Optimum Spray Congealing Conditions for Masking the Bitter Taste of Clarithromycin in Wax Matrix

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The effects of operating conditions in the spray-congealing process on the release and the micromeritic properties of clarithromycin (CAM) wax matrix were evaluated. CAM wax matrix with 30% CAM, 60% glyceryl monostearate (GM) and 10% aminoalkyl methacrylate copolymer E (AMCE) was manufactured at various atomizer wheel speeds and liquid feed rates with a spray dryer. Release of CAM from the matrix exhibited a two-phase pattern, probably due to the dissolution of the fine portions broken on the surface of the matrix. The slope and the extrapolated *y*-intercept of the subsequent release pattern were defined as the release rate and the initial amount of release of CAM from the matrix, respectively. These release parameters, as well as the volume median diameter and the specific surface area of matrix, were selected as response variables, and multiple regression analysis was performed. For specific surface area and initial amount of release, a minimum point was observed on the contour curve when the atomizer wheel speed was constant and the liquid feed rate was varied. For the release rate, a maximum point was observed on the contour curve under the same conditions. These points were considered preferable for masking the bitter taste of CAM preparation. Microscopic observation revealed that a small spherical matrix with a smooth surface could be obtained with a high atomizer wheel speed and optimum liquid feed rate. This matrix also possessed excellent properties for taste masking, with small initial amount of release and subsequent high rate of release.

In conclusion, the congealing speed of melt droplets was the dominant factor in masking the bitter taste of CAM.

Key words taste-masking; spray-congealing; atomizer wheel speed; liquid feed rate; initial amount of release; release rate

Spray agglomeration includes both a spray-drying technique and a spray congealing technique. Many studies of the spray-drying technique have been conducted. The engineering literature includes a number of studies reporting the relationships between the particle size characteristics of atomized materials and the condition of atomization.[1—5] The relationships between particle size and centrifugal-disk atomizers have also been examined.[6] A variety of particles formed by spray-drying agglomeration have been studied.[7] However, there have been few studies reported spray congealing agglomeration.

Clarithromycin (CAM), a macloride antibiotic, has a bitter taste, which has been one of the obstacles to developing a pediatric formulation of it. In our previous study, a spray congealing technique was introduced to mask the bitter taste of CAM preparation, and an optimum wax matrix formula with 30% CAM, 60% glyceryl monostearate (GM) and 10% aminoalkyl methacrylate copolymer E (AMCE) was experimentally determined.[8]

For spray congealing agglomeration, the operating conditions affect not only physical properties, but also the degree of taste masking of the CAM formulation. Atomizer wheel speed and liquid feed rate are known to be the dominant factors in the operating conditions. In this study, the optimum CAM wax matrix noted above was manufactured at various atomizer wheel speeds and liquid feed rates with a spray dryer, and the effect of these conditions on the release and micromeritic properties of the CAM matrix was experimentally evaluated.

Experimental

Materials CAM was synthesized at Taisho Pharmaceutical Co., Ltd.. GM was of the grade specified in the Pharmacopoeia of Japan. AMCE was of commercial grade.

Spray-Congealing Agglomeration AMEC was dissolved in melted GM at 120 °C. CAM was added to the solution and homogeneously suspended. Subsequently, the suspension was transferred to a spray dryer (CL-12, Ohkawara Kakouki Co., Ltd.) and atomized under the conditions summarized in Table 1.

Experimental Design The atomizer wheel speed (X_1) and liquid feed rate (X_2) were selected as independent variables. The experimental design used in this study is summarized in Table 2.

Release Studies The release of 100 mg CAM from the matrix was evaluated in 900 ml of buffer solution at 37 °C, using the paddle method described in the Pharmacopoeia of Japan, twelfth edition. Release media of pH 6.5 phosphate buffer solution were used as solvents, and the paddle speed was set at 100 rpm. Aliquots of the solution were taken at specified intervals and the volume of the solution was returned to the original amount by adding the release medium. The amount of CAM released into the dissolution medium was quantitatively determined by HPLC under the following operating conditions: ultraviolet absorption photometer wavelength: 210 nm; column: 4.6 mm i.d. ×15 cm stainless-steel column packed with octadecyl

Table 1. Spray Dryer Operating Conditions

Inlet air temp.	50 °C
Wheel speed	5000—20000 rpm
Liquid feed temp.	120 °C
Liquid feed rate	33.6—93.5 g/min.

Table 2. Two Factor Experimental Design

Formulation	Wheel speed (rpm×100)	Feed rate (g/min)
A	162.5	93.5
B	87.5	93.5
C	200.0	61.0
D	125.0	61.0
E	50.0	61.0
F	162.5	33.6
G	87.5	33.6

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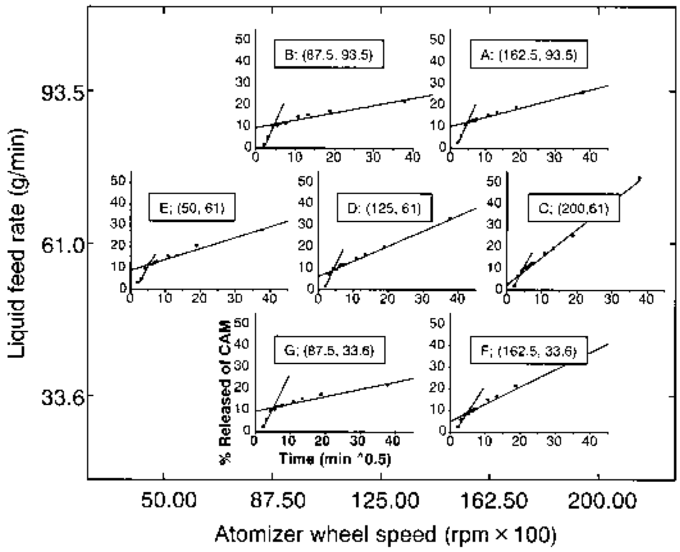

Fig. 1. The Profiles of Release of CAM for Wax Matrices Manufactured with Various Atomizer Wheel Speeds and Liquid Feed Rates

( ); each point of experimental design.

silica (ODS)-80TM (Tosoh); column temperature: 50 °C; mobile phase: mixture of 1/15 M monobasic potassium phosphate and acetonitrile (13 : 7); and a flow rate of 1 ml/min.

Measurement of Micromeritic Properties Particle size was measured using a laser diffraction method (Microtrac FRA, Nikkiso Co., Ltd.). The specific surface area was measured using an automatic gas adsorption apparatus (Belsorp 28SA, BEL Japan, Inc.) Particle characterization was performed using a scanning electron microscope (SEM) (S-2500, Hitachi Ltd.) and an optical microscope (Microphot-FXA, Nikon).

Preparation of Matrix Disk A matrix disk was prepared to determine the effect of congealing speed on CAM matrix properties. A hot suspension comprised of CAM, GM and AMCE was transferred into a cylindrical mold with an inner diameter of 4 cm and a height of 3 cm. It was allowed to stand at ambient temperature, and congealed slowly.

Results and Discussion

Profile of Release of CAM from Wax Matrices Manufactured under Various Conditions The profiles of release of CAM from wax matrices manufactured with various atomizer wheel speeds and liquid feed rates summarized in Table 2 are shown in Fig. 1, where percent release of CAM is plotted with the square root of time. Each release profile exhibited a two-phase pattern. The initial quick release appeared to be due to the dissolution of the fine portions broken on the surface of the matrix, as described below. The slope and the extrapolated y-intercept of the subsequent release pattern were defined as the release rate and the initial amount of release of CAM from the matrix, respectively. The release rate was increased as the atomizer wheel speed increased. When the liquid feed rate was not more than 61 g/min, the initial amount of release decreased as the atomizer wheel speed increased, but with a high liquid feed rate (=93.5 g/min), the initial amount of release was intrinsically independent of this atomizer wheel speed.

Microscopic Observation of CAM Wax Matrix A microscopic photograph of each matrix is shown in Fig. 2. When the liquid feed rate was higher than 61 g/min, the matrix was spherical, and the particle size decreased as the atomizer wheel speed increased. When the liquid feed rate was 33.6 g/min, the shape of the matrix was irregular.

Effect of Operating Conditions on the Micromeritic Properties of CAM Wax Matrix To make the above findings numerically precise, multiple regression analysis was performed. Median particle size (Y_1), specific surface area (Y_2), initial amount of release (Y_3) and release rate (Y_4) were selected as response variables. Each set of experimental data is summarized in Table 3.

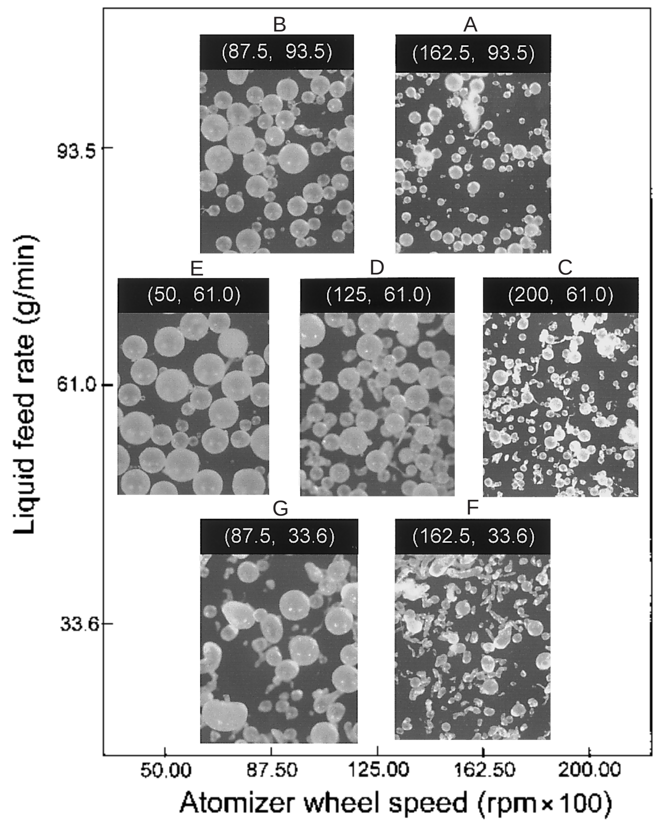

Fig. 2. Microscopic Photograph of Wax Matrices Manufactured with Various Atomizer Wheel Speeds and Liquid Feed Rates

( ); each point of experimental design.

The following second-order polynomial Eq. 1 was used to predict each response variable:

Table 3. Experimental Values for Response Variables

Formulation	Y_1[a] (μm)	Y_2[b] (cm^2/g)	Y_3[c] (%/min$^{1/2}$)	Y_4[d] (%)
A	90.9	1591	0.423	10.1
B	140.1	789.2	0.342	9.52
C	82.5	1518	1.290	2.44
D1	117.4	1022	0.828	7.13
D2	114.0	930.5	0.845	7.05
D3	111.5	1113	0.783	7.11
E	169.9	502.0	0.511	8.90
F	98.6	1298	0.801	4.82
G	142.5	933.4	0.340	9.45

a) Volume median particle size. *b*) Specific surface area. *c*) Release rate. *d*) Initial amount of release.

Table 4. Optimum Regression Equations for Each Response Variable Determined by Multiple Regression Analysis

Coefficient	Regression coefficient value			
	Y_1	Y_2	Y_3	Y_4
b_0	193.017	1546.56	−1.9065	26.2898
$b_1(X_1)$	−0.59533	—	0.01025	−0.11342
$b_2(X_2)$	—	−31.9081	0.0604	−0.36727
$b_3(X_1X_2)$	—	0.11315	−0.00009	0.0012
$b_4(X_1^2)$	—	—	—	—
$b_5(X_2^2)$	—	0.14895	−0.00041	0.00206
r[a]	0.9815	0.9895	0.9889	0.9685
s[b]	5.7	63.6	0.0658	0.884
F_O[c]	183**	77.2**	44.4**	15.5*

a) Multiple correlation coefficient. *b*) Standard deviation. *c*) Observed *F* value. * $p<0.05$, ** $p<0.01$.

$$Y=b_0+b_1\cdot X_1+b_2\cdot X_2+b_3\cdot X_1\cdot X_2+b_4\cdot X_1^2+b_5\cdot X_2^2 \quad (1)$$

where b_i is the regression coefficient, X_1 is the atomizer wheel speed, and X_2 is the liquid feed rate. The optimum regression equations with good multiple correlation coefficient, standard deviation and observed *F* value are shown in Table 4.

Figs. 3 and 4 show the contour curves as a function of atomizer wheel speed (X_1) and liquid feed rate (X_2) for median particle size and specific surface area. Median particle size decreased as the atomizer wheel speed increased, probably due to enhancement of shearing stress on the droplet. However, the liquid feed rate did not affect the matrix particle size.

The specific surface area increased as the atomizer wheel speed increased, due to the reduction of particle size. When the atomizer wheel speed was constant and the liquid feed rate changed, a minimum specific surface area existed for each speed. These findings suggest that two conflicting factors affect specific surface area. One factor is dominant in the region of high liquid feed rate, which increases the specific surface area as the liquid feed rate increases; the other is dominant in the region of low liquid feed rate, which increases the specific surface area as the liquid feed rate decreases.

Fig. 5 shows a photograph of a matrix disk after cooling. A hollow is present on the surface. When the cooling speed is slow, since the congealing speed differs between the surface and the inner portion of the matrix, reduction of the inner volume occurs, resulting in formation of the hollow.

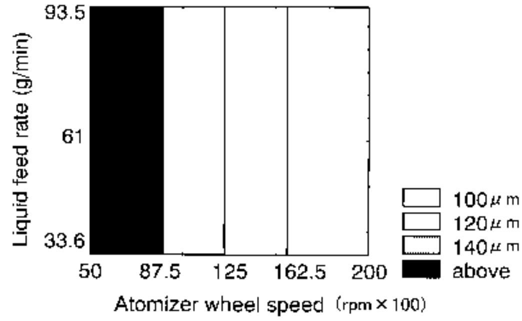

Fig. 3. Contour Graph of Median Particle Size as a Function of Atomizer Wheel Speed and Liquid Feed Rate for Median Particle Size

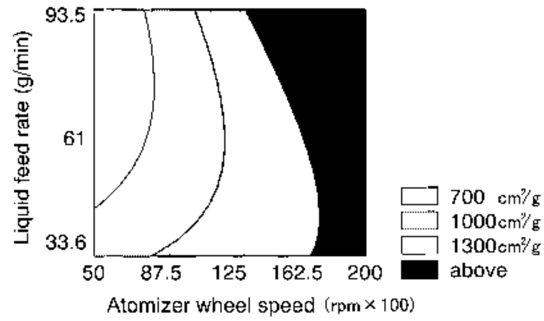

Fig. 4. Contour Graph of Specific Surface Area as a Function of Atomizer Wheel Speed and Liquid Feed Rate for Specific Surface Area

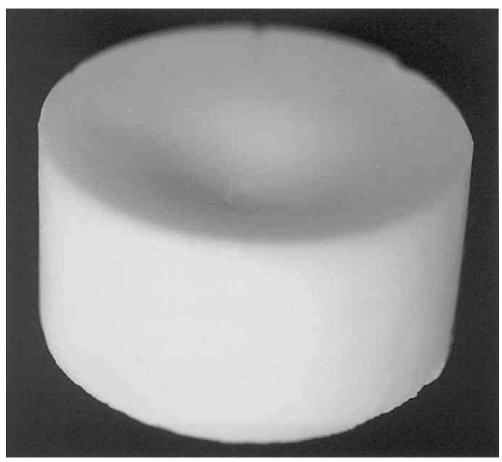

Fig. 5. Photograph of Matrix Disk Allowed to Stand at Ambient Temperature and Congeal Slowly

For the matrix, the same phenomenon occurs during the spray congealing process.

Fig. 6 shows photographs of matrices manufactured at different liquid feed rate and the same atomizer wheel speed. The matrix manufactured with a certain liquid feed rate has less folds than that manufactured with 1.25 times that. This can be explained by the slower cooling speed due to the presence of many melt droplets before congealing in the spray dryer chamber. The formation of many folds on the surface of the matrix appeared to increase the specific surface area. As the liquid feed rate increases, the cooling speed of the matrix decreases due to consumption of the capacity of cooling in the spray dryer chamber by the accelerated formation of melt droplets. From this result, the specific surface area in-

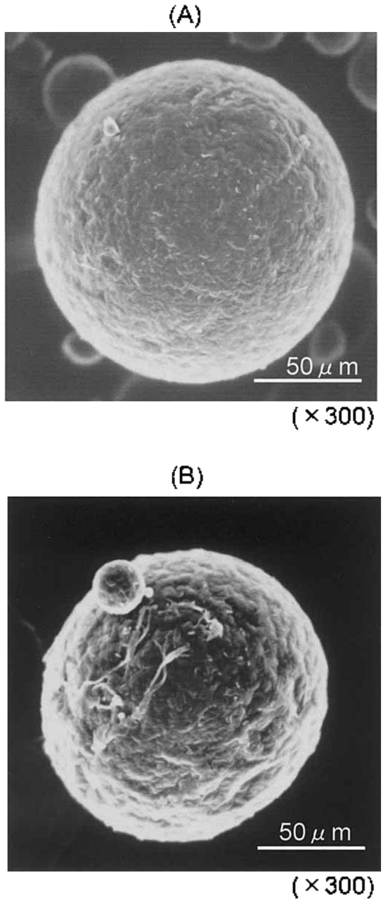

Fig. 6. SEM Photographs of the Surface of Matrix Manufactured with a Certain Liquid Feed Rate (A) and 1.25 Times That Rate (B)

The atomizer wheel speed was the same.

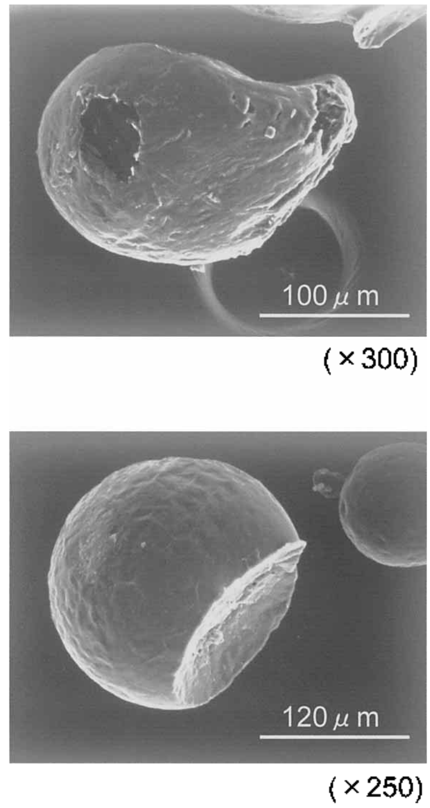

Fig. 7. SEM Photographs of the Surface of Matrix with Formation of a Large Hollow with Rapid Volume Reduction Due to Cooling

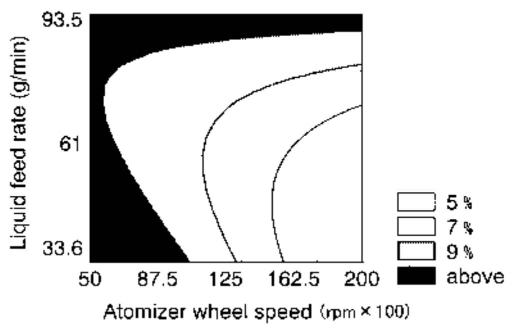

Fig. 8. Contour Graph of Initial Amount of Release as a Function of Atomizer Wheel Speed and Liquid Feed Rate

creases in the region of high liquid feed rate.

On the other hand, in the region of low liquid feed rate, rapid volume reduction occurs with cooling, resulting in the formation of a large hollow on the surface of the matrix, as shown in Fig. 7. This may increase the specific surface area.

Effect of Operating Conditions on the Release of CAM Wax Matrix The contour curve for the initial amount of release is shown in Fig. 8. The initial amount of release increased as atomizer wheel speed decreased. Since the specific surface area decreased and median particle size increased as the atomizer wheel speed decreased, as shown in Figs. 3 and 4, the initial amount of release decreases as the atomizer wheel speed decreases. This inconsistency can also be explained by the micromeritic properties of the matrix.

Figure 9 shows photographs of matrices with different particle sizes taken from the same batch. The large matrix has many larger hollows made by folds than the small matrix. This is due to reduction of the inner matrix volume with slower cooling speed resulting from the increase of matrix size. Since this portion on the surface is very fragile, it is easily broken into small portions during the initial dissolution period. The available surface area is then abruptly increased, resulting in increased initial amount of release. When the atomizer wheel speed was constant and the liquid feed rate was changed, a minimum initial amount of release existed for each atomizer wheel speed. This point coincided well with the minimum of the specific surface area in Fig. 4.

The contour curve for the release rate is shown in Fig. 10. The release rate increased as the atomizer wheel speed increased, due to increase in the specific surface area. When the atomizer wheel speed was constant and the liquid feed rate changed, a maximum release rate existed for each wheel speed. These findings suggest that two conflicting factors affect release rate. One factor is dominant in the region of high liquid feed rate, which reduces the release rate as the liquid feed rate increases, while the other is dominant in the region of low liquid feed rate, which reduces the release rate as the liquid feed rate decreases.

In the region of high liquid feed rate, the cooling speed decreases due to the formation of many melt droplets in the spray dryer chamber as the liquid feed rate increases. Fig. 11 shows cross-sections of matrices manufactured at or/and below a certain congealing speed. When the congealing speed was low, packing of the inner component resulted in a

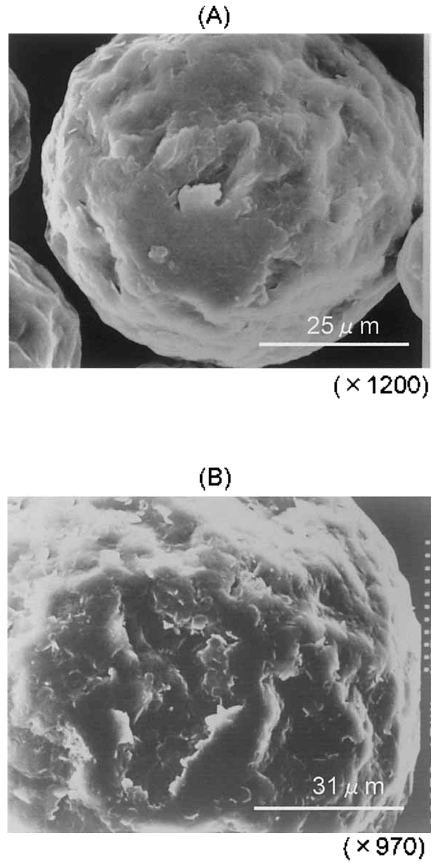

Fig. 9. SEM Photographs of Small Matrix Surface with Few Hollows (A) and Large Matrix Surface with Many Large Hollows (B) Made by Folds

Median particle size was 55 μm for A, and 139 μm for B.

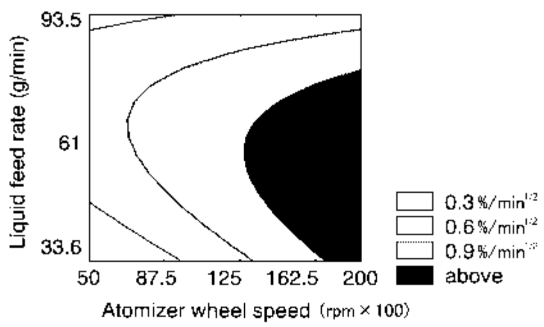

Fig. 10. Contour Graph of Release Rate as a Function of Atomizer Wheel Speed and Liquid Feed Rate

dense layer and spherical voids. For these portions with a dense layer, the available surface area for release decreased due to the difficulty of penetration by the solution, resulting in reduction of the release rate. When the congealing speed is certain, homogeneous packing with high porosity can be attained, the solution can then easily penetrate the inner portion of the matrix, and the rate of release becomes high.

In the region of low liquid feed rate, rapid volume reduction occurs, since the congealing speed is very high due to the presence of few melt droplets in the spray dryer chamber, resulting in the formation of homogeneous dense packing with dense layering except for hollows, as shown in Fig. 7. The solution then can barely penetrate into the portion of the matrix, and the release rate becomes low.

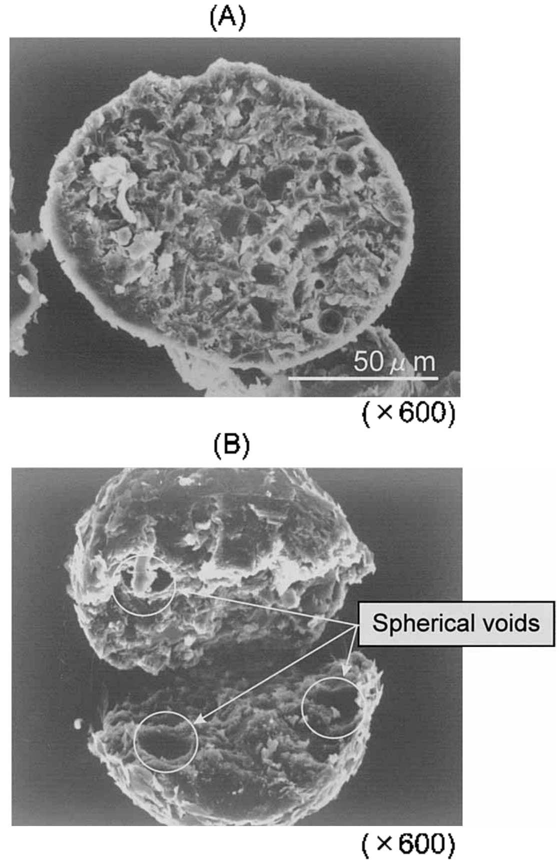

Fig. 11. SEM Photographs of Cross-Sections of Matrices Manufactured with a Certain Congealing Speed (A) and Lower than That (B)

Thus, the matrix manufactured with minimum initial amount of release and maximum release rate with a fast atomizer wheel speed was spherical with a smooth surface and had optimum release characteristics for taste masking.

Conclusion

CAM wax matrix manufactured using a spray congealing technique exhibited various micromeritic properties with variation of operation conditions. The micromeritic properties affected the release performance of the matrix. The matrix congealing speed was the dominant factor in masking the bitter taste of CAM. A high atomizer wheel speed, for manufacturing a small matrix, and an optimum liquid feed rate, for manufacturing a spherical matrix with a smooth surface, thus provided excellent operating conditions for taste masking, with a low initial amount of release and subsequent high rate of release.

In this study, an atomizer wheel speed of 20000 rpm and a liquid feed rate of 61.0 g/min provided optimum spray congealing conditions for masking the bitter taste of clarithromycin wax matrix.

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