Improved Dissolution of an Insoluble Drug Using a 4-Fluid Nozzle Spray-Drying Technique

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A solid dispersion of the drug can be made using a polymer carrier to improve solubility. Generally, drugs become amorphized when solid dispersion is formed using a polymer carrier. In such high energy conditions, the solubility of the drug molecule is increased. We previously prepared solid dispersion using a spray-drying technique and reported its solubility and crystallinity. In this study, hydroxypropylmethylcellulose (HPMC) was used as the carrier, and tolubutamide was the model drug, which is water-insoluble. Solubility was evaluated by preparing a solid dispersion using a newly developed 4-fluid nozzle spray dryer. Observation of particle morphology by scanning electron microscopy (SEM) revealed that the particles from the spray drying were atomized to several microns, and they had also become spherical. Assessment of the crystallinity of the spray-dried particles by powder X-ray diffraction and differential scanning calorimetry demonstrated that the tolbutamide had been amorphized, forming a solid dispersion. The apparent release rate constant *K* of the drug from the spray-dried particles was 4 to 6 times faster than the original drug in pH 1.2, and it was also 1.5 to 1.9 times faster than the original drug in pH 6.8. The 70% release time (T_{70}) of the drug from the spray-dried particles was 20 to 30 times faster than the original drug in pH 1.2 solution as well as 2 to 3 times faster than the original drug in pH 6.8 solution. Pharmaceutical preparations prepared in this way using the 4-fluid nozzle system spray dryer formed composite particles, resulting in a remarkably improved dissolution rates of the drug.

Key words spray drying; tolubutamide; hydroxypropylmethylcellulose (HPMC); solubility; amorphous

Even though numerous studies have shown that coprecipitation with polyvinylpyrrolidone (PVP) can markedly enhance the dissolution of drugs,[1—3] the mechanism responsible for this enhanced dissolution has been debated. Some have proposed that the increased drug dissolution rate is due to the formation of a high energy amorphous drug phase.[4—8] Others have attributed the effect to the molecular dispersal of the drug[9,10] or an increased complexity in PVP,[11] while coacervation was suggested by Sekikawa *et al.*[12] and Baddawi and EI-Sayed.[13] Several water-soluble polymer carrier systems, such as polyethylene glycol (PEG), PVP and hydroxypropylcellulose[14—18] have been used in fast-release preparations. The mechanism for the interaction between the drug and the carrier in solid dispersions has also been studied.[19—22] However, few have studied of solid dispersions using low molecular weight substances as carriers.[23—25]

Recently, a spray drying technique yielded an amorphous form of crystalline drugs using a carrier such as PVP[26] or lactose.[27] The dissolution rate of the drug increases when solid dispersion is formed by using the polymer as a carrier.

In this study, the physicochemical properties of spray-dried tolbutamide-hydroxypropylmethylcellulose (HPMC) systems were investigated to clarify their amorphous nature. We tried various combinations of composite particles, which had properties of release, by changing the mixture ratio of the drug and the carrier, prepared by using a newly developed 4-fluid nozzle spray dryer.

Experimental

Materials Tolbutamide, model drug, was purchased commercially from Wako Pure Chemical Industries. Hydroxypropylmethylcellulose (HPMC), the carrier, was supplied by Shin-Etsu Chemical Industries.

Preparation of Composite Particles. Preparation from Suspension Three grams of tolbutamide were suspended in 1000 ml of 1.5% HPMC aqueous solution. This suspension was spray-dried under the following conditions: the inlet temperature was 110 °C, the drying air flow was 5 or 10 ml/min, the atomizing air pressure was 35 kPa, and the outlet temperature was 55—70 °C. The composite particles were prepared by spray drying using a 4-fluid-nozzle system spray dryer micromist dryer MDL-050B (Fujisaki Electric Co., Ltd. Japan).

Preparation from Solution One gram of tolbutamide was dissolved in 1000 ml of 20 w/v% methanol solution. This solution and a 0.5% aqueous HPMC solution were supplied from separated lines and spray dried using a 4-fluid-nozzle system (4.F.N) and a 3-fluid-nozzle system (3.F.N).

Preparation of Physical Mixtures The physical mixtures were prepared using a test tube (Scientific Industries, Vortex-Genie 2, Japan) for 10 min at a constant amplitude and rate mixing the drug and the carrier at ratios of 1 : 1, 1 : 3, and 1 : 5.

Determination of the Particle Morphology A scanning electron microscope (SEM, JEOL Type JSM-T20, Japan) was used to observe the morphology of the samples.

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

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

(b) Thermal analysis of differential scanning calorimetry (DSC) was carried out with a DSC-60 instrument (Shimadzu Co., Ltd. Japan). The operating conditions in the open pan system were: sample weight, 10 mg; heating rate, 10 °C/min; heating range, 30—200 °C.

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

Dissolution Test Dissolution tests were performed according to the JP XIV paddle method using sample powders. Fifty milligrams of the drug and 1000 ml of the dissolution medium at pH 1.2 or pH 6.8 at 37±0.1 °C were used. The rotation speed of the paddle was 50 rpm. The quantity of tolbutamide was assayed using an ultraviolet spectrophotometer (Shimadzu Co.,

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Ltd., Type UV-160, Japan) at 226 nm.

Results and Discussion

Confirmation of Composite Particles Figure 1 shows SEM photographs of each sample. Tolbutamide consisted of acicula particles and agglomerated particles. The spray-dried particles were spherical and became composite. Confirmation of the coating of the particle surface was not possible from the SEM photograph of the 3-fluid nozzle system.

Particle size distributions are shown in Fig. 2. The size of particles prepared from the solution using the 4-fluid nozzle system was considerably smaller than the particles prepared from suspension. The 4-fluid nozzle (4.F.N) system and the 3-fluid nozzle (3.F.N) systems produced almost the same particle sizes when they were prepared from the solution.

Confirmation of the Crystallinity of Tolbutamide in the Composite Particles Powder X-ray diffraction patterns for tolbutamide, HPMC, their physical mixtures, and the samples prepared using spray-drying techniques are shown in Fig. 3. Many sharp peaks were observed in the diffraction pattern of tolbutamide. HPMC exhibited signs of amorphousness because diffraction peaks were not observed. In the physical mixture, the diffraction peaks decreased with an increase in the mixing ratio of HPMC; however, crystallinity was still confirmed. On the other hand, in the 4.F.N suspension system sample, since the drug was not perfectly dissolved in water and was not perfectly amorphized, the tolbutamide peaks resembled those in the physical mixture. In the samples from the 4.F.N and 3.F.N solution systems, the diffraction peaks of tolbutamide disappeared indicating that the spray-dried samples from the 4-fluid and 3-fluid nozzle system spray dryers had formed amorphous.

In the 4.F.N suspension sample, since the drug was not dissolved in water, the diffraction peaks of the tolbutamide

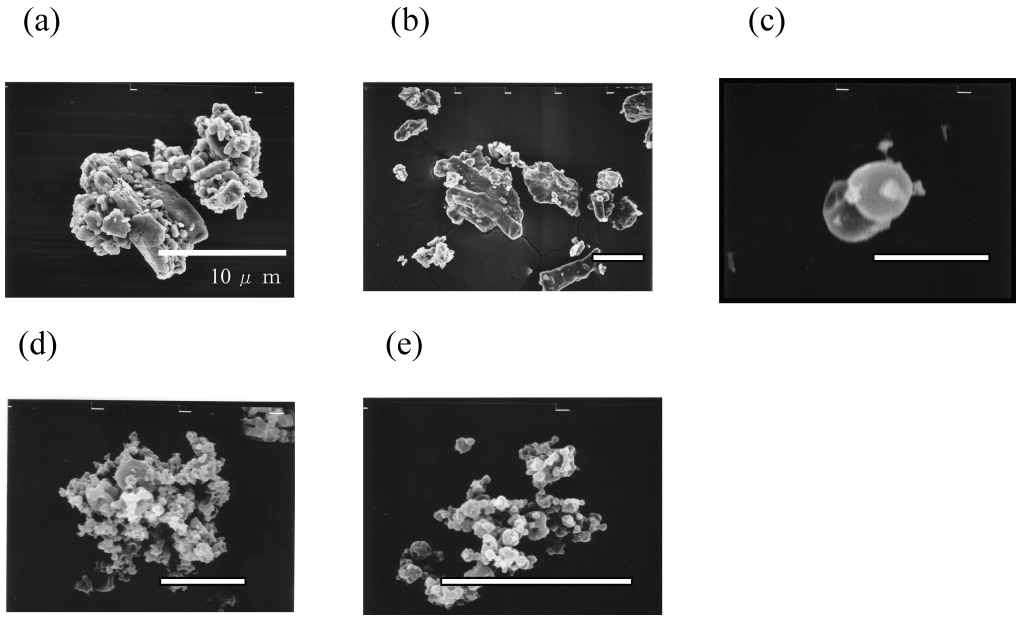

Fig. 1. Scanning Electron Micrographs of Tolbutamide-HPMC Systems

(a) Tolbutamide; (b) HPMC; (c) TLB : HPMC=1 : 5 4.F.N Sus; (d) TLB : HPMC=1 : 5 4.F.N Sol; (e) TLB : HPMC=1 : 5 3.F.N Sol. 4.F.N Sus, suspension was sprayed using a 4-fluid nozzle; 4.F.N Sol, solution was sprayed using a 4-fluid nozzle; 3.F.N Sol, solution was sprayed using a 3-fluid nozzle.

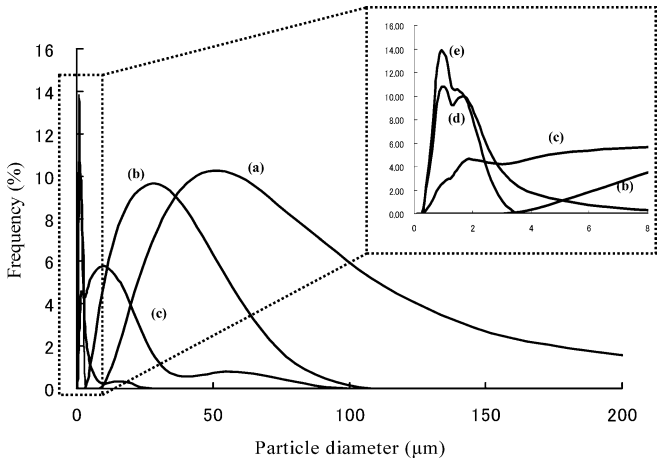

Fig. 2. Particle Size Distribution for Samples

(a) HPMC; (b) Tolbutamide; (c) TLB : HPMC=1 : 5 4.F.N Sus; (d) TLB : HPMC=1 : 5 4.F.N Sol; (e) TLB : HPMC=1 : 5 3.F.N Sol.

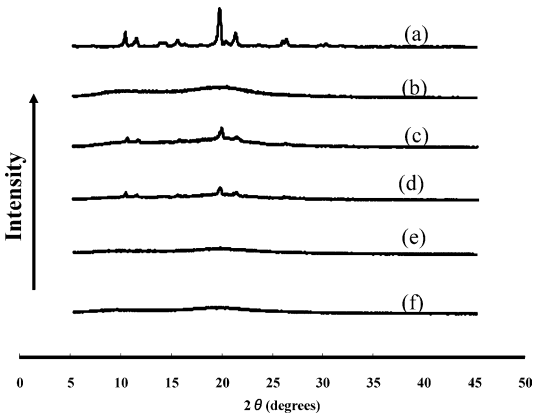

Fig. 3. Powder X-Ray Diffraction Patterns of Tolbutamide-HPMC Systems

(a) Tolbutamide; (b) HPMC; (c) TLB : HPMC=1 : 5 PM; (d) TLB : HPMC=1 : 5 4.F.N Sus; (e) TLB : HPMC=1 : 5 4.F.N Sol; (f) TLB : HPMC=1 : 5 3.F.N Sol. PM, physical mixture.

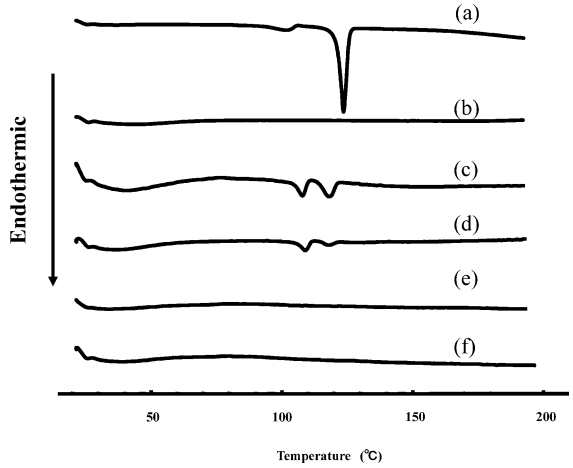

Fig. 4. DSC Thermograms of the Tolbutamide-HPMC Systems

(a) Tolbutamide; (b) HPMC; (c) TLB : HPMC = 1 : 5 PM; (d) TLB : HPMC = 1 : 5 4.F.N Sus; (e) TLB : HPMC = 1 : 5 4.F.N Sol; (f) TLB : HPMC = 1 : 5 3.F.N Sol.

remained similar to those in the physical mixture, indicating that the drug was not amorphized. The diffraction peaks of tolbutamide prepared using the 4.F.N solution system and the 3.F.N solution disappeared, indicating that the drug had formed a solid dispersion. Yamaguchi *et al.*[28] prepared amorphous solids by dissolving MAT (4″-*O*-(4-methoxyphenyl)acetyltylosin) in dichloromethane using a spray-drying method. On the other hand, Dangprasirt and Ritthidej[29] prepared solid dispersions of dicrefenac sodium by spray drying using ethylcellulose, chitosan, and hydroxypropyl methylcellulose as carriers. Recently, since solid dispersions can be prepared by spray-drying techniques solid dispersion can be formed because the composite particles of the spray-drying technique are amorphized.

DSC measurements were carried out to confirm the composite particles suggested by the X-ray diffraction results. DSC thermograms for tolbutamide, HPMC, their physical mixtures, and the samples prepared using the spray-drying technique are shown in Fig. 4. There was an endothermic peak with a melting point for tolbutamide near 123 °C. In the physical mixture, only the endothermic peak decreased compared with tolbutamide because of a dilution effect caused by HPMC. The endothermic peak with fusion of the tolbutamide was not observed in the 4.F.N solution or 3.F.N solution samples. The results of these DSC thermograms also indicated the amorphizability of the tolbutamide, as the results from the powder X-ray analysis.

The melting point, the heat of fusion, and the crystallinity of the samples are shown in Table 1. The heat of fusion of the samples (ΔH), used as an index of crystallinity, Xc, is listed in Table 1. 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 samples.

ΔH of T : H = 1 : 5. in the 4.F.N solution and the 3.F.N solution systems were not caluculated, because their samples had no endothermic peaks.

Release of Tolbutamide from Composite Particles Figure 5 shows the results of the release of tolbutamide at pH 1.2 and 6.8. When the release rates were compared to an acidic medium (pH 1.2), the release rate of the spray-dried particles was faster than the original drug. However, the release rates of the two forms in pH 6.8 medium were almost the same. The release rate was obtained by plotting the Higuchi equation:

$$Q=K\cdot t^{1/2} \quad (2)$$

where Q is the percentage of release of the drug, t is the release time, and K is the apparent release rate constant. In addition, the 70% release time (T_{70}) was compared to the latter half of the release. The results of the Higuchi equation are shown in Fig. 6, and the calculation results are shown in

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

Sample	Melting point (°C)	ΔH (J/g)	Xc (%)
Tolbutamide	126.32	78.48	100
HPMC	—	—	—
TLB : HPMC = 1 : 5 PM	121.44	5.96	45.6
TLB : HPMC = 1 : 5 4-F.N Sus	121.46	2.96	16.4
TLB : HPMC = 1 : 5 4-F.N Sol	—	—	—
TLB : HPMC = 1 : 5 3-F.N Sol	—	—	—

PM, physical mixture; 4-F.N Sus, 4-fluid nozzle with suspension; 4-F.N Sol, 4-fluid nozzle with solution; 3-F.N Sol, 3-fluid nozzle with solution; —, peaks were not detected.

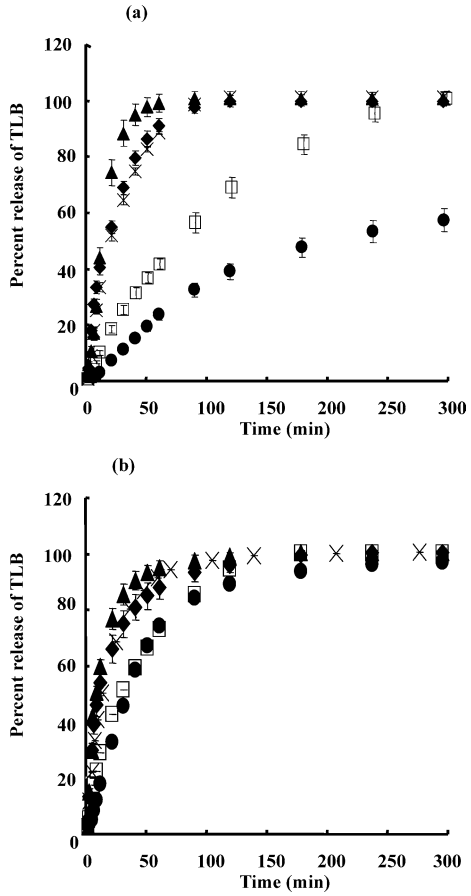

Fig. 5. Release Profiles of the Tolbutamide-HPMC Systems

(a) pH 1.2; (b) pH 6.8. ●, Tolbutamide; □, TLB : HPMC = 1 : 5 PM; ×, TLB : HPMC = 1 : 5 4.F.N Sus; ◆, TLB : HPMC = 1 : 5 4.F.N Sol; ▲, TLB : HPMC = 1 : 5 3.F.N Sol. Values plotted are mean ± S.D. (n = 3).

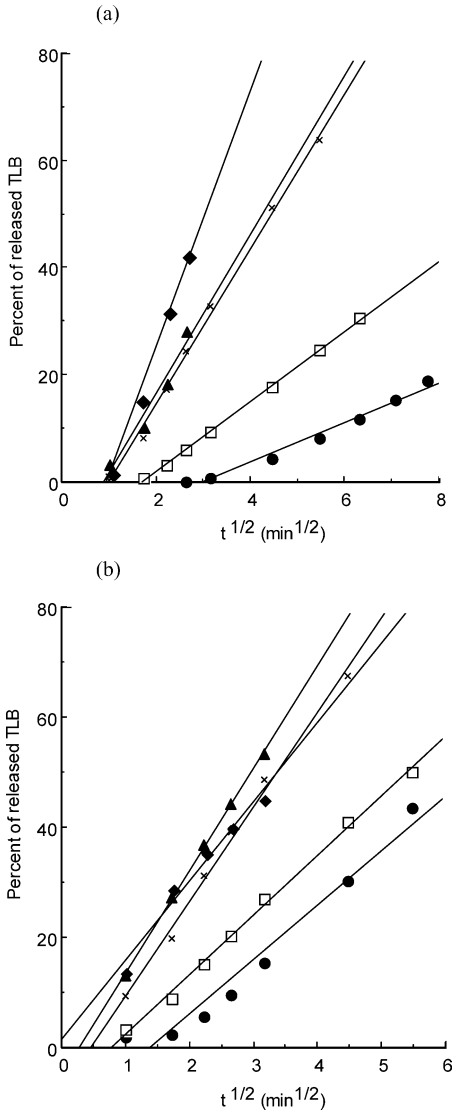

Fig. 6. Higuchi Plots of the Tolbutamide-HPMC Systems

(a) pH 1.2; (b) pH 6.8. ●, Tolbutamide; □, TLB : HPMC=1 : 5 PM; ×, TLB : HPMC=1 : 5 4.F.N Sus; ◆, TLB : HPMC=1 : 5 4.F.N Sol; ▲, TLB : HPMC=1 : 5 3.F.N Sol.

Table 2.

Tolubutamide merely exhibited a release of about 60%, even when left in the acid solution for 5 h. On the other hand, the 4.F.N samples showed an almost 100% release in 1 h. These samples showed a considerably faster rate release.

Table 2 shows that the apparent release rate constant of the 4.F.N samples in the pH 1.2 medium increased by 4 to 6 times compared to those of the original drug. On the other hand, the release rates of the 4.F.N samples in the pH 6.8 medium increased by about 1.5 to 1.9 times compared to those of the original drug. The T_{70} values of the 4.F.N samples increased by 20 to 30 times compared to those of the original drug in pH 1.2 medium. On the other hand, the T_{70} values of the 4.N.F samples in the pH 6.8 medium were 2 to 3 times smaller than those of the original drug.

Confirmation of the Interaction between Tolbutamide and Hydroxylpropyl-methylcellulose The formation of each solid dispersion was examined by measuring the FT-IR spectra of the pharmaceutical preparation made by spray drying tolbutamide as shown in Fig. 7. Tolbutamide showed bands at 3336.2 cm^{-1} and 3102.9 cm^{-1} due to a stretching vibration in the NH group at 1658.5 cm^{-1} due to an NH bending vibration, and at 1700.9 cm^{-1} due to a stretching vibration in the carbonyl group. HPMC showed broad bands at 3469.3 cm^{-1} due to due a stretching vibration in the hydroxyl group. These bands were similarly observed for the physical mixture of tolbutamide and HPMC, suggesting no interaction between tolbutamide and HPMC in the physical mixture. The bands due to NH group (at 3102.9, 3336.2 cm^{-1}) stretching vibration of tolbutamide in the 4.F.N sol and 3.F.N sol samples did not appear, while the band due to the OH group of HPMC at 3469.3 cm^{-1} was shifted to a lower wavenumber. These observations suggest that the interaction was caused by the NH group of tolbutamide and the OH group of HPMC. As other possibilities, stretching vibration of the carbonyl group in 1700.9 cm^{-1} of tolbutamide shifted to 1800.0 cm^{-1} for 4.F.N sol and 3.F.N sol samples. A hydrogen bond occurred between this carbonyl group of tolburamide and the hydroxyl group of HPMC as shown in Fig. 7. Although, we cannot determined at present which cases are the main interactions, we think that the former interaction is prominent.

Table 2. Apparent Release Rate Constant K and 70% Release Time T_{70}

Sample	pH 1.2		pH 6.8	
	K (%/min$^{1/2}$)	T_{70} (min)	K (%/min$^{1/2}$)	T_{70} (min)
Tolbutamide	3.69	742.9	9.89	56.1
TLB : HPMC=1 : 5 PM	6.55	128.7	10.82	57.3
TLB : HPMC=1 : 5 4-F.N Sus	14.49	36.3	17.18	22.2
TLB : HPMC=1 : 5 4-F.N Sol	23.05	24.9	14.39	31.1
TLB : HPMC=1 : 5 3-F.N Sol	14.83	23.0	18.67	18.9

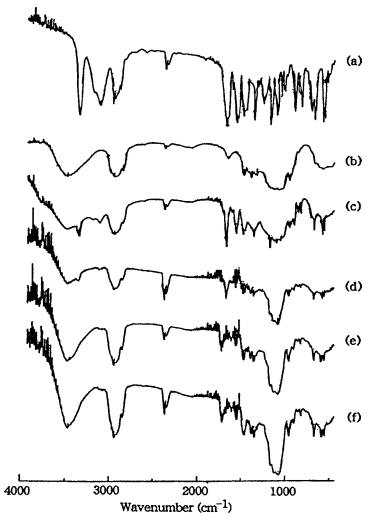

Fig. 7. FT-IR Spectra for the Tolbutamide-HPMC Systems

(a) Tolbutamide; (b) HPMC; (c) TLB : HPMC=1 : 5 PM; (d) TLB : HPMC=1 : 5 4.F.N Sus; (e) TLB : HPMC=1 : 5 4.F.N Sol; (f) TLB : HPMC=1 : 5 3.F.N Sol.

Conclusions

A newly developed 4-fluid-nozzle type atomization drying method successfully prepared solid dispersions with particle sizes aimed at improving the release rate of the drug. When

the carrier was used, it formed a solid dispersion, and the drug amorphized and showed an increased rate of release compared to the original drug.

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