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Preparation and Evaluation of Controlled-Release Solid Dispersion Granules Containing a Poorly Water-Soluble Drug, Hydrated Silicon Dioxide, and Polyvinylpyrrolidone

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Abstract

The study aim was to develop controlled-release, solid dispersion granules containing a poorly water-soluble drug, Hydrated Silicon Dioxide (HSD), and Polyvinylpyrrolidone (PVP), and to elucidate the mechanism underlyingsustained release from the soliddispersion granules. To achieve this purpose, we used the wet granulation method to prepare the first-release granules containing a poorly water-soluble drug and HSD. Then, the effect of PVP on the dissolution of the poorly water-soluble drug was estimated. Initially, the selection of a binder and contentsof drug and binder were investigated to determine the optimum formulation fora rapidly dissolving granule with HSD. First-release granules containing Nifedipine (NIF) as a poorly water-soluble drug, erythritol as a binder, and HSD were developed. Differential scanning calorimetry confirmed reduced NIF crystallinity in the granules. To investigate the first-release granules' applicabilityto other drugs, six poorly water-soluble drugs (griseofulvin, indomethacin, ibuprofen, carbamazepine, progesterone, and phenytoin) were prepared. Rapid dissolutionof all tested drugs from the granule with the same NIF formulation was observed. These findings suggest that HSD is useful for improving dissolution ratesof poorly water-soluble drugs insoliddispersion granules. Next, we investigated PVP's effect on the dissolution of drug from the first-release granules. The effects of PVP on sustained release from the granules containing the seven drugs weredivided into three types: Type 1 was no effect (rapid dissolution), type 2 was a middle effect, and type 3 was a strong effect (sustained release). To elucidate the mechanism underlying sustained release from the solid dispersion granules, the intermolecular interactions between the drugs and HSD or PVP were investigated by Fourier transform infrared spectroscopy. The results suggested that the balance between the interaction of a drug and HSD and the interaction of a drug and PVP is important for sustained release of the drug.

Introduction

Oral drug administration is preferred because of its convenience, good patient compliance, and low production costs. Biopharmaceutical Classification System (BCS) class II compounds exhibit low solubility and high permeability, which results in poor bioavailability after oral administration [1]. Thus, improving these drugs' water solubility is one of pharmaceutical scientists' current strategies. To date, several approaches have been developed to overcome this problem, including amorphous solid dispersions [2], co-crystallization [3], and salt formation [4]. Particularly, an amorphous solid dispersion is a system in which a poorly soluble drug is dispersed throughout a water-soluble carrier. Polyethylene glycols, Hydroxypropyl Methylcellulose (HPMC), Poloxamer, and Polyvinylpyrrolidone (PVP) are widely used solid dispersion carriers because of their strong hydrophilic properties and ability to form molecular adducts with many compounds [5,6].

In addition, inorganic materials, such as silica gel and calcium silicate,improve the solubility of poorly water-soluble drugs [7-11]. Porous Calcium Silicate (PCS) and magnesium aluminosilicate (Neusilin®) have huge surface areas and are used as solid dispersion carriers to improve the dissolution of poorly water-soluble drugs [10-12]. We reported the development of solid dispersion tablets via a simple and easily manufactured wet granulation method using PCS [13,14]. These materials contain silanol groups and metal ions. The interaction between the drug and silanol groups or metal ions likely affects the stability of the amorphous state and drug dissolution rates [15,16]. Moreover, we have reported a hydrogen bond between Nifedipine (NIF) and PCS as well as salt formation between indomethacin and PCS [17]. Silicon dioxide (Carplex®, Sylisia®, and Aerosil®) contains silanol groups but no metal ions. Therefore, the effect of hydrogen bonds on the amorphous state and drug dissolution rate may be investigated. The effect of silicon dioxide on drug dissolution in the powder has been reported [18]. However, there are few reports on the effect of silicon dioxide in the granules and tablets.

Controlled-release, solid dispersion formulations should be prepared for BCS class II drugs with short half-lives [19]. For this purpose, different polymers, both hydrophobic (e.g., ethyl cellulose and Eudragit) and hydrophilic (e.g., hydroxypropyl cellulose, HPMC, and methylcellulose), have been used [20-23]. In the polymer matrix system, a drug is homogeneously distributed throughout a matrix, and drug release is controlled by water-swell able or hydrophobic polymeric excipients. Moreover, silica is used to prepare controlled-release solid dispersion formulations along with a hydrophobic polymer to control drug release [24]. Recently, we reported sustained release from NIF-PCS granules containing a hydrophilic polymer,

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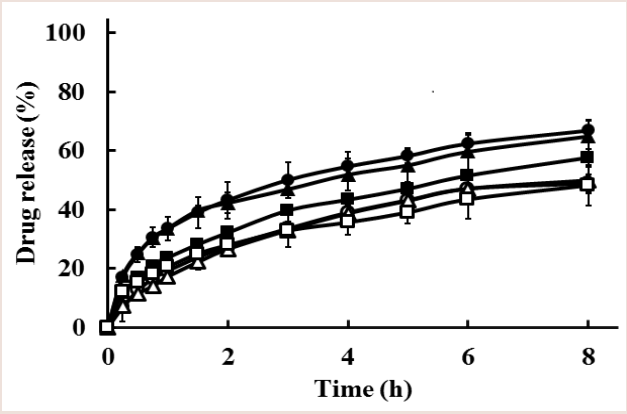

Figure 1: Effects of binder on the nifedipine dissolution profiles from the granules.

Erythritol (●), D-mannitol (▲), xylitol (■), trehalose (⍰), fructose (□), and sorbitol (□). Data are presented as the mean±SD (n=3-4).

PVP, and rapid release from indomethacin-PCS granules containing PVP [17]. We suggested that hydrogen bonds among the drug, PCS, and PVP contribute to this sustained release. However, it is not clear whether PVP affects the release of a poorly water-soluble drug from the solid dispersion formulation containing other silicates, and the underlying mechanism of the sustained release also remains unclear.

The purpose of this study was to develop controlled-release solid dispersion granules, containing poorly water-soluble drugs, Hydrated Silicon Dioxide (HSD), and PVP, and to elucidate the mechanism underlying sustained release from the solid dispersion granules. We prepared first-release granules containing a poorly water-soluble drug and HSD. Then, the effect of PVP on the dissolution of several poorly water-soluble drugs was estimated. Because we hypothesized that one of the mechanisms underlying the sustained release may involve interaction between the drug and polymer, we also measured the interactions between the drugs and HSD or PVP by Fourier transform infrared (FT-IR) spectroscopy.

Materials and Methods

Materials

NIF and indomethacin were purchased from Permachem Asia Ltd. (Tokyo, Japan) and KONGO CHEMICAL Co., Ltd. (Toyama, Japan), respectively. Griseofulvin, ibuprofen, and carbamazepine were obtained from Wako Pure Chemical Industries Co., Ltd. (Osaka, Japan). Phenytoin and progesterone were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan) and Nacalai Tesque Ltd. (Kyoto, Japan), respectively. HSD (Carplex® #80) was obtained from DSL Japan Co., Ltd. (Tokyo, Japan). PVP K-90 was purchased from Nacalai Tesque Ltd. Mannitol, trehalose, fructose, sorbitol, erythritol, and xylitol, which were used as binders, were obtained from Nacalai Tesque Ltd., Asahi Kasei Corp. (Tokyo, Japan), Kato Kagaku Co., Ltd. (Aichi, Japan), Towa Chemical Industry Co., Ltd. (Osaka, Japan), Mitsubishi-Chemical Foods Corp. (Tokyo, Japan), and B Food Science Co., Ltd. (Tokyo, Japan), respectively. All other chemicals were of reagent grade and used without further purification.

Preparation of solid dispersion granules

To prepare the rapidly dissoluble, solid dispersion granules, the drug was dissolved in an appropriate amount of ethanol (50 g) by heating at 60 °C. The solution was added to HSD (40 g) and mixed for 15 min by using a high-speed agitation granulator (High-Speed Mixer, EARTHTECHNICA Co., Ltd., Tokyo, Japan) at 250 rpm with an agitator and 2500 rpm with a chopper. After drying at 70 °C for 12 h, the powdery binder and water (50 g) were added to this dried mixture to prepare the granules by using the granulator at 250 rpm with an agitator and 2500 rpm with a chopper. For the experiment to estimate the effect of PVP on dissolution from the solid dispersion granule, PVP (10 g) was added to the binder suspension. The granulation end point was visually determined. The granules were dried at 70 °C for 12 h and then pulverized in a speed mill (Okada Seiko Co., Ltd., Tokyo, Japan). Granules ranging in size from 500 to 850 μm were used in this study.

Preparation of the adsorption solid dispersion (ASD) and physical mixture (PM)

To prepare an ASD of drug and HSD, an appropriate amount of drug was dissolved in ethanol (10 g) by heating at 60 °C. Then, this solution was added to HSD (8 g) and mixed for 15 min by using a rotation mixer. The mixture was dried at 70 °C for 12 h. The PM was prepared by mixing an appropriate amount of drug and HSD (8 g).

Drug-release experiments

Dissolution tests were performed, according to the JP17 paddle method, using Riken's Dissolution Tester (Miyamoto Riken Ind Co., Ltd., Osaka, Japan). Granules containing 10 mg of drug were added to the dissolution medium (900 mL of purified water) at 37 °C±0.5 °C, and the paddle was rotated at 50 or 75 rpm. The amounts of dissolved NIF, indomethacin, carbamazepine, progesterone, griseofulvin, and phenytoin were analyzed by using an Ultraviolet (UV) spectrophotometer (UV-1200; Shimadzu Corp., Kyoto, Japan) at 350, 320, 285, 241, 292, and 258 nm, respectively. The amount of dissolved ibuprofen and granules' contents were analyzed by high-performance liquid chromatography using a Shimadzu LC-10ADvp pump (Shimadzu Corp.), a Shimadzu SPD-20A detector (Shimadzu

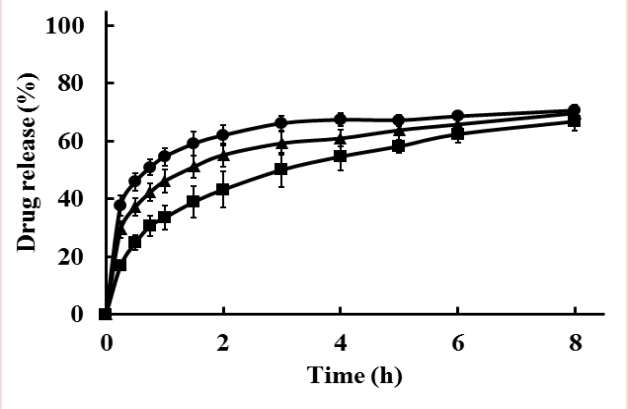

Figure 2: Effects of Nifedipine (NIF) content in granules on the NIF dissolution profiles from granules.

Formula 1 (■), formula 2 (▲), formula 3 (●). Data are presented as the mean±SD (n=4).

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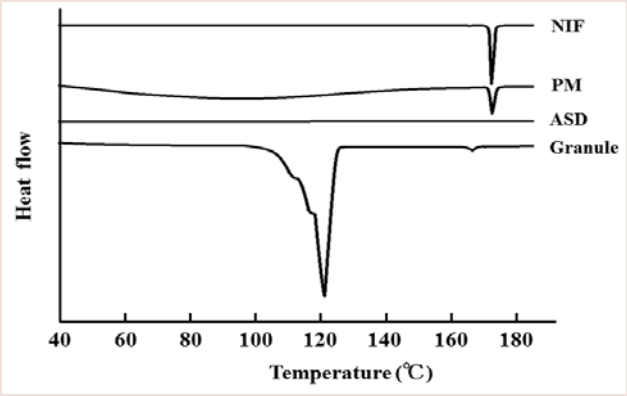

Figure 3: Differential scanning calorimetry (DSC) plots of Nifedipine (NIF), Physical Mixture (PM) (NIF: Hydrated Silicon Dioxide (HSD) = 5:80), Absorptionsolid dispersion (ASD) (NIF: HSD = 5:80), and granules (formula 1).

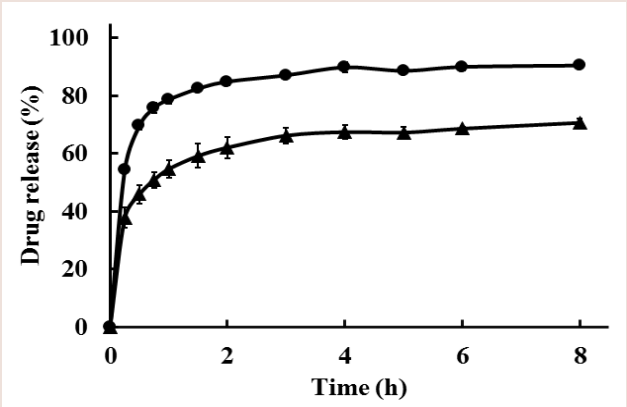

Figure 4: Effects of the paddle speed on the Nifedipine (NIF) dissolution profiles from granules (formula 3).
75rpm (●), 50rpm (▲). Data are presented as the mean±SD (n=3-4).

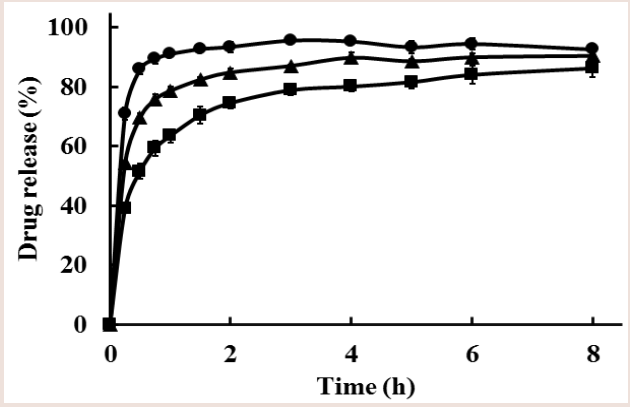

Figure 5: Effect of erythritol amount on the Nifedipine (NIF) dissolution profiles from granules.
Formula 3 (▲), formula 4 (■), formula 5 (●), raw NIF (□). Data are presented as the mean±SD (n=3-4).

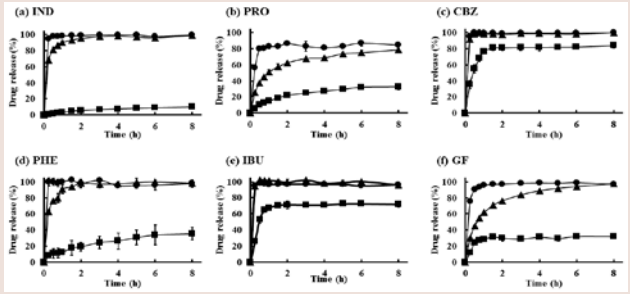

Figure 6: Effect of Polyvinylpyrrolidone (PVP) on the drug dissolution profiles from granules.
Formula 5 (●), formula 6 (▲), and raw drug (■). (a) Indomethacin (IND); (b) Progesterone (PRO); (c) Carbamazepine (CBZ); (d) Phenytoin (PHE); (e) Ibuprofen (IBU); and (f) Griseofulvin (GF).
Data are presented as the mean±SD (n=3-4).

Corp.) set at 230 nm, and an L-column ODS (4.6 mm x 150 mm, 5 µm; Chemicals Evaluation and Research Institute, Japan). The mobile phase consisted of acetonitrile-10 mM KH_2PO_4 in a 55:45 (v/v) ratio, and the flow rate was 1.0 mL/min. All analyses were performed at 40 °C. Three granule samples were tested in each batch, and the mean values were calculated. The drug content in the granules was estimated using a UV spectrophotometer. An adequate amount of granules equivalent to 10 mg drug was accurately weighed, dissolved, and suitably diluted in methanol and measured by using a UV spectrophotometer.

Differential scanning calorimetry (DSC)

DSC analyses were performed using an automatic thermal analyzer (DSC-60 Plus; Shimadzu Corp.) and an indium standard for temperature calibrations. Holed aluminum pans were employed in the experiments for all samples, and an empty pan, prepared in the same way, was used as a reference. Samples (1-10 mg) were sealed in the aluminum pans, and heating curves were recorded by using a constant heating rate of 5°C/min from 30 °C to 350 °C.

Fourier transforms infrared spectroscopy (FT-IR)

IR spectra of powder samples were obtained using a spectrophotometer (IRAffinity-1; Shimadzu Corp.) and the potassium bromide (KBr) pellet method. KBr disks were prepared by mixing several milligrams of the sample with KBr and compacting. The scan range was 400-4000 cm^{-1}.

Results and Discussion

Preparation and optimization of rapidly dissolving solid dispersion granules containing NIF and HSD

To obtain the optimum formulation of rapidly dissolving granules with HSD, the selection of the binder and contents of the drug and binder were investigated.NIF was used as the model of a poorly water-soluble drug. Four sugar alcohols (erythritol, D-mannitol, xylitol, and sorbitol) and two sugars (trehalose and fructose) were selected for preparing granules on the basis of formula 1 using the wet granulation method Table 1. The dissolution rates of granules prepared with D-mannitol and erythritol were higher than those of granules prepared with other sugar alcohols. Granules prepared with sorbitol had the lowest dissolution rate (Figure 1). Sugimoto et al. have suggested that the dissolution rate of oral tablets was in the order of erythritol>mannitol> xylitol> glucose>sorbitol [25]. These results

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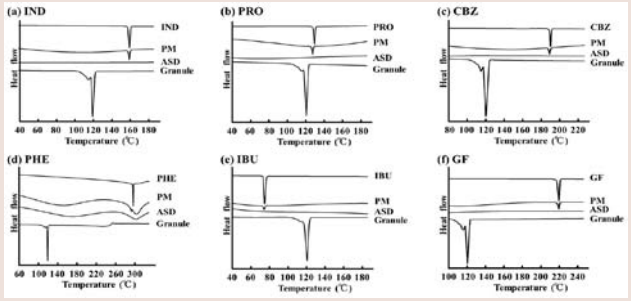

Figure 7: Differential scanning calorimetry (DSC) plots of drug, physical mixture (PM) (drug and HSD; 5:80), Adsorptionsolid dispersion (ASD) (drug and HSD; 5:80), and granules (formula 5).
(a) Indomethacin (IND); (b) Progesterone (PRO); (c) Carbamazepine (CBZ); (d) Phenytoin (PHE); (e) Ibuprofen (IBU); and (f) Griseofulvin (GF).

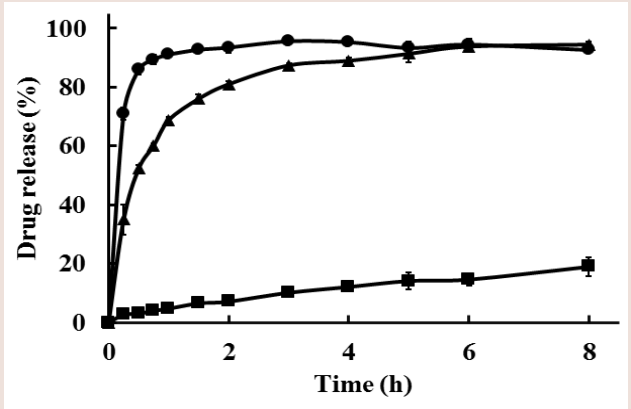

Figure 8: Effect of Polyvinylpyrrolidone (PVP) on the Nifedipine (NIF) dissolution profiles from granules.
Formula 5 (●), formula 6(▲), raw drug (■).Date are presented as the mean±SD (n=3-4).

Table 1: Compositions of hydrate silicon dioxide (HSD) formulations.

	Formula					
	1	**2**	**3**	**4**	**5**	**6**
NIF (g)	2.5	1.25	0.625	0.625	0.625	0.625
PVP K-90 (g)	0	0	0	0	0	10
HSD (g)	40	40	40	40	40	40
Binder (g)	100	100	100	70	150	150
Ethanol (g)	50	50	50	50	50	50
Water (g)	50	50	50	50	50	50

NIF: Nifedipine; PVP: Polyvinylpyrrolidone; HSD: Hydrate Silicon Dioxide

indicate that erythritol is the best substance for penetration of water into granules or tablets.

Furthermore, the effect of NIF content in granules on the NIF dissolution rate was investigated (formulas 1-3). The granules' dissolution rates improved with decreasing NIF content (Figure 2). Since the NIF content used in the dissolution test was constant (10 mg), a decrease in the granules' NIF content was proportional to a required increase in granules used in the dissolution test. There are two possible reasons for this effect: 1) increased NIF dissolution rates from the granules and 2) a portion of the NIF in the granules existed in a crystalline state rather than anamorphous state. To confirm

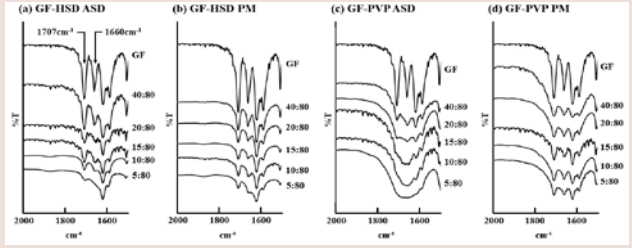

Figure 9: FT-IR spectrum of griseofulvin (GF).
(a) Adsorptionsolid Dispersion (ASD) of GF and Hydrated Silicon Dioxide (HSD), (b) Physical Mixture (PM) of GF and HSD, (c) ASD of GF and Polyvinylpyrrolidone (PVP), and (d) PM of GF and PVP. Each ratio represents the ratio of drug: HSD or drug: PVP.

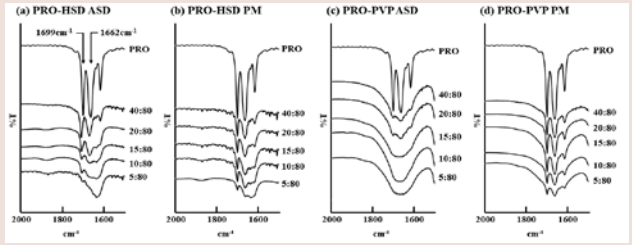

Figure 10: Fourier transforms infraredspectrum of progesterone (PRO).
(a) Adsorptionsolid Dispersion (ASD) of PRO and Hydrated Silicon Dioxide (HSD), (b) Physical Mixture (PM) of PRO and HSD, (c) ASD of PRO and Polyvinylpyrrolidone (PVP), and (d) PM of PRO and PVP. Each ratio represents the ratio of drug: HSD or drug: PVP.

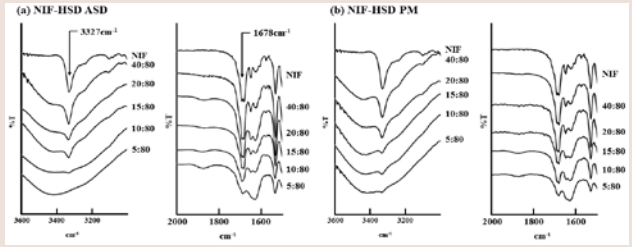

Figure 11: Fourier transform infrared spectrum of nifedipine (NIF).
(a) Adsorptionsolid Dispersion (ASD) of NIF and Hydrated Silicon Dioxide (HSD), (b) Physical Mixture (PM) of NIF and HSD, (c) ASD of NIF and Polyvinylpyrrolidone (PVP), and (d) PM of NIF and PVP. Each ratio represents the ratio of drug: HSD or drug: PVP.

this, DSC was performed. Figure 3 shows the DSC thermograms of the ASD, PM, and granules (formula 1). NIF exhibited a melting endotherm at 172 °C. A DSC peak was not observed in the ASD and granules because of the NIF crystals but it was observed in the PM. These results suggested that the main reason for improved granules' dissolution rates as the NIF content decreased was the increased NIF dissolution rate from the granules.

When more granules were used in the dissolution test, many of them were not stirred well and precipitated. Therefore, the paddle speed's effect on NIF dissolution was investigated (formula 3). The NIF dissolution rate increased with an increase in paddle speed from 50 to 75 rpm (Figure 4). On the basis of these results, the paddle speed was set to 75 rpm in the following dissolution study.

To further optimize the NIF granules' solid dispersion

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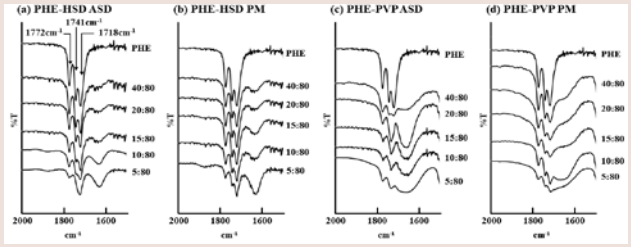

Figure 12: Fourier transform infrared spectrum of indomethacin (IND). (a) Adsorptionsolid Dispersion (ASD) of IND and Hydrated Silicon Dioxide (HSD), (b) Physical Mixture (PM) of IND and HSD, (c) ASD of IND and Polyvinylpyrrolidone (PVP), and (d) PM of IND and PVP. Each ratio represents the ratio of drug: HSD or drug: PVP.

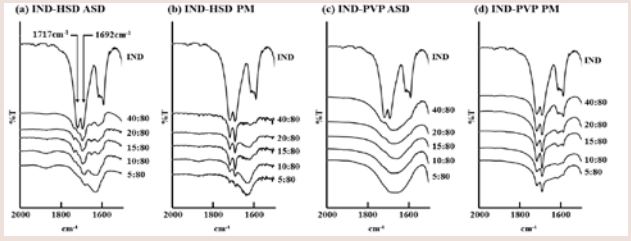

Figure 13: Fourier transform infrared spectrum of phenytoin (PHE). (a) Adsorptionsolid Dispersion (ASD) of PHE and Hydrated Silicon Dioxide (HSD), (b) Physical Mixture (PM) of PHE and HSD, (c) ASD of PHE and Polyvinylpyrrolidone (PVP), and (d) PM of PHE and PVP. Each ratio represents the ratio of drug: HSD or drug: PVP.

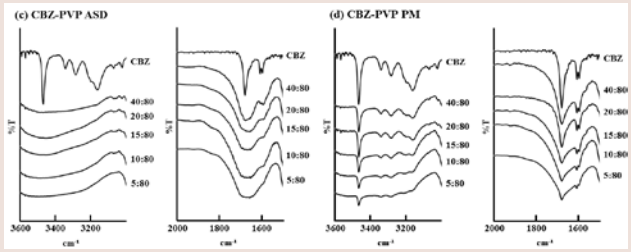

Figure 14: Fourier transform infrared spectrum of carbamazepine (CBZ). (a) Adsorptionsolid Dispersion (ASD) of CBZ and Hydrated Silicon Dioxide (HSD), (b) Physical Mixture (PM) of CBZ and HSD, (c) ASD of CBZ and Polyvinylpyrrolidone (PVP), and (d) PM of CBZ and PVP. Each ratio represents the ratio of drug: HSD or drug: PVP.

formulation, the effect of binder content (erythritol) on the NIF dissolution rate from the granules was investigated (formulas 3-5). The dissolution rate increased with increasing erythritol content (Figure 5). The increased dissolution rate was because of the granules' faster disintegration time as the amount of erythritol was increased. On the basis of these results, formula 5 was selected as the best formulation in this study.

Development of HSD granule to other drugs

To investigate the possibility of applying the preparation method of the rapidly dissolving granules to other drugs (formula 5), six poorly water-soluble drugs [Griseofulvin (GF), Indomethacin (IND), Ibuprofen (IBU), Carbamazepine (CBZ), Progesterone (PRO), and Phenytoin (PHE)] were selected. Figure 6showsthese drugs' dissolution rates from the granules as well as the raw drugs. All drugs used in this study showed rapid dissolution. However, the

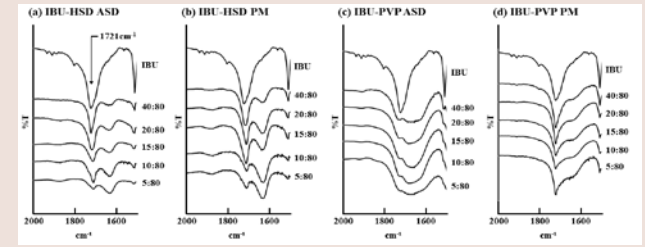

Figure 15: Fourier transform infrared spectrum of ibuprofen (IBU). (a) Adsorptionsolid Dispersion (ASD) of IBU and Hydrated Silicon Dioxide (HSD), (b) Physical Mixture (PM) of IBU and HSD, (c) ASD of IBU and Polyvinylpyrrolidone (PVP), and (d) PM of IBU and PVP. Each ratio represents the ratio of drug: HSD or drug: PVP.

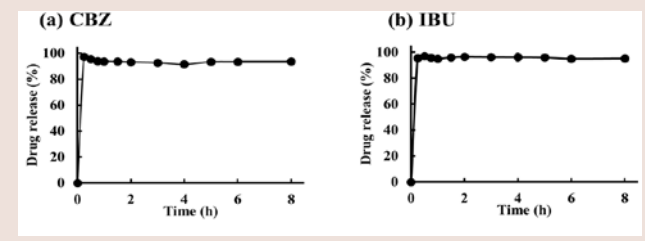

Figure 16: Dissolution profiles of Carbamazepine (CBZ) and Ibuprofen (IBU) from the Adsorption Solid Dispersion (ASD). ASD was prepared with drug and Polyvinylpyrrolidone (PVP) =5:80. Data are presented as the mean±SD (n=3).

dissolutions of NIF, GF, PRO, and IND within shorter times (from 15 min to 60 min) appeared to be different from those of other drugs. This difference may be because of the interaction between the drug and HSD.

DSC thermograms were examined to investigate the drugs' crystallinity in HSD formulations (Figure 7). Samples of ASD or PM at a 5:80 drug to HSD ratio and granules (formula 5) were used in this study. The drugs' endothermic peaks were observed for the raw drugs and the PM samples. However, endothermic peaks were not observed in the ASD samples. From these results, all six drugs may exist in the amorphous state in the ASD samples. Because the amount of drug in formula 5 was lower than that in the ASD sample, shown in (Figure 7), we considered that all six drugs in the HSD granules existed in the amorphous state.

Effect of PVP on the dissolution of drugs from HSD granules

Recently, we studied the effect of a hydrophilic polymer, PVP, on the dissolution of a poorly water-soluble drug (NIF) from PCS granules (rapidly dissolving granules) and reported the sustained release from PCS granules [17]. In the present study, we prepared rapid dissolution granules containing a poorly water-soluble drug, binder, and HSD. Granules containing PVP were prepared (formula 6) to investigate PVP's effect on the dissolution from the rapid dissolution granules. Figure 8 shows PVP's effect on the dissolution of NIF from the granules. Sustained NIF release was observed with addition of PVP. PVP's effects on the dissolution of the other six drugs from the granules were also investigated (Figure 6). In CBZ and IBU, no effect of PVP on dissolution was observed. On the other hand, in PRO and GF, sustained release of the drugs was observed from the granules containing PVP. In NIF, IND, and PHE, sustained release of

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Table 2: Ratios observed FT-IR spectra peaks for each drug in ADS sample.

	GF	PRO	NIF	PHE	IND	CBZ	IBU
Drug:HSD	40:80	20:80	15:80	10:80	15:80	10:80	Under 5:80
Drug:PVP	20:80	20:80	40:80	40:80	40:80	Over 40:80	Over 40:80

drugs was observed at early dissolution times. From the effect of PVP to sustained release, we divided these drugs into three types: Type 1 (IBU and CBZ) was no effect, type 2 (NIF, IND, and PHE) was a moderate effect and type 3 (PRO and GF) was a strong effect.

Interaction of drug with PVP or HSD

We previously suggested that sustained NIF release was due to hydrogen bonding among NIF, PVP, and PCS [17]. Therefore, the interactions among a drug, PVP, and HSD may affect the drug release from the granule. To further investigate PVP's effect on dissolution, the intermolecular interactions between a drug and HSD or PVP were measured by FT-IR. To measure the interaction of drug and polymer in more detail, we prepared ASD and PM at drug: HSD or drug: PVP ratios ranging from 5:80 to 40:80.

The FT-IR spectra of GF are shown in (Figure 9). The spectrum of raw GF shows characteristic peaks at 1660 cm^{-1} and 1707 cm^{-1} (C=O stretching) [26]. These peaks were observed in all PM samples (Figure 9b and d), whereas the 1660 cm^{-1} peak in the ASD samples was not observed at GF: HSD ratios of 20:80 and GF: PVP of 15:80 but was observed at GF: HSD ratios of 40:80 and GF: PVP of 20:80 (Figure 9a and c).

The PRO's FT-IR spectra are shown in Figure 10. The raw PRO spectrum shows characteristic peaks at 1662 cm^{-1} and 1699 cm^{-1} (C=O stretching) [26], which were observed in all PM samples (Figure 10b and d). Additionally, the ASD samples of HSD showed a peak of 1662cm^{-1} at PRO: HSD ratios above 20:80 (Figure 10a). In the ASD samples with PVP (Figure 10c), the characteristic two peaks were observed at PRO: PVP ratios above 20:80.

The FT-IR spectra of NIF are shown in (Figure11). The spectrum of raw NIF shows the characteristic peaks at 1678 (C=O stretching) and 3327 cm^{-1} (secondary -NH) [27]. These peaks were observed in the PM samples of all ratios of NIF: HSD and PVP (Figure 11b and d). In the ASD samples, the peaks were observed at ratios of NIF: HSD=15:80 and NIF: PVP=40:80 (Figure 11a and c).

The PHE's FT-IR spectra are shown in (Figure 12). The spectrum of raw PHE shows characteristic peaks at 1718, 1772cm^{-1} (C=O stretching), and 1741 cm^{-1} (bending -NH) [28]. These peaks were observed in all PM samples (Figure 12b and d). In the sample at PHE: HSD=5:80, the peak at 1741 cm^{-1} was not observed but was observed at PHE: HSD=10:80 (Figure 12a). In the ASD samples with PVP (Figure 12c), the characteristic three peaks were observed at ratios above PHE: PVP=40:80.

The IND's FT-IR spectra are shown in Figure 13. The spectrum of raw IND shows characteristic peaks at 1717 cm^{-1} (acid C=O stretching) and 1692 cm^{-1} (benzoyl C=O stretching) [29]. These peaks were observed in all PM samples (Figure 13b and d) and in the sample of ASD at IND: HSD=15:80 (Figure 13a). In the ASD samples with PVP (Figure 13c), the characteristic two peaks were observed at ratios above IND: PVP=40:80.

Figure 14 shows the CBZ's FT-IR spectra. The raw CBZ spectrum shows characteristic peaks at 1595 and 1605 cm^{-1} (bending -NH), 1677cm^{-1} (C=O stretching), and 3466 and 3161 cm^{-1} (secondary -NH) [30]. These peaks were observed in all PM samples (Figure 14b and d). In the sample of ASD at CBZ: HSD=10:80, these peaks were observed (Figure 14a). On the other hand, these peaks were not observed in the sample of ASD with PVP (Figure 14c).

The IBU's FT-IR spectra are shown in Figure 15. The raw IBU spectrum shows the characteristic peak at 1721cm^{-1} (acid C=O stretching) [31]. In HSD, this peak was observed in all samples of both PM and ASD (Figure 15a and b). On the other hand, in PVP, the peak was not observed in any of the ASD samples (Figure 15c).

Table 2 shows the ratios at which the FT-IR spectra peaks for each drug were observed in the ASD sample of drug and HSD or PVP. FT-IR spectroscopy can provide information on molecular states, including the components, their crystal forms, and the formation of intermolecular interactions. Peak shifts and broadening in the spectra reflect the interactions in solid dispersions and co-amorphous systems. In this study, the drug peaks were not observed at ratios smaller than the drug ratios listed in Table 2. These phenomena may be explained by the polymers' dilution effect. However, the peaks of drug were observed in the PM samples at all ratios. The broadening (disappearance) of drug peaks in the ASD samples reflects the interaction in the solid dispersion between the drug and polymer. The drug peaks were observed at higher ratios of drug than the ratios listed in Table 2. This finding suggests that drugs in the ASD samples present more than drugs able to interact with a polymer. Drugs that are unable to interact with a polymer may be in a crystalline form in the system. Therefore, the observation of peaks at a higher drug ratio might be explained by the stronger interaction of the drug with a polymer than that of other drugs or other polymers.

In type 1 (CBZ and IBU), the drug peaks were observed in the samples at all ratios with PVP and at low ratios with HSD. These results suggest that type 1 drugs in the granules strongly interact with PVP and weakly interact with HSD. This indicates the release rate from the granules containing HSD and PVP may be controlled only by PVP. Figure 16 shows the dissolution curves from ASD with PVP and CBZ or IBU. Similar release curves are shown in (Figure 6c,e and Figure 16). The interaction of type 2 with HSD may be stronger than that of type 3, and the interaction of type 2with PVP may be weaker than that of type 3. The interaction of type 2 with PVP may be stronger than that with HSD, and the interaction of type 3 with HSD may be nearly the same strength as that with PVP. From these considerations, the balance between the interaction of drug and HSD and the interaction of drug and PVP appear to be important for the drugs' sustained release.

Conclusion

Solid dispersion formulations of NIF with HSD were prepared by using the wet granulation method and evaluated. The formulations exhibited much higher dissolution rates than the NIF powder. NIF was present in an amorphous state in the granules. The formulation can also be applied to other poorly water-soluble drugs. Solid dispersion granules with HSD may be useful for improving the dissolution rates of poorly water-soluble drugs. Furthermore,

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granules containing one of six poorly water-soluble drugs, HSD, and PVP were prepared to evaluate PVP's effect on the drugs' sustained release. The effects of PVP were divided into three types: Type 1 was no effect, type 2 was a moderate effect, and type 3 was a strong effect. To elucidate the mechanism underlying sustained release from the solid dispersion granules, the intermolecular interaction between a drug and HSD or PVP was investigated by FT-IR. The study results suggest that the balance between the interaction of a drug and HSD and the interaction of a drug and PVP is important for the sustained release of drugs.

References

1. Amidon GL, Lennernas H, Shah VP, Crison JR (1995) A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and in vivo bioavailability. Pharm Res 12: 413-420.
2. Lu J, Cuellar K, Hammer NI, Jo S, Gryczke A, et al. (2016) Solid-state characterization of Felodipine-Soluplus amorphous solid dispersions. Drug Dev Ind Pharm 42: 485-496.
3. Sowa M, Ślepokura K, Matczak-Jon E (2014) Improving solubility of fisetin by cocrystallization. Cryst Eng Comm 46: 10592-10601.
4. Serajuddin AT (2007) Salt formation to improve drug solubility. Adv Drug Deliv Rev 59: 603-616.
5. Baghel S, Cathcart H, O'Reilly NJ (2016) Polymeric amorphous solid dispersions: A review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. J Pharm Sci 105: 2527-2544.
6. Knopp MM, Olesen NE, Holm P, Langguth P, Holm R, et al. (2015) Influence of polymer molecular weight on drug-polymer solubility: A comparison between experimentally determined solubility in PVP and prediction derived from solubility in monomer. J Pharm Sci 104: 2905-2912.
7. Hanada M, Jermain SV, Williams RO 3rd (2018) Enhanced dissolution of a porous carrier-containing ternary amorphous solid dispersion system prepared by a hot melt method. J Pharm Sci 107: 362-371.
8. Xia Y, Yuan M, Deng Y, Ke X, Ci T (2017) Different effects of silica added internal or external on *in vitro* dissolution of indomethacin hot-melt extrudates. Int J Pharm 534: 272-278.
9. Ozeki T, Takashima Y, Nakano T, Yuasa H, Kataoka M, et al. (2011) Preparation of spray-dried microparticles using Gelucire 44/14 and porous calcium silicate or spherical microcrystalline cellulose to enhance transport of water-insoluble pranlukast hemihydrate across Caco-2 monolayers. Adv Powder Technol 22: 623-628.
10. Sharma S, Sher P, Badve S, Pawar AP (2005) Adsorption of meloxicam on porous calcium silicate: Characterization and tablet formulation. AAPS PharmSciTech 6: 618-625.
11. Kinoshita M, Baba K, Nagayasu A, Yamabe K, Shimooka T, et al. (2002) Improvement of solubility and oral bioavailability of a poorly water-soluble drug, TAS 301, by its melt adsorption on a porous calcium silicate. J Pharm Sci 91: 362-370.
12. Censi R, Gigliobianco MR, Dubbini A, Malaj L, Martino PD (2016) New nanometric solid dispersions of glibenclamide in Neusilin(®) UFL2. AAPS PharmSciTech 17: 1204-1212.
13. Fijimoto Y, Hirai N, Takatani-Nakase T, Takahashi K (2016) Preparation and evaluation of solid dispersion tablets by a simple and manufacturable wet granulation method using porous calcium silicate. Chem Pharm Bull (Tokyo) 64: 311-318.
14. Fijimoto Y, Hirai N, Takatani-Nakase T, Takahashi K (2016) Novel tablet formulation of amorphous indomethacin using wet granulation with a high-speed mixer granulator combined with porous calcium silicate. J Drug Deliv Sci Technol 33: 51-57.
15. Madieh S, Simone M, Wilson W, Mehra D, Augsburger L (2007) Investigation of drug-porous adsorbent interactions in drug mixtures with selected porous adsorbents. J Pharm Sci 96: 851-863.
16. Guo X, Wu J, Yiu YM, Hu Y, Zhu YJ, et al. (2013) Drug-nanocarrier interaction-tracking the local structure of calcium silicate upon ibuprofen loading with X-ray Absorption Near Edge Structure (XANES). Phys Chem Chem Phys 15: 15033-15040.
17. Uegaki Y, Hirai N, Takatani-Nakase T, Takahashi K (2018) Development of controlled-release solid dispersion granules containing a poorly water-soluble drug, porous calcium silicate, and the water-soluble polymer polyvinylpyrrolidone. J Pharmaceu Pharmacol 6: 1-7.
18. Planinšek O, Kovačič B, Vrečer F (2011) Carvedilol dissolution improvement by preparation of solid dispersions with porous silica. Int J Pharm 406: 41-48.
19. Tran PH, Tran TT, Park JB, Lee BJ (2011) Controlled release systems containing solid dispersions: strategies and mechanisms. Pharm Res 28: 2353-2378.
20. Dereymaker A, Scurr DJ, Steer ED, Roberts CJ, Van den Mooter G (2017) Controlling the release of indomethacin from glass solutions layered with a rate controlling membrane using fluid-bed processing. Part 1: Surface and cross-sectional chemical analysis. Mol Pharm 14: 959-973.
21. Hasan EI, Amro BI, Arafat T, Badwan AA (2003) Assessment of a controlled release hydrophilic matrix formulation for metoclopramide HCl. Eur J Pharm Biopharm 55: 339-344.
22. Abdel-Rahman SI, Mahrous GM, El-Badry M (2009) Preparation and comparative evaluation of sustained release metoclopramide hydrochloride matrix tablets. Saudi Pharm J 17: 283-288.
23. Kumar S, pandey M, Saraf SA (2009) Novel sustained release gastro retentive floating matrix tablets of acyclovir: formulation and in vitro evaluation. J Pharm Res 2: 717-722.
24. Tran HT, Park JB, Hong KH, Choi HG, Han HK, et al. (2011) Preparation and characterization of pH-independent sustained release tablet containing solid dispersion granules of a poorly water-soluble drug. Int J Pharm 415: 83-88.
25. Sugimoto M, Narisawa S, Matsubara K, Yoshino H, Nakano M (2006) Effect of formulated ingredients on rapidly disintegrating oral tablets prepared by the crystalline transition method. Chem Pharm Bull (Tokyo) 54: 175-180.
26. Al-Obaidi H, Ke P, Brocchini S, Buckton G (2011) Characterization and stability of ternary solid dispersions with PVP and PHPMA. Int J Pharm 419: 20-27.
27. Cilurzo F, Selmin F, Minghetti P, Gennari CG, Demartin F, et al. (2008) Characterization and physical stability of fast-dissolving microparticles containing nifedipine. Eur J Pharm Biopharm 68: 579-588.
28. Moribe K, Ogino A, Kumamoto T, Ishikawa T, Limwikrant W, et al. (2012) Mechanism of nanoparticle formation from ternary coground phenytoin and its derivatives. J Pharm Sci 101: 3413-324.
29. Taylor LS, Zografi G (1997) Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res 14: 1691-1698.
30. Sethia S, Squillante E (2004) Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. Int J Pharm 272: 1-10.
31. Lu XU, San Ming LI, Sunada H (2007) Preparation and evaluation of ibuprofen solid dispersion systems with kollidon particles using a pulse combustion dryer system. Chem Pharm Bull (Tokyo) 55: 1545-1550.