, PG and TA reduce it.

The softening temperatures of EC films containing the additives are plotted in terms of the amount of additive applied in Fig. 2. Water soluble PEG and PG exhibit only a weak plasticizing effect; PEG in particular hardly plasticized EC. The solution containing 20% or more CH exhibited a very slow evaporation of solvent, resulting in formation of an uneven film. Therefore, with EC–CH film, the softening temperature was determined only with the film containing 10% CH. Since the inlet air temperature was 40°C (Table 1), the membrane could not melt during the operation. The particle agglomeration was not related to the softening of membranes.

Typical examples of the particle size distribution of the products and the physical properties of the particles in each sieved fraction are shown in Fig. 3 for EC alone, EC–TA, EC–CH and EC–PA. EC–PA and –TA exhibited the largest and smallest mean particle size, respectively. The drug content and the percent released in 5 h show that the particles smaller than 53 μm were insufficiently coated. Clearly, this resulted from retardation in recycling within the coating chamber.

The membrane thickness was estimated to be 6 μm under the assumption that 1) the density of EC3) and phenacetin4) were 1.11 and 1.24 g/cm³, respectively, 2) EC and phenacetin independently contributed to the membrane volume and 3) the membrane material was homogeneously coated on the spherical cores of 38 μm (mean of sieve openings used in preparing the cores). Theoretically, the mean particle diameter of the product without agglomeration should be 50 μm (44–56 μm). If three particles of 56 μm (the largest single core microcapsule) were agglomerated with a triangular conformation and two contact points each, the diameter of the circumscribed circle would become 121 μm. If the smallest cores of 32 μm were to be agglomerated in the same manner at the beginning stage of the process and thereafter coated to the thickness of 6 μm, the particle size would become 81 μm. Therefore, the agglomerates composed of three cores would have a size between 81 and 121 μm. Under a microscope, the fraction larger than 75 μm clearly contained agglomerates. In the

![Fig. 4. Release of Phenacetin from EC–Additive (10:1) Microcapsules Coated by 25% as EC.](image)

Additives: ——— EC alone; ○, TA; ●, PG; △, TEC; ▲, PEG; ▼, CH; ▽, AMG; ◼, LA; ■, PA.

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![Fig. 5. Effect of the Amount of EC–CH (10:1) Applied on Phenacetin Release](image)

EC applied relative to calcium carbonate core (%): O, 6.25; ●, 12.5; △, 25.

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![Fig. 6. Apparent Dissolution Rate Constant According to the First Order Kinetics against the Coating Level on a log-log Scale with EC-Additive (10:1) Microcapsules](image)

Additives: ——— EC alone; ○, TA; ●, PG; △, TEC; ▲, PEG; ▼, CH; ▽, AMG; ◼, LA; ■, PA.

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![Fig. 7. Effects of CH on the Mean Particle Size (○), the Coarse Fraction (Larger than 106 μm, ●) and Apparent Dissolution Rate Constant (△) of EC–CH Microcapsules Coated by 25% as EC Plus CH EC–CH concentration in spray solution: 2.5% (w/v).](image)
fraction of 53 to 75 μm, agglomerates were not observed apparently, but from the above estimation this fraction might partially contain agglomerates with two cores or one core and small fragments. These results implied that the particles recycling without adhesion were agglomerates and that single core microcapsules tended to adhere to the chamber wall or filter. This is a serious problem in practical use.

The effect of additives on the dissolution of phenacetin from 25% coated microcapsules is shown in Fig. 4. Only CH reduces the release, while the other additives enhance it. In the coating of fine particles, a large amount of coating material would generally be required; therefore, additives such as CH which can restrain the release have great practical advantages.

The phenacetin release from EC–CH (10:1) microcapsules at three coating levels is shown in Fig. 5. Clearly, only 6.25 or a lesser percent coating should be sufficient for prolonged release. The apparent dissolution rate constant,\(^1\) estimated according to the first order kinetics, is plotted against the coating level on a log–log scale in Fig. 6. The EC–CH (10:1) membrane is a permeation barrier about three times stronger than the EC membrane; PEG most enhances the release.

**Effect of CH Content** As shown in Table II, CH only slightly reduced particle agglomeration, though it most strongly restrained the drug release. Therefore, conditions which could produce fewer agglomerated microcapsules were sought.

Microcapsules were produced with varying CH contents at a constant EC–CH concentration of 2.5%. Coating was performed up to the level of 25% as EC plus CH. The effect of CH on mean particle size, a fraction coarser than 106 μm, a measure of agglomeration, and the apparent

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**Fig. 8.** DSC Thermograms of CH and EC–CH Films
(EC:CH): a, 0:1 (CH recrystallized in ethanol); b, 1:0; c, 5:1; d, 2:1; e, 1:1.

**Fig. 9.** SEM Photograph of EC–CH (2:1) Microcapsules Coated by 25% as EC plus CH

**Fig. 10.** Effects of CH on Variation of Phenacetin Content and 5 h Release with Particle Size Fractions of EC–CH Microcapsules Coated by 25% as EC plus CH

EC–CH concentration in spray solution: 2.5% (w/v). (EC:CH): a, 1:0; b, 2:1; c, 1:1. Mean particle size (μm): a, 89; b, 58; c, 53. The one-dot chain line shows the theoretical value of phenacetin content.
dissolution rate constant\textsuperscript{11} are shown in Fig. 7. With increase in CH content, the agglomeration is reduced rapidly at first, and with more than a 50% addition to EC (EC:CH=2:1), is almost leveled. This means that CH affords the maximum effect at the 50% addition. Figure 7 also shows that EC–CH (2:1) membrane was a permeation barrier about thirteen times stronger than EC membrane, offering a great advantage in fine powder coating.

The DSC thermograms of EC–CH films are shown in Fig. 8. The glass transition temperature of EC film was 146°C, which agreed well with its softening temperature (144°C, Fig. 2). Films containing 20% or more CH exhibited a glass transition at 115°C. The EC–CH (1:1) film showed an endotherm at 140°C. Hot-stage polarizing microscopy\textsuperscript{13} showed the endotherm to result from melting of the crystalline material, which were probably CH crystals (Fig. 8). A very small amount of crystalline material was also observed with the EC–CH (2:1). These thermograms showed that the softening of EC–CH films did not occur during the coating operation. The crystallization of CH may have been related to the reduction of agglomeration. In fact, particles like crystal were observed on the surfaces of EC–CH (2:1 and 1:1) microcapsules (Fig. 9). Details of the physicochemical properties of EC–CH mixtures and their relations to particle agglomeration will be reported in the future.

The effects of CH on the particle size dependency of 5h release and drug content of products are shown in Fig. 10. The drug content is constant in the fraction larger than around 63–75μm, but in the smaller fraction exhibits a strong dependency on particle size regardless of CH content. The 5h release exhibits the minimum around 63–75μm. Thus, the properties of EC–CH microcapsules remained strongly dependent on the particle size. A particular problem to be further studied was that EC–CH (1:1) microcapsules still exhibited a strong size dependency in spite of their narrow size distribution (Fig. 10c). This clearly resulted from retardation in recycling within the chamber. The coating was performed under a dry condition to avoid agglomeration; therefore, the retardation mainly arose from the adhesion to walls due to electrostatic charge.

**Effect of the Concentration of Spray Solution** Coating was performed at 1.5–5% (w/v) EC–CH concentrations up to 25% (EC plus CH) coating level; the CH content was fixed at EC:CH=2:1. The mean particle size and the coarse fraction were only slightly varied, though they seemed to have the minimum value at 3.5% (w/v) (Fig. 11). The particle size dependency of drug content and 5h release were not significantly improved.

**Operating Conditions in Fine Powder Coating** In the Wurster process, the inlet air rate had to be limited within a narrow range to achieve a steady recycling of particles with low ejection to the filter; therefore, the air rate could not be changed freely. Of course, one acceptable method might be to eject all particles at once and let them fall by shaking the filter. However, the core size used here was very small; therefore, such an operation would lead to a large loss due to leakage from the filter. The spray rate was also hardly changeable, because it also had to be limited within a narrow range to restrain the particle adhesion due to electrostatic charge and to keep agglomeration to

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**Figures**

**Fig. 11.** Effects of EC–CH Concentration in Spray Solution on the Mean Particle Size (○) and the Coarse Fraction (Larger than 106μm, ●) of EC–CH (2:1) Microcapsules Coated by 25% as EC plus CH

**Fig. 12.** Effects of Surfactant on Variation of Phenacetin Content and 5h Release with Particle Size Fractions of EC–CH–Surfactant (2:1:0.03) Microcapsules Coated by 25% as EC plus CH

EC–CH concentration in spray solution: 3.5% (w/v). Surfactants: a, none; b, PS 80; c, STAC. Mean particle size (μm): a, 57; b, 58; c, 56.
a low degree. The spray pressure was also unchangeable. Too high pressure caused particle ejection to the filter and too low pressure caused adhesion of wet particles within the partition. The only condition which seemed to be changeable was the inlet air temperature. However, as the temperature rose, the particle adhesion due to electrostatic charge became greater. These facts showed that improvement of properties of the product by shifting the above operating conditions was difficult.

Effect of Surfactant. There thus seemed to be no way to overcome both particle agglomeration and retardation in particle recycling except to change the surface-chemical property of the membrane material so that the dry particles could not adhere to the wall.

For such a modification of coating material, surfactants were selected as additives. Figure 12 shows the effect of PS 80 and STAC. The mean particle size is not changed. While PS 80 has no significant effect, STAC decreases the size dependency of drug content. The size dependency of drug release is reduced in the fine fractions, while it is increased in the coarse fractions. However, the weight percent in coarse fractions (larger than 106 μm) significantly decreases. Thus, STAC could improve the properties of fine microcapsules.

SEM photographs of EC–CH–STAC (2:1:0.03) microcapsules are shown in Fig. 13. Some degree of agglomeration is observed. This could be the reason the mean particle size (56 μm) was larger by 6 μm than the theoretical mean diameter (50 μm). Figure 13b suggests that the interparticle void of large agglomerates might be insufficiently covered with membrane. This may be the reason the phenacetin released was increased in the coarse particle fractions (Fig. 12c).

Figure 14 shows the phenacetin release to be increased by STAC. The dissolution profiles for EC–CH (2:1) microcapsules with or without surfactant are shown only for 6.25% (as EC plus CH) coating level. Although STAC enhances the phenacetin release, the membrane remains a strong permeation barrier.

Conclusion
There were two main problems in microencapsulation with the Wurster process: particle agglomeration and retardation in particle recycling. These caused variation in physical properties among size fractions of the microcapsules. In this study, EC:CH:STAC = 2:1:0.03 was proposed as a candidate for membrane formulation. This membrane material significantly reduced the agglomeration and the retardation of particles, resulting in production of microcapsules with a narrow particle size distribution. CH in the formulation remarkably restricted phenacetin release. As a result, 6.25% or less coating material was sufficient for prolonged release pharmaceuticals.

References