Particle Design for Taste-Masking Using a Spray-Congealing Technique[1)]

Toshio YAJIMA,* Akemi NOGATA, Miki DEMACHI, Nobuo UMEKI, Shigeru ITAI, Nobuo YUNOKI, and Masami NEMOTO

Department of Pharmaceutics, Research Center, Taisho Pharmaceutical Co., Ltd. No. 403, Yoshino-cho 1-chome, Ohmiya, Saitama 330, Japan. Received July 11, 1995; accepted October 3, 1995

A method of taste-masking using a spray-congealing technique was developed. Clarithromycin (CAM), a macloride antibiotic with a bitter taste, was selected as the model compound. The fundamental objective was to prevent the preparation from dissolving in the mouth, while ensuring that rapid release of CAM from the preparation could be attained in the gastrointestinal tract, resulting in bioequivalence to the conventional dosage form. Glyceryl monostearate (GM) and aminoalkyl methacrylate copolymer E (AMCE) were selected as ingredients, since GM, a substance with a low melting point, is able to be decomposed by an enzymatic reaction in the intestinal tract where the solubility of AMCE is very low. On the other hand, AMCE was selected because it is freely soluble at low pH levels (*e.g.* the pH level in the stomach), but insoluble in neutral and high pH levels (*e.g.* the pH level in the mouth).

Spherical particles of the matrix (spherical matrix) and disks of matrix with various ratios were prepared, and the optimum ratios of CAM, GM and AMCE for the following release criterion were determined by experimental design (the simplex method). That is, 100 mg/l of CAM in the spherical matrix should be completely released within 20 min in pH 4.0, and less than 14 mg/l of CAM in spherical matrix should be released at 60 min in pH 6.5.

As a result, the optimum formula for the matrix in consistency with the criterion was 3:6:1 for CAM, GM and AMCE, respectively.

Key words taste-masking; spray-congealing technique; glyceryl monostearate; aminoalkyl methacrylate copolymer E; experimental design; particle size decrease rate

Recently, there have been many reports on the granulation and coating of drugs with a substance with a low melting point for the purpose of taste-masking and better compliance.[2)]

The spray-congealing technique, which uses a spray dryer, is an effective method of taste-masking because this method is cost effective and requires no solvent, and it can produce a more dense film than other methods without moving materials or drying. Also since this method is easy to industrialize, many attempts using this technique have been undertaken. However in most cases, ensuring both satisfactory taste-masking and good release at the same time was found to be quite difficult, and without satisfactory results.

In this paper, it was found that aminoalkyl methacrylate copolymer E (AMCE) dissolved glyceryl monostearate (GM), which is known to be decomposed by an enzymatic reaction in the intestinal tract,[3,4)] at 120 °C. Therefore, a particle design for good release and satisfactory taste-masking, with manufacturing feasibility, was investigated. Matrices comprising clarithromycin (CAM), GM and AMCE were prepared in various ratios, and the optimum ratio was determined by the experimental design method. The fundamental objective of the particle design was to prevent the preparation from dissolving in the mouth, while ensuring that rapid release of CAM from the preparation was attained in stomach. Since the solubility of the matrix decreased as the pH increased, the lowest pH in the mouth and the highest pH in the stomach significantly influenced the taste masking and release profiles, respectively. Thus, the following criteria were established, where pH 4.0 and 6.5 were estimated to be the highest pH in the stomach and the lowest pH in the mouth, respectively. The Paddle Method was adopted for evaluation of taste because of its simplicity.

(1) The unit dose of the matrix comprised 100 mg of CAM.

(2) The release of CAM was accomplished within 20 min in pH 4.0, taking the dissolution rate in the stomach into consideration.

(3) Less than 14 mg/l (the threshold of bitter taste for CAM) of CAM in matrix was released at 60 min in pH 6.5.[5)]

(4) A spherical matrix of less than 100 μm (approximately 80 μm) is preferable for preventing a "sandy" feeling mouth.[5,6)]

(5) The viscosity of the melting suspension should be less than 4 poise at 120 °C, in order to continuously spray the melting solution into the spray dryer.

Experimental

Material CAM was synthesized at Taisho Pharmaceutical Co., Ltd. GM was of the grade specified in Pharmacopoeia of Japan. AMCE was of commercial grade. All other chemicals were of reagent grade.

Formulas of Preparation The preparation formulas designed using the simplex method are summarized in Table 1.[7-10)] The ratios of CAM (X1) and AMCE (X2) were selected as independent variables. Each preparation was regulated to 100% with GM.

Table 1. Experimental Design for Two Factors

Formulation	CAM (%) [*X*1]	AMCE (%) [*X*2]	Monoglyceride (%)
A	20	5	75
B	40	5	55
C	30	20	50
D	20	15	65
E	40	15	45
F	30	0	70
G1	30	10	60
G2	30	10	60
G3	30	10	60

* To whom correspondence should be addressed.

Preparation of Disk AMCE was dissolved in melting GM at 120 °C. CAM was added to the melting solution and suspended homogeneously. Subsequently, the suspension was transferred into a plastic cylindrical mold with an inner diameter of 3 cm and a height of 0.5 cm, and then it was cooled. After the mass was solidified, one side of the disk surface was covered with epoxy resin so that another surface alone became available for the release study.

Spray-Congealing Technique The suspension described in Preparation of Disk was transferred into a spray dryer (CL-12, Ohkawara Kakohki Co., Ltd.) and atomized under the following conditions: liquid temp.: 120 °C, inlet air temp.: 80 °C, spray rate: 61 g/min, disk revolutions: 20,000 rpm, spray amount: 4 kg.

Measurement of Viscosity The viscosity of the suspension at 120 °C was measured with a soliquid meter (MR-3, Rheology Co., Ltd.).

Release Studies The release of CAM from the disk and spherical matrix was evaluated in 500 and 1000 ml of buffer solution at 37 °C, respectively, using the Paddle Method in the Pharmacopoeia of Japan, Twelfth Edition. The release media of pH 4.0 acetate buffer solution and pH 6.5 phosphate buffer solution were selected 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 volume by adding the release medium.

Then the amount of CAM released into the dissolution medium was quantitatively determined by HPLC with the following operating conditions: ultraviolet absorption photometer; wavelength: 210 nm; column: 4.6 mm i.d. × 15 cm stainless-steel column packed with ODS-80TM (Tosoh); column temperature: 50 °C; mobile phase: a mixture of 1/15 M monobasic potassium phosphate and acetonitrile (13 : 7); and a flow rate of 1 ml/min.

Measurement of Physical Properties The bulk density of the spherical matrix was measured with a powder tester (PT-E, Hosokawa Micromeritics Laboratory). The particle size was measured using a laser diffraction method (Microtrac FRA, Nikkiso Co., Ltd.). The particle characterization was performed using a Scanning Electron Microscope (SEM) (S-2500, Hitachi, Ltd.).

Results and Discussion

The Miscibility of MG and AMCE MG and AMCE were a liquid with low viscosity and a clear glass with high viscosity at 120 °C, respectively, and they adulterated excellently. Furthermore, when MG was added to AMCE, the mixture changed from a clear glass with high viscosity to a clear liquid with low viscosity. Then, when the mixture was cooled, the mixture changed to a solid with a milk-white color.

The Release of CAM from the Disk The release of CAM from one surface of each disk was evaluated in pH 4.0 and 6.5 buffer solutions, as shown in Figs. 1 and 2. A linear relation was obtained between the amount dissolved and the time for each disk. The slope of the line varied as the ratio of the ingredients changed. That is, moderately rapid release was attained in formulations C and E. On the other hand, the release rate of formulation A was the slowest of all formulations. With the linear regression of each data, the release rate of each disk was obtained, as shown in Table 2, where $Y1$ and $Y2$ denote the release rate in pH 4.0 and 6.5 buffer solutions, respectively.

Determination of Particle Size Reduction Rate In general, the release of a substance from a matrix is considered to proceed in proportion to time squared ($\sqrt{t}$), if the diffusion of the substance in the matrix is the dominant rate-limiting step.[11,12] But, as indicated in Figs. 1 and 2, the release of CAM from each disk at an early stage was proportionate to time (t). One possible explanation is that the simultaneous release of the disk itself may have occurred as the release of CAM proceeded. In this case, Nernst's equation, shown in Eq. 1, can be applied for the release from the matrix system[13]:

$$dC/dt = k \cdot (S/V) \cdot (Cs - C) \quad (1)$$

where k, S, V, Cs and C are the intrinsic dissolution rate constants (cm/min), available surface area (cm^2), medium volume (ml), solubility (μg/ml) and dissolved amount at time t in medium volume (μg/ml).

Under the sink condition ($Cs \gg C$), Eq. 1 can be solved as follows:

$$C = k \cdot (S/V) \cdot Cs \cdot t \quad (2)$$

Table 2. Experimental Values of Response Variables

Formulation	$Y1$[a] μg/(ml·min)	r[b]	$Y2$[c] μg/(ml·min)	r[b]	$Y3$[d] (P)
A	0.9874	0.9452	0.02381	0.9766	0.338
B	3.7787	0.9924	0.01275	0.9802	7.45
C	7.1640	0.9997	0.04177	0.9960	5.45
D	1.7001	0.9981	0.01913	0.9964	1.3
E	9.4756	0.9951	0.03961	0.9994	11.4
F	2.0114	0.9741	0.003932	0.9616	1.12
G1	3.4625	0.9993	0.0202	0.9985	3.02
G2	3.4764	0.9990	0.01554	0.9965	3.07
G3	3.3861	0.9967	0.01826	0.9950	2.96

a) Released rate in pH 4.0. *b*) Multiple correlation coefficient. *c*) Released rate in pH 6.5. *d*) Viscosity.

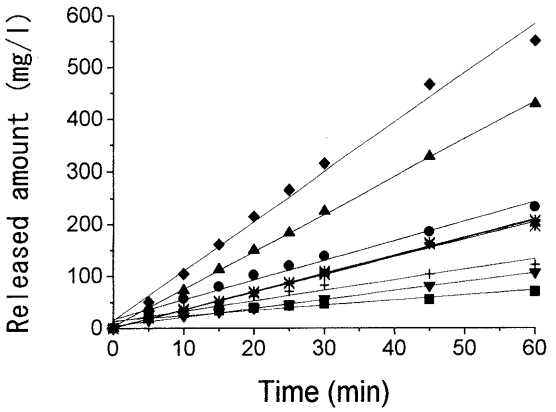

Fig. 1. Released Rate of CAM from Various Disks Obtained by Experimental Design for Two Factors at pH 4.0

■, A; ●, B; ▲, C; ▼, D; ◆, E; +, F; ∗, G1, G2, G3.

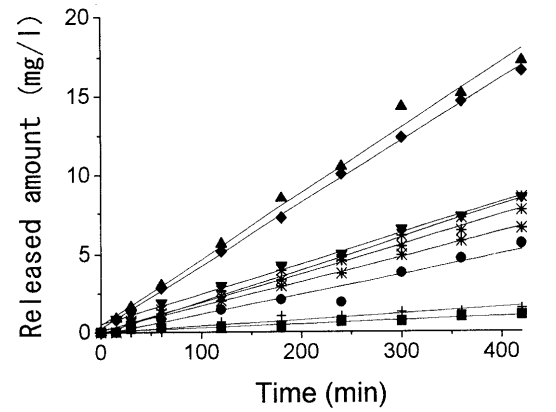

Fig. 2. Released Rate of CAM from Various Disks Obtained by Experimental Design for Two Factors at pH 6.5

■, A; ●, B; ▲, C; ▼, D; ◆, E; +, F; ∗, G1, G2, G3.

On the other hand, if Eq. 1 is applied to spherical particles under the sink condition, the decreased rate of particle weight can be expressed as follows:

$$-dW/dt = k \cdot S \cdot Cs \quad (3)$$

where W is particle weight.

When the particle is spherical, the surface area is as shown in Eq. 4.

$$S = \pi \cdot X^2 \quad (4)$$

where X is particle size (μm).

By substituting Eq. 4 to Eq. 3, Eq. 3 can be rewritten as shown in Eq. 5.

$$-dW/dt = k \cdot \pi \cdot X^2 \cdot Cs \quad (5)$$

Furthermore, W is shown in Eq. 6.

$$W = \pi \cdot X^3 \cdot \rho/6 \quad (6)$$

where ρ (g/cm^3) is density.

By differentiating Eq. 6 with time t, Eq. 7 can be obtained.

$$-dW/dt = \pi \cdot X^2 \cdot \rho/2 \cdot dX/dt \quad (7)$$

From Eqs. 5 and 7, Eq. 8 can be derived.

$$dX/dt = 2 \cdot k \cdot Cs/\rho \quad (8)$$

By integrating Eq. 8 with time t, Eq. 9 can be obtained:

$$X = X_0 - (2 \cdot k \cdot Cs/\rho) \cdot t \quad (9)$$

where X_0 and X denote the initial particle size and particle size at t. In this case, the particle size is linearly decreased due to dissolution. When K is defined as follows,

$$K = 2 \cdot k \cdot Cs/\rho \quad (10)$$

K can be expressed as the particle size reduction rate during the release process.[14] That is, in the case of a spherical particle under the sink condition, K is constant and is not influenced by the original particle size. Equation 2 can be rewritten as follows:

$$C = (K \cdot S \cdot \rho/(2 \cdot V)) \cdot t \quad (11)$$

Then, K can be determined with the slope of the release rate from a disk (S=constant).

Furthermore, if K can be determined, the % released in a mono-dispersion system with an original particle size of X_0 can be simulated as follows:

$$D = ((X_0^3 - (X_0 - K \cdot t)^3)/X_0^3) \cdot 100 \quad (12)$$

In our introduction, we established two release criteria. Namely, 100 mg/l of CAM in a spherical matrix should be completely released within 20 min in pH 4.0; and less than 14 mg/l of CAM in a spherical matrix should be released at 60 min in pH 6.5.

To meet the criteria, K of the spherical particle (ρ= 1 g/cm^3) with X_0 of 80 μm should be more than 4 μm/min and less than 0.0654 μm/min in pH 4.0, and in pH 6.5 solutions, respectively. In other words, the release rate of CAM from a disk (as shown in Figs. 1 and 2) should be more than 2.83 μm/(ml·min) and less than 0.0462 μm/(ml·min) for pH 4.0 and 6.5 solutions, respectively.

Effect of AMCE and CAM Ratios on the Release Rate from Matrix The experimental values of the release rate in Table 2 ($Y1$, $Y2$) were adopted in Eq. 13, and the value of each parameter for deriving the optimum equation was obtained by multiple regression analysis.

$$Y = b_0 + b_1 \cdot X1 + b_2 \cdot X2 + b_3 \cdot X1 \cdot X2 + b_4 \cdot X1^2 + b_5 \cdot X2^2 \quad (13)$$

where $X1$ and $X2$ are defined as the ratio of CAM and of AMCE, respectively. The results are shown in Table 3. When the ratio of AMCE ($X2$) was constant, the release rates at pH 4.0 and 6.5 increased in proportion to the ratio of CAM, as shown in Eq. 14. On the other hand, proportion to the square of the ratio of AMCE, as shown in Eq. 15.

$$Y = (b_0 + b_2 \cdot X2 + b_5 \cdot X2^2) + (b_1 + b_3 \cdot X2) \cdot X1 \quad (14)$$

$$Y = (b_0 + b_1 \cdot X1) + (b_2 + b_3 \cdot X1) \cdot X2 + b_5 \cdot X2^2 \quad (15)$$

Table 3. Optimum Regression Equation for Each Response Variable Determined by Multiple Regression Analysis

Coefficient	Regression coefficient value		
	$Y1$	$Y2$	$Y3$
b_0	3.597	0.0176	3.124
$b_1 \cdot (X1)$	2.157	0.0063	3.5134
$b_2 \cdot (X2)$	1.970	0.01406	1.59948
$b_3 \cdot (X1 \cdot X2)$	1.439	0.00292	0.86257
$b_4 \cdot (X1^2)$	—	—	1.33201
$b_5 \cdot (X2^2)$	0.538	0.00252	—
$r^{a)}$	0.997	0.994	0.999
$s^{b)}$	0.32	0.0021	0.69
$F_0^{c)}$	142**	83**	68**

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

Figures 3 and 4 show the contour lines of the release rate at pH 4.0 and 6.5, respectively, obtained by substituting each parameter in Table 3 into Eq. 13.

Effect of AMCE and CAM Ratios on the Viscosity of the Suspensions The viscosity of each suspension at 120 °C, as well as the release rates from the disks, is shown in Table 2. The experimental data of viscosity in Table 2 ($Y3$) were adopted in Eq. 13, and the value of each parameter for the optimum regression equation was obtained by multiple regression analysis. The result is shown in Table 3. When the ratio of AMCE ($X2$) was constant, the viscosity increased in proportion to the square of the ratio of CAM, as shown in Eq. 16. On the other hand, when the ratio of CAM ($X1$) was constant, the viscosity increased in proportion to the ratio of AMCE ($X2$), as shown in Eq. 17

$$Y = (b_0 + b_2 \cdot X2) + (b_1 + b_3 \cdot X2) \cdot X1 + b_4 \cdot X1^2 \quad (16)$$

$$Y = (b_0 + b_1 \cdot X1 + b_4 \cdot X1^2) + (b_2 + b_3 \cdot X1) \cdot X2 \quad (17)$$

Figure 5 shows the contour line of the viscosity at 120 °C, obtained by substituting each parameter in Table 3 into Eq. 13. The effect of the ratio of CAM on viscosity was dominant, in comparison with that of AMCE.

Determination of the Optimum Matrix Formulation The contour lines of the release rate at pH 4.0 and 6.5 and the viscosity (Figs. 3 to 5) were superimposed on each other, and the optimum region for meeting both the

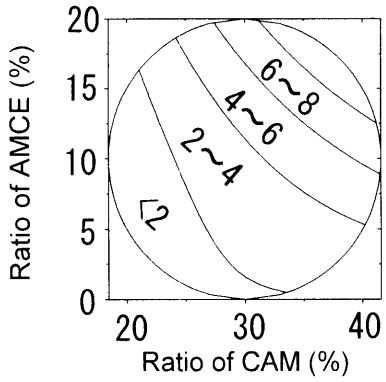

Fig. 3. Contour Lines for Released Rate at pH 4.0 as Ratios of CAM and AMCE

The unit of numerical value in this graph is μg/(ml·min).

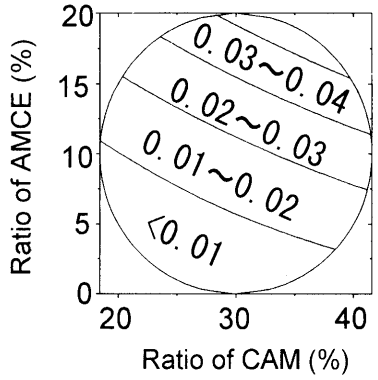

Fig. 4. Contour Lines for Released Rate at pH 6.5 as Ratios of CAM and AMCE

The unit of numerical value in this graph is μg/(ml·min).

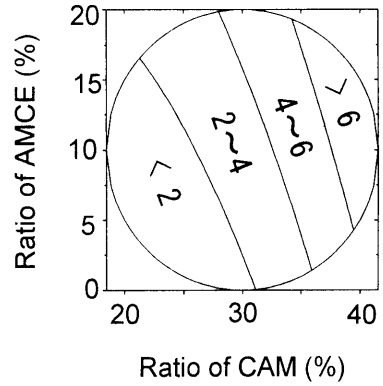

Fig. 5. Contour Lines for Viscosity at 120 °C as Ratios of CAM and AMCE

The unit of numerical value in this graph is poise.

release and manufacturing criteria were obtained. The result is shown in Fig. 6, where the shaded portion is the optimum region for meeting all the criteria. The released amount in pH 6.5 at 60 min was less than 14 mg/l in all regions, so the optimum region could be determined by superimposing the contour lines of the release rate at pH 4.0 (Fig. 3) and the viscosity (Fig. 5). According to the results shown in Fig. 6, the optimum ratios for the matrix were determined as 30 : 10 : 60 for CAM, AMCE and MG, respectively.

The Physical Properties of the CAM Matrix A matrix

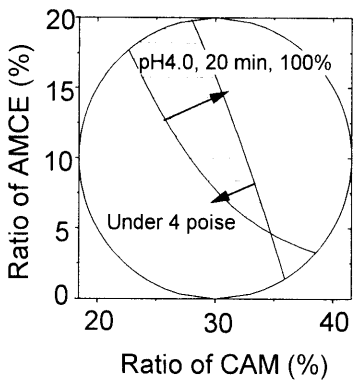

Fig. 6. Optimum Region for Meeting both the Release and Manufacturing Criteria as Ratios of CAM and AMCE

Table 4. Physical Property of Matrix

Aerated bulk density	0.55 g/cc	
Packed bulk density	0.65 g/cc	
Particle size distribution	D_{10}%	39 μm
	D_{50}%	79 μm
	D_{90}%	136 μm

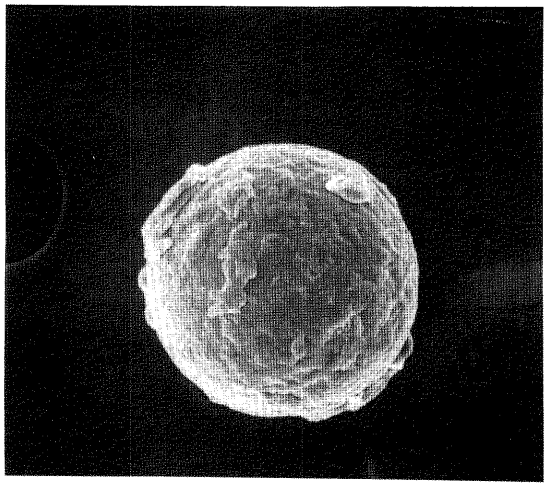

Fig. 7. SEM Photograph of Matrix (× 350)

comprised of 30% CAM, 10% AMCE and 60% GM was actually manufactured by the spray-congealing technique, and the physical properties and particle characterization were determined. The results are summarized in Table 4. The median diameter (D_{50}%) of the matrix was approximately 80 μm, and the size distribution was very narrow. Figure 7 shows the SEM photograph of the matrix. A spherical particle with a smooth surface was obtained.

The Release Profile of CAM from the Matrix Figure 8 shows the release of CAM from the matrix manufactured by the spray-congealing technique in pH 4.0 and 6.5 buffer solutions. The release of CAM was accomplished within 20 min (approximately 5 min) in pH 4.0. The amount of CAM released in pH 6.5 was less than 14 mg/l at 60 min (approximately 12 mg/l). That is, a satisfactory release profile of the matrix was obtained. The lines of A and B in Fig. 8 show the simulation curves for the release of CAM from the matrix, with 80 μm of the original particle size in pH 4.0 and 6.5 solutions. These lines were obtained

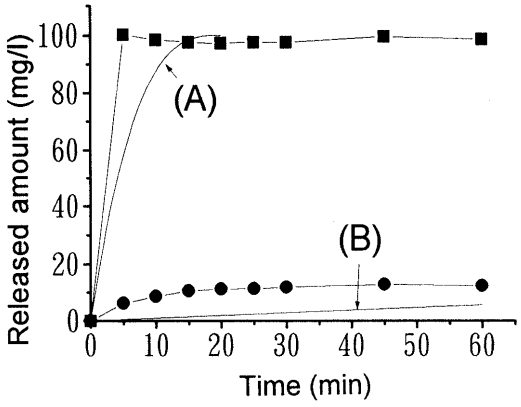

Fig. 8. The Release of CAM from the Matrix Manufactured Using a Spray-Congealing Technique in pH 4.0 and 6.5 Buffer Solutions

■, pH 4.0; ●, pH 6.5.

by substituting the K of the disk prepared with the optimum ratios of CAM, AMCE and GM (30 : 10 : 60) in Eq. 12.

The experimental data in pH 4.0 and 6.5 solutions in Fig. 8 were larger than each of the theoretical data. One possible explanation for this phenomenon may be that the matrices may have a quickly released CAM at an early stage, because the matrices of CAM had a larger specific surface area than the disk. However, the difference is not considered to be an essential factor in the taste-masking and bioavailability of the formulation, because the released amount was under the threshold of bitter taste (14 mg/l).

The Sensory Evaluation of the Formulation The reconstituted liquid dosage form (dry syrup), compromising 10% CAM, consisted of the spherical matrix, excipient, binder, thickener, sweetener and perfume. In regard to the dry syrup, the panel test was carried out. It was found that the palatability and taste of the dry syrup were better than that of the granules coated by the air spray method.

Conclusion

The optimum formula for a matrix comprising CAM, AMCE and GM was determined by multiple regression analysis, taking the taste-masking of CAM, the bioavailability and the manufacturing feasibility into consideration. The matrix with the optimum ingredient ratio was actually manufactured using the spray-congealing technique, and the physical properties and release profiles were measured. The experimental data of the matrix coincided well with the anticipated values. A dry syrup was prepared by granulating the mixture of the matrix and other ingredients, and a panel test was carried out.

The palatability and the taste of the formulation were significantly improved, compared with conventionally coated granules.

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References and Notes

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