Acetaminophen Particle Design Using Chitosan and a Spray-Drying Technique

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In this study matrices were prepared from particles of poorly water-soluble drugs such as acetaminophen (Act) to determine the drug release rate from these matrix particles. The matrix particles were prepared by incorporating drugs into chitosan powder (Cht, carrier) using a spray-drying method. The formation of composite particles was confirmed by scanning electron microscopic (SEM) analysis. The matrix particles prepared by spray-drying were spherical with a smooth surface. The crystallinity of acetaminophen in the composite particles was evaluated by powder X-ray diffraction and differential scanning calorimetry (DSC). The degree of crystallinity of acetaminophen in the matrix particles decreased with a reduction in the weight ratio of acetaminophen relative to the carrier. These results indicate that a solid dispersion of acetaminophen in chitosan forms matrix particles. The interaction between acetaminophen and chitosan was also investigated by FT-IR analysis. FT-IR spectroscopy of the acetaminophen solid dispersion suggested that the carbonyl group of acetaminophen and the amino group of chitosan formed a hydrogen bond. There were some differences at pH levels of 1.2 and 6.8 in the release of acetaminophen from the physical mixture compared to the matrix particles. At pH 1.2, the release from the matrix particles (Act : Cht=1 : 5) was more sustained than from the physical mixtures. The 70% release time, T_{70}, of acetaminophen from the matrix particles (Act : Cht=1 : 5) increased in pH 1.2 fluid by about 9-fold and in pH 6.8 fluid by about 5-fold compared to crystalline acetaminophen. These results suggest that matrix particles prepared by spray-drying are useful as a sustained release preparation.

Key words acetaminophen; chitosan; matrix particles; release; solid dispersion

Previous studies have shown that coprecipitation with polyvinylpyrrolidone (PVP) can markedly enhance the dissolution of poorly water-soluble drugs.[1,2] The mechanism responsible for such enhanced dissolution has been the subject of debate. Some authors have proposed that the increased drug dissolution rate is due to the formation of a high-energy amorphous drug phase.[3,4] Several water-soluble polymer carrier systems, such as polyethylene glycol (PEG), PVP, and hydroxypropylcellulose (HPC),[5—7] have been used in fast-release preparations. The interaction mechanisms between the drug and the carrier in solid dispersions have been studied.[8,9] Previous studies of naproxen-α-lactose monohydrate solid dispersions,[10,11] prepared using melting methods, supported the existence of a high-energy amorphous drug phase in systems containing more than 50% α-lactose monohydrate. The dissolution data suggested that the dissolution rate of this phase was 7—20-fold greater than the crystalline drug.

Recently, a spray-drying technique has yielded an amorphous form of such crystalline drugs as cimeditine that becomes amorphous when spray-dried with chitosan, as reported by He *et al.*[12] This indicates that a solid dispersion was formed when cimeditine was dispersed in the chitosan molecules by spray drying. Corrigan *et al.*[13] tried to make an amorphous drug by spray drying using PVP as a carrier. Generally, the dissolution rate of a drug increases when a solid dispersion is formed using a polymer as a carrier, as described above. However, only a few studies have investigated the slow release of a drug after the formation of a solid dispersion using spray-drying. Shaikh *et al.*[14] performed spray-drying using acetaminophen (Act) and ethylcellulose (EC) and tried to achieve a sustained release of Act. Their results demonstrated that it is possible to form a solid dispersion by dispersing Act using a spray-drying technique with EC molecules in a molecular state. They concluded that the sustained release of Act from this solid dispersion was caused by an increase in the viscosity of EC.

In this study, we designed matrix particles to slowly release Act by changing the mixture ratio of chitosan and Act. Slow release in the digestive tract is attempted in this formation by using chitosan powder (Cht) as a carrier and the solid dispersion in Cht and between drugs. As expected, the absorbability of the drug from the mucosa increased, because Cht easily harmonizes with biological membrane. In addition, the dosage form design of the administration to the lung is also possible, because fine particles are prepared by a spray-drying technique. Then, the design of the particles for the slow release of the drug was tried by forming a solid dispersion by a spray-drying technique that used chitosan as the carrier.

Experimental

Materials The acetaminophen (model drug) was supplied by Fujisawa Astor Co., Ltd., Chitosan (carrier), whose degree of deacetylation was calculated at 89.0% by amino group content with a coefficient viscosity of 70 mPa·s, was supplied by Japan Chelate Co., Ltd.. Other materials and solvents were of analytical reagent grade. The solubility of acetaminophen was 19.3 mg/ml in water, 21.3 mg/ml in a pH 1.2 solution, and 17.8 mg/ml in a pH 6.8 solution at 37 °C, respectively. The solubility of chitosan was 15.0 mg/ml in a pH 1.2 solution at 37 °C.

Preparation of Matrix Particles Particles were dissolved in mixtures of 1 : 1, 1 : 3, and 1 : 5 (6 : 6, 3 : 9, and 2 : 10 g/l) by acetaminophen (Act) and chitosan (Cht) in a 0.5% acetic acid aqueous solution. The solution was spray-dried under the following conditions: the inlet temperature was 90 °C, the drying air flow rate was 0.74 m^3/min, the atomizing air pressure was 100 kPa, and the outlet temperature was 65—75 °C. The matrix particles were spray-dried using an SD-1000 spray-drying instrument (Tokyo Rikakikai Co., Ltd.).

Preparation of Physical Mixtures The physical mixtures were prepared by mixing the drug and the carrier (the tested ratios of the drug and

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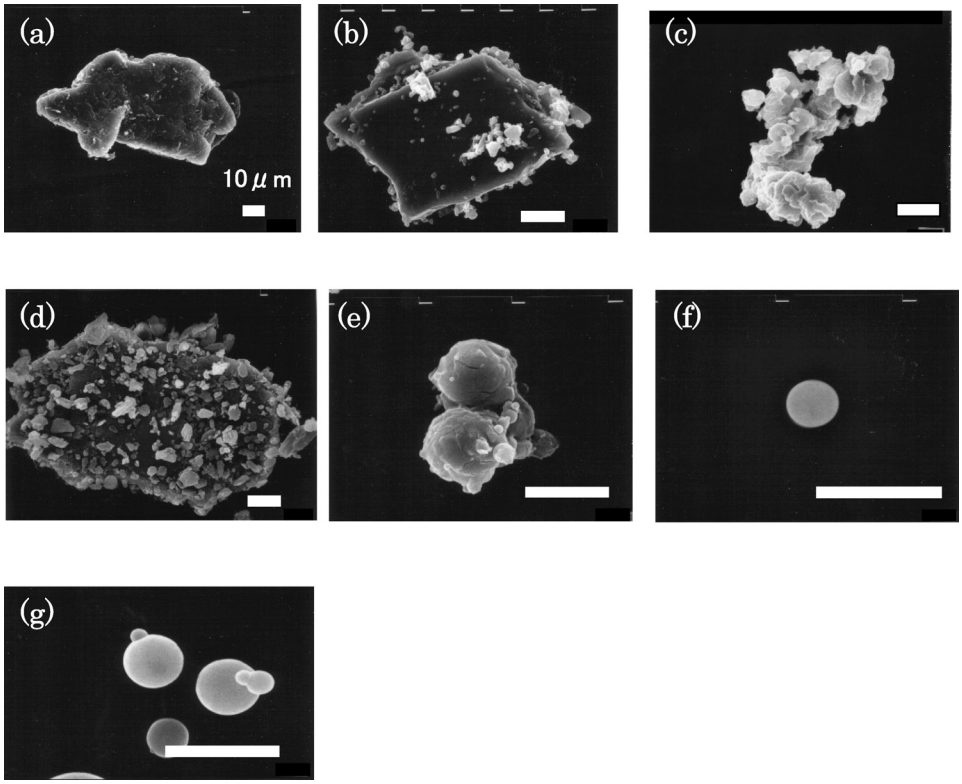

Fig. 1. SEM Photographs of Samples

(a) Chitosan; (b) acetaminophen; (c) acetaminophen-S.D.; (d), Act : Cht=1 : 1 P.M.; (e) Act : Cht=1 : 1 S.D.; (f) Act : Cht=1 : 3 S.D.; (g) Act : Cht=1 : 5 S.D. (P.M.: physical mixture, S.D.: spray drying).

the carrier were 1 : 1, 1 : 3, and 1 : 5) using a test tube mixer (Scientific Industries, Vortex-Genie 2) for 10 min at a constant amplitude and rate.

Confirmation of Particle Morphology A scanning electron microscope (SEM, JEOL Type JSM-T20) was used to observe the morphology of the matrix particles.

Measurement of Particle Size Distribution The particle size was measured using a laser diffraction scattering particle size distribution measurement equipment (LSM-30, Seishin Kigyo Co., Ltd.).

Confirmation of the Crystallinity of the Drug Powder X-Ray Diffraction Powder X-ray diffraction analysis was performed with a Rigaku Geiger-Flex diffractometer (Rad-2VC) using a Ni-filter, Cu$K\alpha$ radiation, a voltage of 40 kV, and a current of 20 mA. The scanning rate was 5°/min over a 2θ range of 5—45°.

Thermal Analysis Differential scanning calorimetry (DSC) was carried out with a 3100 instrument (MAC Science Co., Ltd.). The operating conditions in the open pan system were: sample weight, 10 mg; heating rate, 10 °C/min.

Infrared Spectroscopy FT-IR spectra were obtained with a FT-200 spectrometer (Horiba Co., Ltd.), using the transformation of 100 scans obtained by the KBr disk method.

Dissolution Test Dissolution tests were performed according to the JPXIV paddle method for sample powders, using 50 mg of the drug and 1000 ml of the dissolution medium at pH 1.2 or pH 6.8 at 37±0.1 °C. The rotation speed of the paddle was 100 rpm. The quantity of acetaminophen was assayed by HPLC at 225 nm. The mobile phase was 0.05 M KH_2PO_4 solution : CH_3OH=4 : 1(v/v), which flowed through an ODS column (Cosmosil 5C18-AR, 4.6×150 mm, Nacalai Tesque) at a rate of 0.8 ml/min.

Results and Discussion

Confirmation of Composite Particle Formation Scanning electron micrographs of the samples are shown in Fig. 1. Acetaminophen and chitosan consisted of irregular shaped particles and included agglomerates of fine particles. Examination of the electron microgrphs confirmed that the drug and the carrier were mixed almost uniformly in the physical mixture. The matrix particles prepared in a 0.5% acetic acid solution system by spray-drying were spherical with smooth surface.

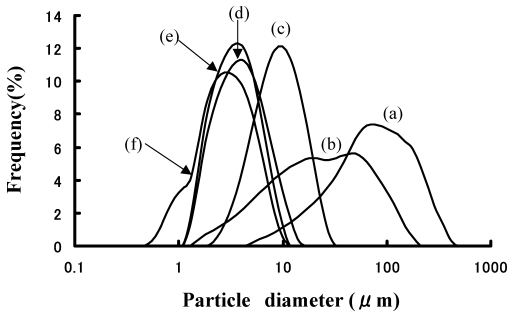

Fig. 2. Particle Size Distribution of Samples

(a) Chitosan; (b) acetaminophen; (c) acetaminophen-S.D.; (d) Act : Cht=1 : 1 S.D.; (e) Act : Cht=1 : 3 S.D,; (f) Act : Cht=1 : 5 S.D.

The particle size distribution obtained under the conditions used here for spray drying is shown in Fig. 2. The mean particle size of the spray-dried samples of Act : Cht=1 : 1 and 1 : 3 were almost the same. However, the mean particle size of the spray-dried sample of Act : Cht=1 : 5 was smaller than the other samples, as shown in Fig. 2. The mean particle size of spray-dried Act was considerably lager than the other spray-dried samples, as shown in Fig. 2.

Degree of Crystallinity of Acetaminophen in Matrix Particles Powder X-ray diffraction patterns for acetaminophen, the carrier, their physical mixtures, and the samples prepared using spray-drying are shown in Fig. 3. Many sharp peaks were observed in the diffraction patterns of ac-

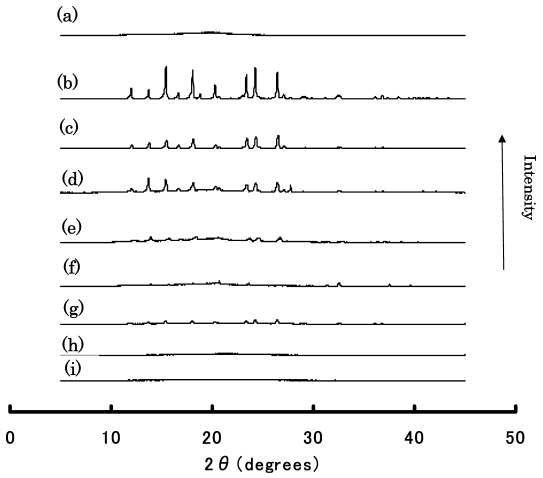

Fig. 3. Powder X-Ray Diffraction Patterns of Samples

(a) Chitosan; (b) acetaminophen; (c) acetaminophen-S.D.; (d) Act : Cht=1 : 1 P.M.; (e) Act : Cht=1 : 3 P.M.; (f) Act : Cht=1 : 5 P.M.; (g) Act : Cht=1 : 1 S.D.; (h) Act : Cht=1 : 3 S.D.; (i) Act : Cht=1 : 5 S.D.

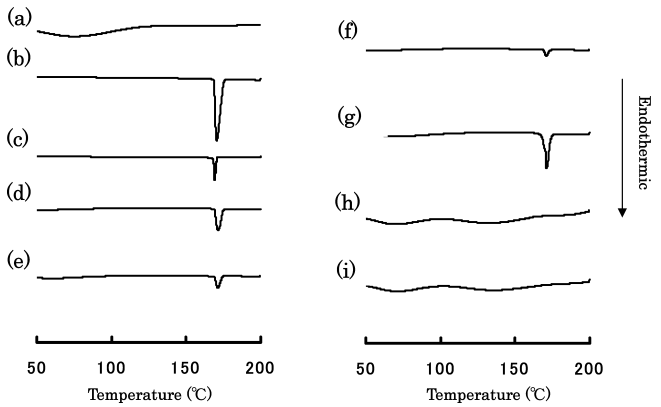

Fig. 4. DSC Thermograms of Samples

(a) Chitosan; (b) acetaminophen; (c) acetaminophen-S.D.; (d) Act : Cht=1 : 1 P.M.; (e) Act : Cht=1 : 3 P.M.; (f) Act : Cht=1 : 5 P.M.; (g) Act : Cht=1 : 1 S.D.; (h) Act : Cht=1 : 3 S.D,; (i) Act : Cht=1 : 5 S.D.

etaminophen. Chitosan was found to be amorphous, as indicated by the absence of diffraction peaks. In the physical mixtures, although the amplitude of the diffraction peaks decreased with increases in the mixing ratio of chitosan, crystallinity was confirmed by the appearance of peaks. Using the 0.5% acetic acid solution system, no diffraction peaks were observed in the spray-dried samples with Act and Cht mixing ratios of 1 : 3 and 1 : 5. These results indicate that the spray-dried samples with 1 : 3 and 1 : 5 mixing ratios in the 0.5% acetic acid system formed solid dispersions, which suggests that the drug was dispersed homogeneously in an amorphous state.

DSC thermograms for acetaminophen, the carriers, their physical mixtures, and the samples prepared by spray-drying are shown in Fig. 4. The melting points of the samples are listed in Table 1 with the heat of fusion results for the samples (ΔH), which were used as an index of crystallinity, Xc. Xc was calculated according to the following equation:

$$\text{Xc}\ (\%)=(\Delta H/\Delta H_0)\times 100 \quad (1)$$

where ΔH_0 is the heat of fusion of the crystalline form and ΔH is the heat of fusion of the sample.

Table 1. Melting Point, Heat of Fusion, and Crystallinity (Xc) of Samples

Sample	Melting point (°C)	Heat of fusion ΔH (J/g)	Xc (%)
Acetaminophen	169.2	180.9	100.0
Acetaminophen SD	168.2	89.9	49.7
Act/Cht=1/1 PM	169.1	166.7	92.2
=1/3 PM	169.1	165.6	91.5
=1/5 PM	169.2	165.4	91.4
Act/Cht=1/1 SD	167.5	125.2	69.2
=1/3 SD	—	—	—
=1/5 SD	—	—	—

PM, physical mixture; SD, spray drying; —, peaks were not detected.

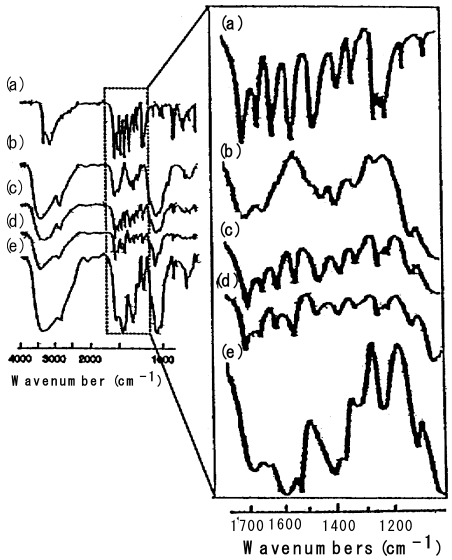

Fig. 5. FT-IR Spectra of Samples

(a) Acetaminophen; (b) chitosan; (c) Act : Cht=1 : 5 P.M.; (d) Act : Cht=1 : 3 S.D.; (e) Act : Cht=1 : 5 S.D.

The ΔH values of the three physical mixtures were almost equal. However, for samples prepared using spray-dryings, the ΔH values were very small, as shown in Table 1, suggesting a decrease in the crystallinity of acetaminophen.

The X-ray diffraction results and the DSC measurements suggested that, although acetaminophen and the carrier could not form solid dispersions with simple physical mixing, solid dispersions could be obtained when the mixtures were spray-dried. The degree of crystallinity of acetaminophen in the solid dispersions was dependent on the ratio of the drug to the carrier.

Interaction Mechanism between the Drug and the Carrier Ozeki *et al.*[15,16] are investigated the interaction between phenacetin and macromolecule by IR. Their results demonstrated that it is possible to form a hydrogen bond between a drug and a macromolecule. Tozuka *et al.*[17] entrapped salicylamide into mesoporous material and is currently examining the interaction between molecules by FT-IR. We have also examined the interaction between a drug and a Cht by FT-IR.

The results of FT-IR spectroscopy of Act, Cht, and the solid dispersions are shown in Fig. 5. Act showed bands at 3324.7 cm^{-1} due to a stretching vibration in the amide group, at 1564.0 cm^{-1} due to an NH bending vibration, and at

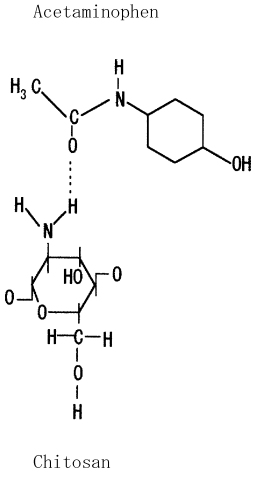

Fig. 6. Possible Structure of Solid Dispersion

1654.6 cm^{-1} due to a stretching vibration in the carbonyl group. Cht showed a broad band at 3414.0 cm^{-1} due to a stretching vibration in the hydroxyl group and a band at 1600.6 cm^{-1} due to an NH bending vibration. These bands were similarly observed for the physical mixture of Act and Cht, suggesting that no interaction occurred between Act and Cht in the physical mixture. The band due to the carbonyl group stretching vibration of Act in the 1 : 5 solid dispersion slightly shifted to a lower wavenumber, while the band due to the amide group of Cht at 1600.6 cm^{-1} disappeared. These observations suggest that the interaction was caused by the carbonyl group of Act and the amide group of Cht, as shown in Fig. 6.

Release Rate of Acetaminophen from the Matrix Particles In the present study, we prepared matrix particles using spray-drying and focused on the sustained release of Act. The relationship between the release rate of Act from the matrix particles and the interaction between the drug and the carrier was examined as follows.

The release profiles of acetaminophen from the physical mixtures and solid dispersions were obtained at pH values of 1.2 and 6.8, as shown in Fig. 7. The mechanism of the drug release from the matrix particles was examined as follows.

It is difficult to apply all of the present release test results to the Higuchi equation because release from a drug and a physical mixture are not release from a matrix. To compare release of all samples, we decided to compare mass of release in a definite period of time.

Therefore, the release results obtained in this study should be compared using 70% release time (T_{70}). T_{70} values are shown in Table 2.

The release rate of a drug is affected by particle size, concentration of the drug, dispersion state of drug, *etc*. In the present experiment, the particle sizes of the original and the matrix differed (Fig. 2). The release rate of the acetaminophen should have been faster, however, its particles were considerably larger than the matrix particles obtained by spray-drying. Therefore, in the present experiments, the release rate was not dependent on the particle size but dependent on the properties of the carrier used in the matrix formation.

As the release rate in pH 1.2 fluid, when the physical mixture (PM) was compared with Act, the release rate of PM decreased about 5 times less than Act. This is the result of chitosan that forms a gel in the acid solution at the initial stage of release, decreasing the release of Act. Since the Act particles by which this adheared to surface of Cht particles were incorporated into the gel of Cht in early stage of the release, the release of a physical mixture was delayed. When PM was compared with spray-dried samples (SD) of 1 : 1 and 1 : 3, both showed almost the same value of T_{70}. As for the samples of 1 : 1 and 1 : 3, the action to which the crystallinity of Act decreased and released retardation by gelation of Cht was successful, and the difference was lost between PM and SD. However, an SD sample of 1 : 5 served as release from the matrix that completely formed solid dispersion, and the gelation effect of Cht became large. In fact, the T_{70} of Act was considerably smaller than the T_{70} of the SD matrix particles (Table 2), indicating that the release rate from the spray-dried particles was delayed. T_{70} of Act/Cht=1/5SD in the pH 1.2 fluid was about 9-fold.

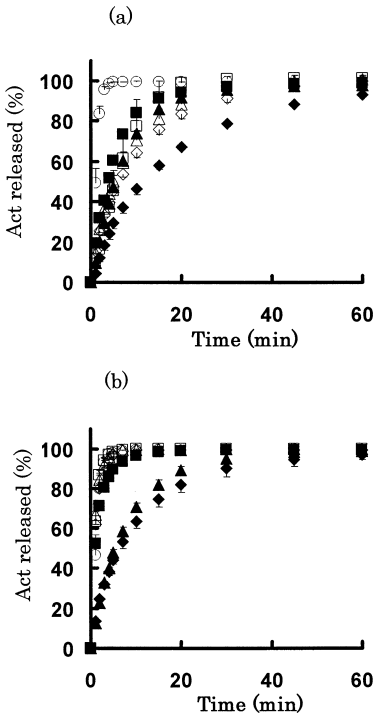

Fig. 7. Dissolution Profiles of Act–Cht Systems (Mean±S.D. (n=3))

○, Acetaminophen; □, Act : Cht=1 : 1 P.M.; △, Act : Cht=1 : 3 P.M.; ◇, Act : Cht=1 : 5 P.M.; ■, Act : Cht=1 : 1 S.D,; ▲, Act : Cht=1 : 3 S.D.; ◆, Act : Cht=1 : 5 S.D. (P.M.=physical mixture, S.D.=spray drying).

Table 2. 70% Release Time T_{70} of Acetaminophen

Sample	pH 1.2 fluid	pH 6.8 fluid
	T_{70} (min)	T_{70} (min)
Acetaminophen	1.72	1.77
Act/Cht=1/1 PM	9.47	1.69
=1/3 PM	7.52	1.78
=1/5 PM	8.44	1.78
Act/Cht=1/1 SD	6.12	2.44
=1.3 SD	8.82	8.17
=1/5 SD	15.23	8.37

PM, physical mixture; SD, spray drying.

In the case of release in pH 6.8, Act and PM showed the almost same value of T_{70}. That is, since Cht swelled in an alkali solution, almost no influence was shown in the release of Act. On the other hand, since the Act molecules were distributed, and SD samples of 1 : 3 and 1 : 5 formed solid dispersion into the molecules of Cht, the imbition effect of Cht greatly appeared, and the value of T_{70} decreased about 5 times more than Act. The release of SD samples in pH 6.8 is mainly based on diffusion. Therefore, it differs from the release accompanying the diffusion and the dissolution of gel in pH 1.2.

Conclusions

Acetaminophen formed solid dispersions with chitosan when the mixtures of the drug and the carrier were spray-dried. Acetaminophen became amorphous as the result of the formation of solid dispersions.

The carbonyl group of Act and the amino group of Cht carried out the hydrogen bond, and formed the solid dispersion.

Although the release of acetaminophen was early in pH 1.2 and 6.8, the release showed a markedly sustained release from the solid dispersion with the drug and the carrier at a ratio of 1 : 5.

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