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Release Behavior of Cilostazol According to the Fabrication Methods and Ratio of HPMC/PVP

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Abstract: In this study, we manufactured a polymer blend, using hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP), by spray drying method to improve the characteristics of polymers. This polymer blend was used to improve the drug delivery of cilostazol, a phosphodiesterase inhibitor that decreases serum triglycerides, is a direct arterial vasodilator, and inhibits platelet aggregation and smooth muscle cell proliferation. Compatibility with this drug was achieved when the polymer blend of HPMC and PVP were spray dried. Various ratios of the two ingredients were blended to determine optimum release rate of this poorly soluble drug. Cilostazol blended with different ratios of HPMC and PVP was analyzed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM) to confirm surface morphology and combination of drug and polymer. Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) were conducted to confirm thermodynamic properties and chemical structure change, respectively. Change in the drug release of cilostazol was expected by adjusting the HPMC and PVP blend ratio in gastric juice (pH 1.2).

Keywords: cilostazol, hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), solid dispersion, blend.

Introduction

The polymer blend (polymer mixture) is a technique that involves the mixture of two or more polymers to create a new material with different physical characteristics from the original polymers.[1] Polymer blends could be broadly divided into two categories: immiscible polymer blends and miscible polymer blends. Immiscible polymer blends (heterogeneous polymer blend) are a physical mixture of two or more polymers. During the blending process, the glass transition temperature (T_g) of each polymer component is observed. Miscible polymer blends (homogeneous polymer blend) are a mixture of two or more polymers resulting in a single-phase structure (one glass transition temperature is observed). In this study, two different polymers: hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP) were used to create a new polymer blend.

HPMC is a cellulose series polymer consisting of a cellulose backbone with the R group replaced by H, $-CH_3$, or $CH_2CH(CH_3)OH$, resulting in higher solubility compared with other cellulose series polymers.[2-5] HPMC has a constant viscosity and is not affected by pH and non-ionic agents. It is generally used as a device for controlled release of drugs since it has the intrinsic property of gradually swelling, forming membranes, and allowing regulated drug release before dissolution.[6,7] PVP, a vinyl series polymer, is used to improve dissolution of poorly soluble drugs or binders.[8-11] Solid dispersions, consisting of dispersed drug and PVP prepared by a solid dispersion manufacturing method are generally used to improve the bioavailability of poorly soluble drugs.[12-16] Another effect of PVP is inhibition of crystallization by various organic interaction.

Cilostazol, a phosphodiesterase inhibitor, is used to alleviate symptom of intermittent claudication in patients with peripheral vascular disease. It is well known as an inhibitor of platelet aggregation and blood clotting by vasodilation, and is also associated with improvement of central blood circulation, anti-inflammatory, anti-ulcer, anti-depressant and prevention to ischemia and asthma.[17-20] One drawback of cilostazol is that is a poorly soluble drug (solubility is about 3 μg/mL) and is mainly absorbed in the upper gastrointestinal tract when orally administered. Recently, mixture of this drug with PVP has been used to solve the issue of low bioavailability.

In this study, a miscible polymer blend of HPMC and PVP was manufactured by a spray drying method. Different mixture ratios of HPMC and PVP were used in the manufacturing of the new miscible polymer and tested for control and improvement of insoluble drug release. After polymer

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blending, the morphology of each polymer was confirmed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) were carried out to confirm interaction between HPMC and PVP and thermodynamic properties. The release pattern of each drug model was measured by HPLC (high performance liquid chromatography).

Experimental

Materials. Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone, Hwawon Pharm, KOREA) was used as a drug model to measure release of drug. Polyvinyl alcohol (PVA, Sigma Aldrich, USA) and polyethylene glycol 6000 (PEG 6000, Samchun Chem, KOREA) were used as appropriate polymers for release of cilostazol. Physical mixture (PM), blend mixture (BM) and solid dispersion (SD) were made of PVP K25 (BASF, Ludwigshafen, Germany) and HPMC 2910 E5 (Hwawon Pharm, KOREA), and other organic chemicals were used (Figure 1). In addition, sodium lauryl sulfate (SLS, SHOWA, JAPAN) was used as a surfactant for dissolution medium. The used solvents were high performance liquid chromatography (HPLC) grade. All other chemical ones were of analytical grade without further purification.

Solubility of Cilostazol with Selective Use of Polymers. The solubility of cilostazol in distilled water (DW) and various aqueous polymer solutions, consisting of PVP, HPMC, PEG, PVA were measured by HPLC (Figure 2). Cilostazol was prepared with a final concentration of 0.1 mg/mL by dissolving 1 mg cilostazol in 10 mL of each aqueous polymers solution and stirred for 24 h at 400 rpm.

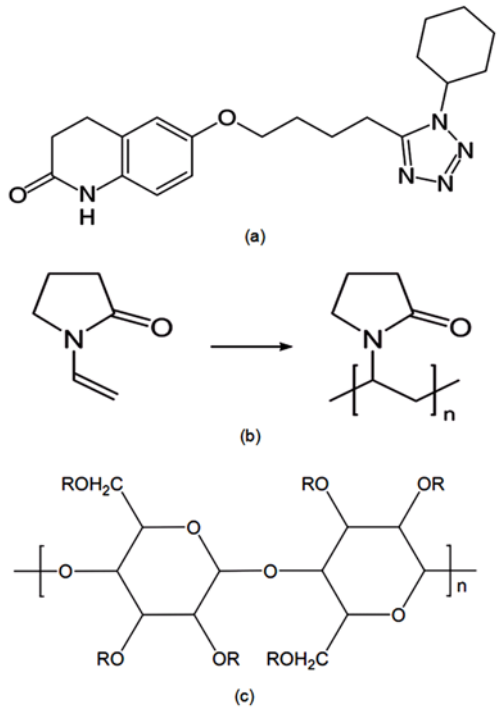

Figure 1. Chemical structure of (a) cilostazol, (b) PVP, and (c) HPMC.

Table I. Conditions for the Preparation of PM, BM, and SD

No.	Cilostazol	HPMC E5	PVP K25
PM 1	10	20	20
PM 2	10	30	10
PM 3	10	10	30
PM 4	10	40	0
PM 5	10	0	40
BM 1	10	20	20
BM 2	10	30	10
BM 3	10	10	30
BM 4	10	40	0
BM 5	10	0	40
SD 1	10	20	20
SD 2	10	30	10
SD 3	10	10	30
SD 4	10	40	0
SD 5	10	0	40

Preparation of Drug Capsules. Drug capsules were prepared with three different methods. First, PMs were physical mixture of cilostazol, HPMC and PVP without any chemical reaction. For preparation of physical mixtures, drug and polymer were passed the sieve and uniformly mixed. After mixed, the mixed powders were filled in gelatin capsules. Second, BMs were made by spray-drying method, and then were physically mixed with cilostazol. Third, SDs were created by spray-drying method using polymers and cilostazol. Table I shows the polymer ratio of HPMC and PVP for the polymer blend. For the preparation of BM, by solid dispersion, the polymer was dissolved in 2:1 solvent mixture of methylene chloride (MC) and methanol. Setup of spray drying is as follows: (1) Inlet Temperature is 130 °C. (2) Outlet Temperature is 75±5 °C. (3) Atomizing is 10 kPa. (4) Flow rate is 0.3 m^3/min. (5) Pump speed is 3 mL/min. The each 50 mg of BM, SD and PM, were filled with gelatin capsules. They were stored in the desiccators under constant humidity (20 %).

Morphology. The morphology of the polymer powder was observed by scanning electron microscopy (SEM, LV-SEM, S-3000N, Hitachi Co, Japan) at 20 kV. A polymer powder was coated with platinum at 30 nm by sputtering at 10 kV for 180 s. After evaporating the dispersion solutions, the surface between polymer blend and the drug was observed by transmission electron microscopy (TEM, H-7650, Hitachi Co, Japan) at 100 kV.

DSC Analysis. Thermal analysis of the drug pellet was conducted by DSC (TA instrument DSC 10Q, Dupont, USA). The DSC was calibrated with indium and zinc standards. Each drug pellet was confirmed for miscibility and crystallinity by DSC using 6~7 mg polymer (HPMC, PVP and cilostazol) by filling in aluminum sample pans. Temperature condition of DSC was gradually scanned at a heating rate of 10 ºC/min up to 250 ºC.

FTIR Analysis. The chemical structures of Blend 1, Blend 2, and Blend 3, PM3, BM3, and SD3 were confirmed by FTIR (GX, Perkin Elmer, USA). To confirm miscibility between the two polymers, Blend 1, 2, and 3 were prepared by spray drying method without drug. The Blend 1, 2, and 3 were HPMC and PVP polymer ratio of 1:1, 3:1, and 1:3, respectively. In order to collect each of powder spectra, a small amount of each powder was compressed in KBr tablets. FTIR spectra was obtained in the spectral region of 400~4000 cm^{-1}

HPLC Analysis. The cumulative amount and release pattern of cilostazol was analyzed by high performance liquid chromatography (HPLC, NS-4000, Futecs, KOREA) using Intersil®OSD-3 C18 column (4.6×150 mm, 5 μm, GL Science Inc). Buffered mobile phases for HPLC was 10:7:3 solvent mixture of triple distilled water (3rd DW), acetonitrile and methanol, respectively. Residual gas in the buffer was removed by ultrasonication. For detection of cilostazol, HPLC was performed at 254 nm (wave length), 1.0 mL/min (flow rate), 20 μL (sample amount), 100~500 ng/mL (sample concentration).

Analysis of Release Pattern. Dissolution studies were performed with capsules-according to USP type II (paddle) specification using 900 mL of 0.1 N HCl as dissolution media with stirring at 50 rpm. The solutions were mixed with artificial gastric juices at pH 1.2 according to USP 23 Method II (paddle) specification, and then mixed with 0.3% SLS before use. A dissolution tester (DST-8, Lab House, KOREA) was used for analysis of release pattern, with the tester paddle speed at 50 rpm and 900 mL of medium equilibrated to 37 ºC. Every 1 mL of released sample was collected, passed through a 0.45 μm polytetrafluoroethylene (PTFE) filter and analyzed by HPLC.

Results and Discussion

Cilostazol Solubility in Polymer Solution. Figure 2 shows the results of cilostazol solubility in polymer solutions. The solubility of cilostazol was determined to be 2.3 μg/mL in distilled water and 4 μg/mL in HPMC solution. In comparison, the solubility of cilostazol in PVP/HPMC solution was found to be 4.3 μg/mL, which is nearly twice that of distilled water and slightly higher than that of HPMC solution alone. Based on these observations, PVP and HPMC were further used in this study.

Morphology. Based on SEM images, cilostazol has a rectangular morphology and smooth surface (Figure 3(a)), HPMC displays a fiber-like shape (Figure 3(b)), and PVP exhibits globular morphology with irregular surface (Figure 3(c)). After cilostazol, PVP and HPMC were mixed by PM, the shape of each polymer component mostly remained intact. However, forms of mixed polymers were changed after chemical reaction by spray dried techniques and were shown in the following Figure 3(d), (e), and (g). After BM, the chemical property of cilostazol remained unchanged, while smaller polymers were attached on the cilostazol surface (Figure 3(j)).

Figure 4 showed the TEM image of the polymers. PVP, HPMC appeared contracted and formed large clusters (Figure 4(c)). In Figure 4(a), blended polymer was bound on the

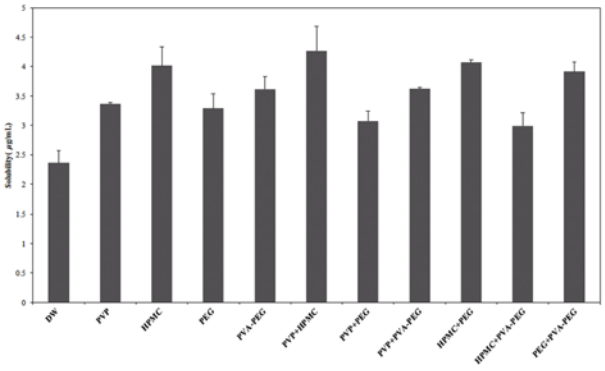

Figure 2. Solubility of cilostazol in the polymer solution.

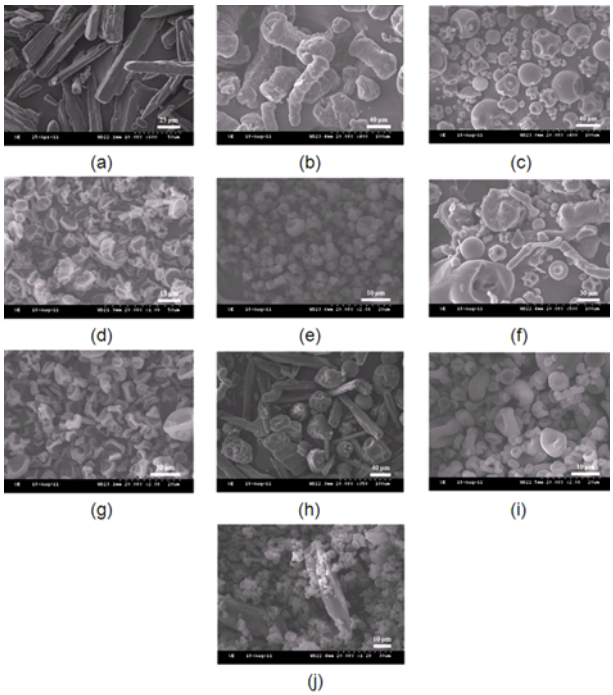

Figure 3. SEM image of (a) cilostazol (Cilo), (b) HPMC, (c) PVP, (d) SD-HPMC, (e) SD-PVP, (f) PM-HPMC/PVP, (g) SD-HPMC/PVP, (h) PM-HPMC/PVP/Cilo, (i) SD-PVP/HPMC/Cilo, and (j) BM-HPMC/PVP/Cilo.

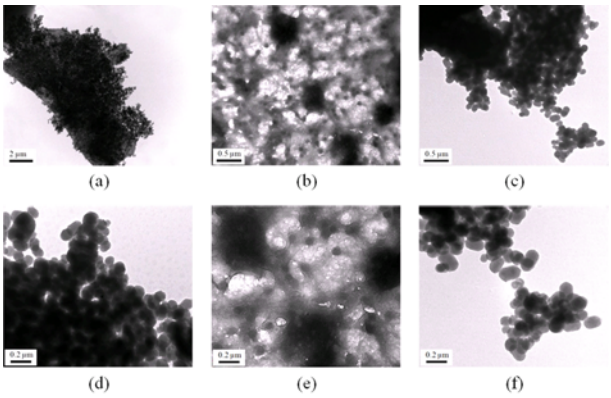

Figure 4. TEM image of (a) BM-HPMC/PVP/Cilo, (b) SD-HPMC/PVP/Cilo, (c) SD-HPMC/PVP, (d) magnified BM-HPMC/PVP/Cilo, (e) Magnified SD-HPMC/PVP/Cilo, and (f) magnified SD-HPMC/PVP.

surface of cilostazol, resulting to an increased surface area and solubility of the blended polymer. Figure 4(c) shows similar morphology with Figure 4(d), indicating that cilostazol did not react physically with the blended polymers. The crystallinity of cilostazol was reduced, resulting in an increased interaction with HPMC and PVP. In addition, the reduced crystallinity of the drug was expected to increase emission.

DSC. Figure 5(a) shows the result of DSC of cilostazol, SD4 (cilostazol:HPMC=1:4), SD5 (cilostazol:PVP=1:4), SD1, BM1 and PM1. T_m (cilostazol) of BM1, PM1, and SD5 were approximately appeared about at 160 °C. The result of DSC of solid dispersion (Figure 5(a)) was very different by ratio PVP and HPMC. Interestingly, the T_m of the cilostazol clearly was disappeared in SD1 and SD4. In contrast, the T_m of cilostazol was observed in SD5, BM1 and PM1. In this result, decreasing the amount of PVP inhibited crystallization of cilostazol.

Experimentally, the minimal criterion for polymer miscibility of two amorphous polymers is detection of a single glass transmission temperature (Figure 5(b)).

One new peak was found among the two peaks of the polymer when the polymer was completely mixed in one phase. For this purpose, a detailed analysis of the T_g of polymers blend was confirmed to identify the blend polymers. HPMC had a T_g of 145 °C, while PVP showed a T_g of 164 °C.[21]

Figure 5(b) showed the result of glass transition temperature of HPMC, PVP, PM1, SD1, SD2, and SD3 without drugs. In the case of PM, the T_g of the polymer appeared as two peaks that corresponds with the original T_g of HPMC and PVP. In contrast, the T_g of SD appeared as a single peak only.[22] This single peak indicates that two polymers blended to make a new miscible polymer. The T_g of the blended polymer was dependent on the ratio of the polymers. The ratio of the blended HPMC/PVP, 10:30, 20:20, and 30:10 (w/w) appeared resulting in the T_g of blended polymers to be 159.8, 155.4, and 151.6 °C, respectively. When the PVP ratio increased, the

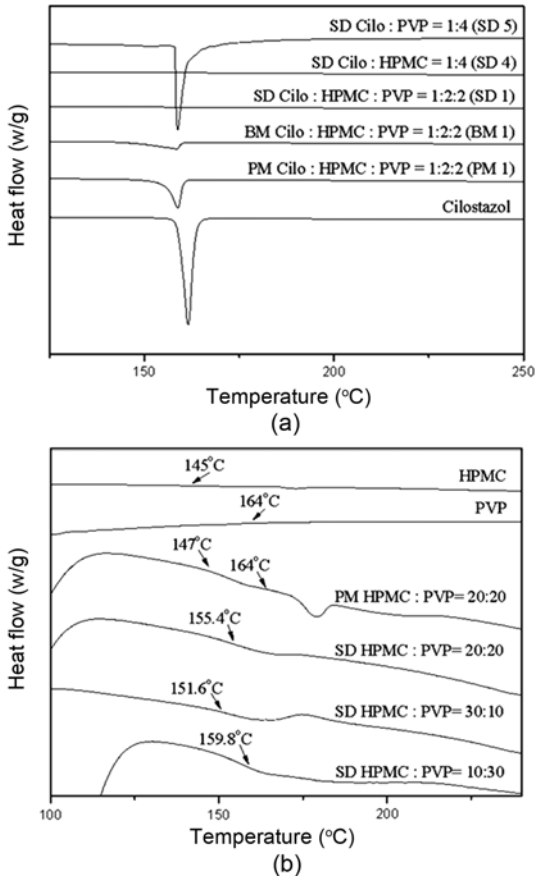

Figure 5. DSC thermograms of (a) the crystallinity and (b) glass transition temperature.

T_g of the blended polymer also increased. This relationship can be predicted using the Fox[23] (1) and Gordon-Taylor[24] (2) equations.

$$\frac{1}{T_{gmix}} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \tag{1}$$

$$T_{gmix} = \frac{(w_1 T_{g1} + K w_2 T_{g2})}{w_1 + K w_2} \tag{2}$$

Where T_{gmix} is the glass transition of blend, w_1 and w_2 are the weight fraction of the initial polymers forming a blend. T_{g1} and T_{g2} are their glass transition temperature. In the Gordon-Taylor equation, the constant K is 0.75. As shown in Figure 6, our results were similar to the values predicted by the Fox equation.

The HPMC inhibited crystallization of cilostazol during the spray drying process. Conversely, PVP was not observed to affect the crystallization of cilostazol.

In addition, the T_g of the blended polymer shifted positions by the ratio of the polymers.[25] So, based on the results of DSC analysis, the blended polymer of HPMC and PVP were found with a miscible polymer conformation.

FTIR. HPMC has two characteristic peaks, one at 3750~

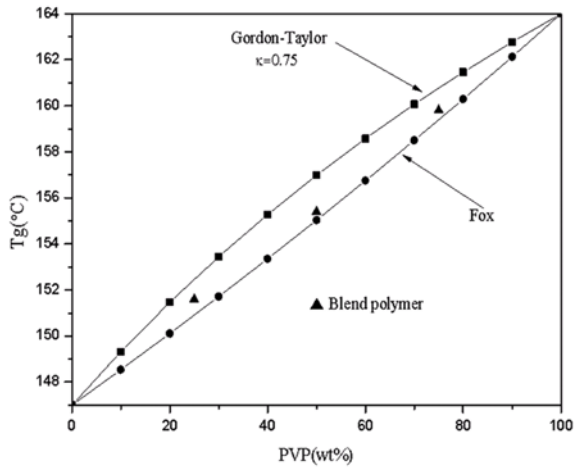

Figure 6. Prediction of T_g-composition dependence by using several equations in comparison with the experimental data as was calculated from DSC thermograms (◆ Gordon-taylor, ● Fox, ▲ experimental data).

3050 cm^{-1} (-O-H), and the other at 1230~960 cm^{-1} (-C-O stretching). Similarly, PVP also has two characteristic peaks, one at 1662~1291 cm^{-1} (-C=O amide group), with the other at 1350~1000 cm^{-1} (-C-N amine group). The amine (C-N) of PVP was confirmed about at 1288 cm^{-1}. Increasing the PVP ratio in the blended polymer, the amine (C-N) of PVP was shifted to the lower site (Figure 7(a)). The C-O stretching interaction of HPMC was confirmed about at 1052 cm^{-1}, and increasing the HPMC ratio in blended polymer was shifted the peak of PVP to the upper site (Figure 7(b)). In Figure 7(c), a strong peak of amide (C=O) group in PVP was shown to be dependent on the PVP ratio. The amine peak

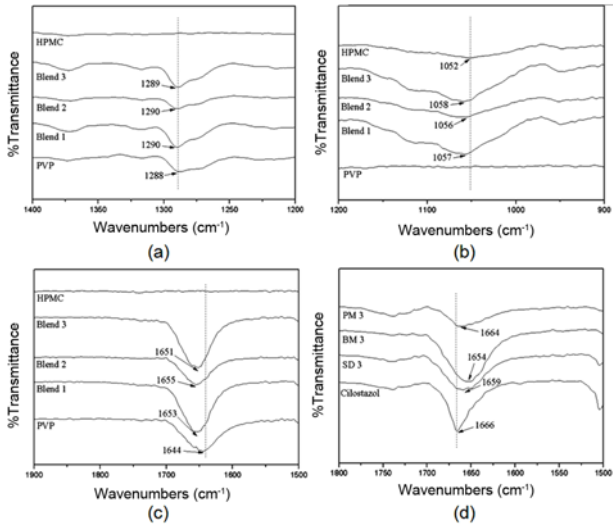

Figure 7. FTIR spectra of (a) -C-N amine group by PVP, (b) -C-O stretching by HPMC, (c) C=O amide group by PVP, and (d) C=O amide group by cilostazol.

of cilostazol was shown at 1666 cm^{-1} (cilostazol), 1664 cm^{-1} (PM3), 1659 cm^{-1} (SD3) and 1654 cm^{-1} (BM3). Despite the same ratio of the polymers, the peaks of cilostazol had depended on the manufacturing methods. The shifted wavelength of amine group to lower site caused a weak hydrogen bond. The strength of weak hydrogen bonds are as follows: BM3>SD3> PM3>cilostazol. It was suggested that the dissolution rate of cilostazol was increased with strength of weak hydrogen bonds.

Dissolution studies. Figure 8 shows the cumulative release of each capsule in the gastric juice (pH 1.2) with 0.3% SLS. PM4 (including only HPMC) has the lowest cumulative release rate (about 45%) compared with the other batch (Figure 8(a)). Conversely, PM5 (including only PVP) has a 75% cumulative release rate. The PVP of PM increased the solubility of cilostazol compared to HPMC. HPMC was observed to form a gel membrane after HPMC comes into contact with water. When physically mixed, PVP acts as a disintegrant while HPMC is expected to delay the release. Cumulative release is dependent on the ratio of PVP to HPMC for the physically mixture.

The cumulative release of drug (Figure 8(c)), which was a solid dispersion (SD5) spray dried with cilostazol and PVP,

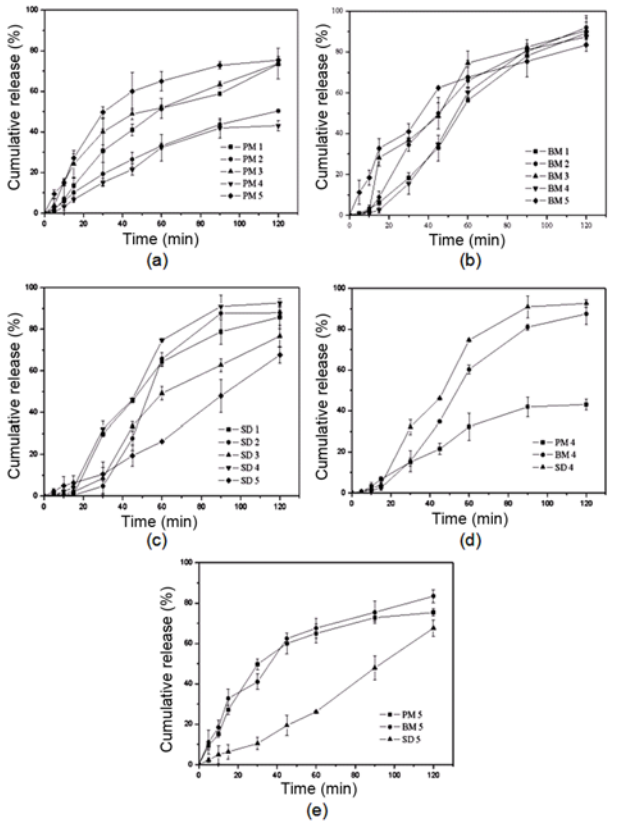

Figure 8. Dissolution behaviors of (a) physical mixture, (b) blend mixture, (c) solid dispersion, (d) prepared batch of only HPMC, and (e) prepared batch of only PVP in simulated gastric juice at pH 1.2 (n=3).

was about 65% at 120 min. When spray dried, the cumulative release rate of PVP (SD) only did not increased. The cumulative releases of drug prepared by blending method were more than 80% (Figure 8(b)). The cumulative releases of drug prepared by blending method were higher than PMs. It seems that size of blended polymer was smaller than polymer in PMs. Figure 8(d) shows a release rate result of PM4, BM4 and SD4 (prepared with HPMC only). According to these results, the cumulative release of drug was ranked by increasing order: SD>BM>PM. Figure 8(e) shows that the release behavior of PM5 and BM5 have similar results, released within 90 min, and SD5 (prepared with PVP only) was released by 120 min consistently.

Conclusions

In this study, after HPMC and PVP were blend mixed by spray drying method (BM), it was physically mixed with cilostazol and were confirmed to raise the dissolution rate. Morphologically, the size of the two polymers after spray drying is reduced. So, SD and BM are expected to increase the wettability, because it increases the surface area in contact with water. Even if the size of PVP is reduced, crystallization of cilostazol was not inhibited. But HPMC and PVP have compatibility at each and crystallization of cilostazol was inhibited in DSC. Characteristic peaks according to the ratio of each polymer were confirmed.

In the result of the FTIR, BM caused an increase in the drug's dissolution rate, relative to the other formulations, due to the hydrogen bond between drugs and polymers in the formulation. Other cases also show some change of the poorly water soluble drug's crystallinity depending on the pharmaceutial process and storage.

SD, in particular, shows a gradual increase of the drug's crystallinity based on the storage. BM has higher stability of the drug than others, because it was mixed with the polymer without any quenching of the drug.

As a result, BM have been developed for the highly efficient dissolution rate among other mixing methods and they should also be effective in the pharmaceutial formation.

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