International Journal of Pharmaceutics 384 (2010) 60–66

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The roles of acidifiers in solid dispersions and physical mixtures

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ARTICLE INFO

Article history:
Received 16 July 2009
Received in revised form
16 September 2009
Accepted 19 September 2009
Available online 25 September 2009

Keywords:
Weakly basic poorly water-soluble drug
Solid dispersion
Physical mixture
Acidifier release
Micro-environmental pH
Drug crystallinity

ABSTRACT

The roles of acidifiers in polyvinylpyrrolidone-based solid dispersions and physical mixtures were originally investigated on dissolution rate of drug, acidifier release, structural crystallinity and micro-environmental pH. A poorly water-soluble and weakly basic isradipine was used as a model drug. The solid dispersion and physical mixtures were prepared with drug and polyvinylpyrrolidone without or with pH modifiers using the solvent evaporation method and then compressed into tablet. The dissolution rate of drug from solid dispersions containing acidifiers were more pronounced when compared to physical mixtures. The dissolution rate of isradipine from solid dispersion was ranked by acidifiers in a decreasing order: fumaric acid, citric acid, glycolic acid and malic acid. In contrast, the acidifiers in physical mixtures had no significant difference in drug dissolution rate. It was attributed by the rank of acidifiers leading to the decrease of micro-environmental pH and slower release rate of acidifier as well as the maintenance of structural amorphousness. The selection of acidifiers with optimal micro-environmental pH, retarded release rate and maintaining structural amorphousness of drug could maximize the dissolution rate of weakly basic drug in solid dispersion.

1. Introduction

Solubilizations of poorly water-soluble drugs have gained much interest in the pharmaceutical industry (Riis et al., 2007; Usui et al., 1998). In general, poorly water-soluble drugs are weakly acidic or basic drug in nature, and show pH-dependent solubility. For this reason, modulating the pH in dosage forms using pH modifiers can modify the release rate of several pH-dependent and ionizable drugs (Doherty and York, 1989; Siepe et al., 2006a,b; Tran et al., 2008). For example, a weakly basic drug is deprotonated and unionized in intestinal fluids, decreasing pH-dependent drug dissolution (Guthmann et al., 2008; Li and Zhao, 2007). The pH modifiers that lower micro-environmental pH (pH_M) of the dosage forms can enhance drug dissolution under basic conditions. Succinic acid/potassium dihydrogen phosphate blends are used as pH modifiers to improve verapamil hydrochloride release from Eudragit RL and RS matrix tablets (Gohel et al., 2003). Previously, Streubel et al. (2000) also used fumaric acid to obtain pH independent release of verapamil hydrochloride from matrix tablets. In addition, Siepe et al. (2006a,b) designed fumaric acid-loaded hydrophilic HPMC matrix tablets to control pH_M.

In general, solid dispersion (SD) is a molecular mixture of drug in various hydrophilic carriers used to enhance drug dissolution by changing drug crystallinity to an amorphous form and reducing particle size for better wettability (Heo et al., 2005; Tran et al., 2009). Dissolution-modulating mechanisms of incorporating alkalizers in non-nanoemulsifying or nanoemulsifying "crystalline" SD were also investigated using pH-dependent model drugs (Tran et al., 2008, 2009). Drug is present in a crystalline form but pH modifiers could readily reduce drug crystallinity and modulate pH_M, resulting in enhanced drug. Despite the wide uses of pH modifiers in dosage forms, the roles of acidifiers in SD or physical mixture (PM) on dissolution rate of drug and acidifier, pH_M and structural crystallinity are not clearly investigated. Release rate of incorporating pH modifiers in SD and PM are regarded as a key factor to maintain pH_M, leading to enhanced dissolution rate of drug.

Here, we incorporated four acidifiers in polyvinylpyrrolidone (PVP)-based SD and PM and then compressed in tablet. The PM was also prepared for comparison. A weakly basic poorly water-soluble isradipine (IDP) was chosen as a model drug. IDP is a calcium antagonist for treating hypertension (Chrysant and Cohen, 1997) and known to be poorly water-soluble in aqueous solution (less than 10 μg/mL) due to the weakly basic amine group (Verger et al., 1998). Then, dissolution rate of drug, release of acidifier, structural crystallinity of drug and pH_M of tablet were investigated. The four acidifiers include fumaric acid, citric acid, glycolic acid and malic acid. At first, IDP solubility in 1.0% acidifier solution was measured. The release rate of acidifiers and the surface and inner pH_M of the tablet were potentiometrically measured as a function of time using a surface pH electrode. We also investigated intermolec-

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doi:10.1016/j.ijpharm.2009.09.039

Table 1
Formulation compositions of binary SD, ternary SD, and ternary PM mixed with binary SD and pH modifier.

No.	Drug	PVP	pH modifier	Comments
1	5 mg	10 mg		Binary SD
2	5 mg	10 mg	10 mg citric acid	Ternary SD
3	5 mg	10 mg	10 mg fumaric acid	Ternary SD
4	5 mg	10 mg	10 mg malic acid	Ternary SD
5	5 mg	10 mg	10 mg glycolic acid	Ternary SD
6	5 mg	10 mg	10 mg citric acid	Ternary PM
7	5 mg	10 mg	10 mg fumaric acid	Ternary PM
8	5 mg	10 mg	10 mg malic acid	Ternary PM
9	5 mg	10 mg	10 mg glycolic acid	Ternary PM

Amount of each component was mixed with lactose (71, or 81 mg), croscarmellose (3 mg) and magnesium stearate (1 mg) to prepare the compressed tablet (100 mg).

ular hydrogen-bonding interactions of IDP with acidifiers within SD using a differential scanning calorimeter (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared (FTIR). Finally, dissolution rate of drug was measured in enzyme-free simulated intestinal fluid (pH 6.8).

2. Materials and methods

2.1. Materials

Isradipine (IDP) was obtained from DaeWoong Pharmaceutical Co., (Seoul, Korea). Kollidon® 30 (PVP) was purchased from BASF (Germany). Fumaric, citric and malic acid were purchased from Sigma–Aldrich (St. Louis, USA), glycolic acid from the Aldrich Chemical Company, Inc. Magnesium stearate was purchased from Katayama Chemical Co. (Osaka, Japan). Croscarmellose sodium (Ac-Di-Sol®) was provided by Seoul Pharm. Co., Ltd. (Seoul, Korea). Lactose was obtained from Meggle (Wasserburg, Germany). The solvents used were high performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade and were used without further purification.

2.2. Methods

2.2.1. Preparation of amorphous SD and its tablet

The amorphous binary SD was prepared by the solvent method. Drug and PVP at a 1:2 weight ratio were dissolved in ethanol under stirring. In our preliminary studies, the ratio of drug to polymer at a 1:2 weight ratio appeared to be optimal with regard to technical feasibility for tabletting process. When a clear solution was obtained, the sample was evaporated and dried in an oven at 50 °C. To obtain ternary SD, 10 mg of the pH modifiers per tablet (citric acid, fumaric acid, malic acid and glycolic acid) was added to binary solution and stirred to form a uniform mixture. To understand clear functioning mechanism of pH modifiers, the plain binary SD was separately mixed with the pH modifiers to obtain physical mixtures (PM).

The dried SD sample was then passed through a 60-mesh sieve to prepare tablets. The resultant mixture was blended with lactose, then with croscarmellose sodium, and finally with magnesium stearate. The homogeneous mixture was directly compressed into 100 mg tablet equivalent to 5 mg IDP by round punches and dies with a 6 mm diameter. The hardness was controlled at 20 ± 2 N. The detail formulations were described in Table 1.

2.2.2. HPLC analysis for determination of drug and acidifier concentration

An HPLC system (Jasco, Tokyo, Japan) was used for the IDP and acidifiers analysis, consisting of the pump (PU-980), the UV–Visible spectrophotometric detector (UV-975), the autosampler (Jasco, AS-950-10), and the in-line degasser (DG-980-50). An analytical column (150 mm × 4.6 mm, Luna 5 μm C18) was used. For drug analysis, the UV detector was set at a wavelength of 325 nm. The mixture of methanol, deionized water, and acetonitrile (7:3:5) was used as a mobile phase. The entire solution was filtered using a 0.45 μM membrane filter (Millipore Corp., Bedford) and degassed before running the HPLC analysis. The system was run at a 1 mL/min flow rate and the running time was 5 min. The injection volume was 20 μl.

For determination of acidifier concentration, HPLC analysis was constructed according to the method presented by Siepe et al. (2006a,b). Briefly, the UV detector was set at 210 nm and mobile phase consisting of 0.1 M $NH_4H_2PO_4$ was adjusted to pH 2.7 with phosphoric acid.

2.2.3. Solubility studies

Deionized water or various enzyme-free solutions (pH 6.8 intestinal fluid, pH 1.2 gastric fluid, pH 12 buffer and 1% solution of pH modifiers in deionized water: fumaric acid, citric acid, malic acid and glycolic acid) was degassed prior to use and added to snap-cap Eppendorf tube (Hamburg, F.R.G). The preparation of intestinal fluid and gastric fluid was described previously (Piao et al., 2008).

An excess of IDP (1 mg) was added to the tube containing 1 mL of media and shaken in a water bath 37 °C (100 rpm) for 48 h. The aliquot was filtered through a 0.45 μm membrane filter (Millipore, USA) and immediately diluted with the mobile phase for determination of IDP content by HPLC analysis. Samples were determined in triplicate.

2.2.4. Dissolution studies

Dissolution was performed in enzyme-free simulated intestinal fluid (pH 6.8) with no solubilizer. The tablet (100 mg) containing PM or SD equivalent to 5 mg IDP was exposed to 900 mL fluid at 37 °C using the USP dissolution method II at a rotation speed of 50 rpm for 1 h (DST-810 dissolution tester – Labfine, Seoul, Korea). Samples were withdrawn at 10, 20, 30 and 60 min and replaced with an equal amount of intestinal fluid. The samples were filtered through a 0.45 μM membrane filter. The concentrations of IDP and acidifiers were finally analyzed by HPLC as described above.

2.2.5. Determination of pH in solution

pH of various solutions used for the solubility study after 48 h and the dissolution media after 1 h dissolution test were measured using pH meter (InoLab pH level 2, WTW, Germany) with the pH electrode SenTix 81.

2.2.6. Micro-environmental pH (pH_M) evaluation

The pH_M of all tablets used in dissolution test was determined according to the method previously described (Tran et al., 2009). Due to fast disintegration of intact tablet, tablets were removed from the dissolution media (pH 6.8) after 5, 10 and 15 min exposure and frozen immediately in a deep freezer for 1 h. Then, the surface pH_M of the tablets were determined potentiometrically using a pH electrode (Metoxy pH Meter HM-17MX, DKK-TOA Corp., Japan). Tablets were then cut at the center to determine pH_M inside the core.

2.2.7. Thermal analysis (DSC)

The thermograms of pure IDP, PVP, binary SD (drug and PVP), and all ternary SDs containing pH modifiers were obtained by scanning from 30 to 200 °C with a scan rate of 5 °C/min using a differential scanning calorimeter (TA Instruments, Model 2910, USA). The samples (0.4–0.5 mg) were weighed in a standard open aluminum pan, with an empty pan used as a reference. Nitrogen was

Table 2
IDP solubility at 37 °C in various solutions for 24 h, 48 h and its solution pH after 48 h.

Solution	Solubility (μg/mL) 24 h	Solubility (μg/mL) 48 h	pH of solution 48 h
Deionized water	6.98 ± 0.01	7.01 ± 0.02	6.38 ± 0.04
Gastric fluid (pH 1.2)	114.01 ± 1.17	114.15 ± 0.49	1.24 ± 0.01
Intestinal fluid (pH 6.8)	8.64 ± 0.05	8.66 ± 0.13	6.84 ± 0.02
Buffer solution (pH 12)	2.99 ± 0.014	3.02 ± 0.05	12.25 ± 0.14
1.0% fumaric acid in deionized water	64.86 ± 1.72	64.74 ± 0.30	2.20 ± 0.02
1.0% citric acid in deionized water	316.22 ± 2.44	316.32 ± 0.47	2.21 ± 0.03
1.0% malic acid in deionized water	19.69 ± 0.31	19.67 ± 0.45	2.29 ± 0.02
1.0% glycolic acid in deionized water	16.69 ± 0.01	16.67 ± 0.11	2.37 ± 0.04

used as a purge gas. Calibration of temperature and heat flow was performed with indium.

2.2.8. Powder X-ray diffraction (PXRD)

A D5005 diffractometer (Bruker, Germany) using Cu-K radiation at a voltage of 40 kV, 50 mA, was used to investigate PXRD patterns of all samples, including pure IDP, PVP, and binary or ternary SD containing pH modifiers. The samples were scanned in increments of 0.02° from 5° to 60° (diffraction angle 2θ) at 1 s/step, using a zero background sample holder.

2.2.9. Fourier transform infrared spectroscopy (FTIR)

A FTIR spectrophotometer (Model Excaliber Series UMA-500, Bio-Rad, USA) was used. The wavelength was scanned from 500 to 4000 cm^{-1} with a resolution of 2 cm^{-1}. KBr pellets were prepared by gently mixing 1 mg of the sample with 200 mg KBr.

3. Results and discussion

3.1. Drug solubility and solution pH

Few of researches have announced about pKa value of IDP except for one article giving pKa 11.4 (Urien et al., 1995). Theoretically, the solubility of IDP was also calculated from the equation given by Varma et al. (2005). IDP solubility at low pH is much higher than its solubility at higher pH, theoretically, implying a weakly basic IDP with pH-dependent solubility.

Our preliminary study showed that weakly basic IDP has pH-dependent solubility. We tested drug solubility in 1.0% acidifier solutions (w/v) to confirm the effect of pH as well as to screen the best pH modifier for enhancing IDP solubility, a factor leading to the capability for enhancing the drug dissolution rate at pH 6.8. Table 2 shows drug solubility at 37 °C in various solutions and solution pH after 48 h solubility test. We tested drug solubility at least for 48 h to reach a steady solubility. In addition, the actual pH of the solutions with the pH modifiers used for the solubility studies was also confirmed after 48 h. The solution pH with pH modifiers could get acidic pH 2.2–2.3 as compared to deionized water while pH values of the other solutions were almost unchanged in comparison with the initial media. For this reason, the pH change of solution by acidifiers to acidic values could enhance IDP solubility. Moreover, the solubility after 24 or 48 h was pretty identical, proving that it has already reached a steady solubility after 24 h.

The solubility of IDP was much higher at pH 1.2 but was lower at pH 6.8 and deionized water solution. Incorporating acidifiers noticeably increased drug solubility compared to intestinal fluid (pH 6.8) and buffer solution (pH 12). Specifically, IDP solubility in citric acid solution was significantly higher, followed in decreasing order by: fumaric acid, malic acid and glycolic acid. In contrast, the IDP solubility in the gastric fluid of pH 1.2 was much higher than those in acidic solutions with acidifiers except for citric acid even though its pH solution was higher than pH 2. In addition to solution pH, some other contributing factors to drug solubility and dissolution such as pH, molecular interaction between pH modifier and drug, and structural recrystallization of drug by acidifiers should be discussed (Tran et al., 2008). Absolutely, the molecular state of drug in this solubility test was different from that in SD system.

3.2. Release of acidifiers and modulation of micro-environmental pH

Release rate of pH modifiers can influence the pH_M leading to the change of drug dissolution. It assumed that soluble acidifiers such as citric acid, glycolic acid and malic acid were released faster as the dissolution fluid penetrated into formulation. Thus, the remaining amount of pH modifier to modulate pH_M may not be sufficient.

In order to find out the possibility of the varied release rate of drug by acidifiers, the release rate of acidifiers in all of those formulations were determined (Fig. 1). Interestingly, dissolution rate of acidifiers was varied the types of acidifiers and preparation methods. There was a large difference in release of acidifier between ternary SD and PM. In general, release rate of acidifier from SD was much slower as compared with PM. The acidifiers in SD are homogeneously dispersed to surround drug particles for efficient modulation of pH_M in dissolution media and intermolecular interaction with drug. In contrast, the PM disperses acidifiers separately for poor interaction.

The initial release of acidifiers within 10 min was rapid except for ternary SD containing malic acid and fumaric acid. After 1 h, the release of fumaric acid from SD and PM was about 30% and 70%, respectively while the other acidifiers reached around 100% release. Fumaric acid dissolved in the slowest manner. Most of acidifier remained within tablets to modulate drug release for an extended period of time (insignificant difference between 30 min and 60 min), subsequently, prolonging acidification of micro-environment for further enhancement of drug dissolution. For efficient pH_M modulation, pH modifiers must stay inside the dosage forms and maintain the pH_M (Kranz et al., 2005; Siepe et al., 2006b).

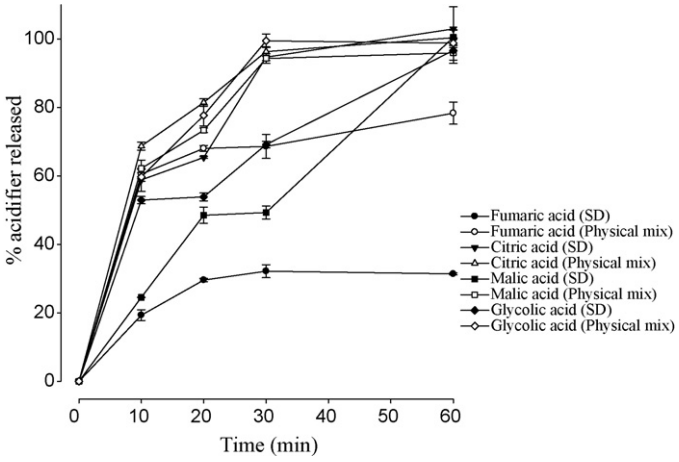

Fig. 1. Release rates of acidifier from compressed tablet containing ternary SD and PM with acidifiers.

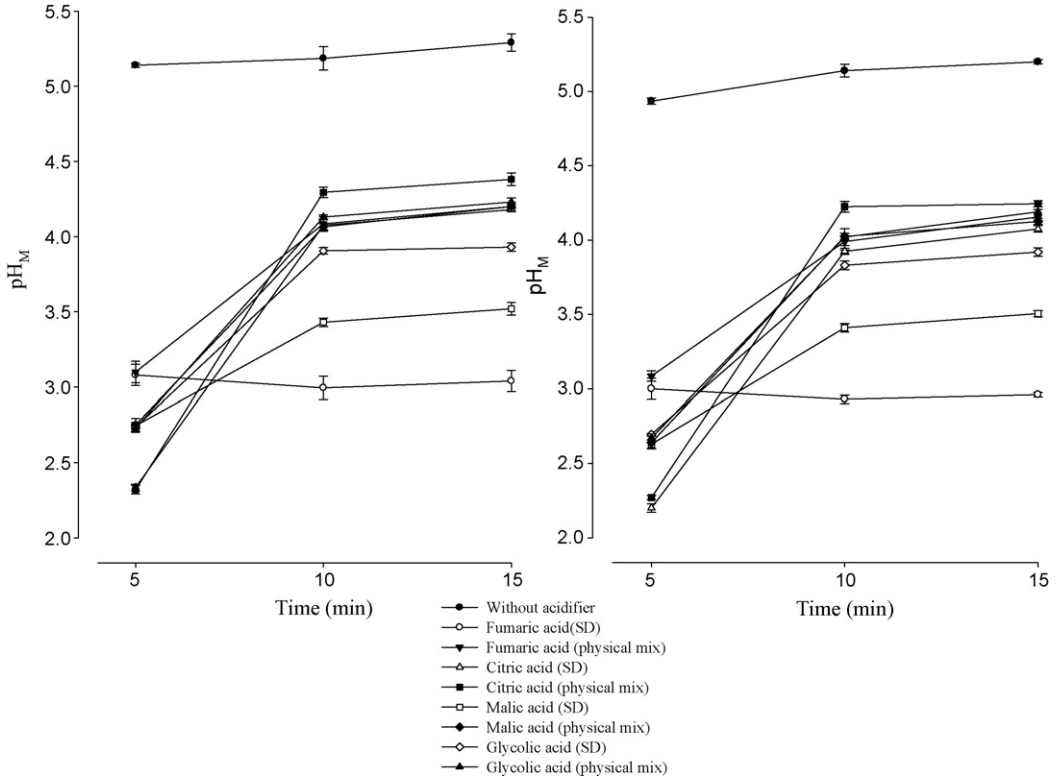

Fig. 2. Surface and inner pH_M of compressed tablet containing binary SD or ternary SD and PM with acidifiers.

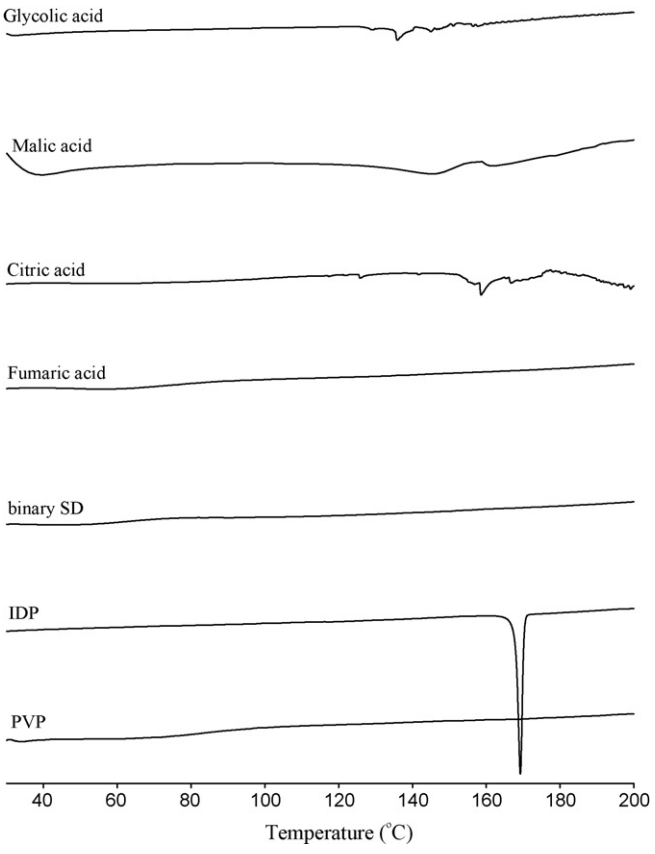

Fig. 3. DSC thermograms of pure drug, PVP, binary SD and ternary SD with acidifiers.

To clearly elucidate the changes of dissolution probably caused by pH modifiers, we also compared pH_M and release of acidifiers from the tablet containing PM and SD with pH modifiers (mainly, fumaric acid and citric acid). As the dissolution fluid penetrates into tablet, acidifier leaches out so that surface and inner pH_M and acidifier release of the tablet can be varied. Concentration gradient of acidifiers in the surface and core tablet was important to decide pH_M and dissolution rate. The acidifier amount on the surface of tablets could be continuously decreased during dissolution test. Thus, we also checked both pH_M in the surface and inner core of tablets. The pH_M measurement is more reasonable than the solution pH since acidifiers can provide an acidic micro-environment surrounding drug particles. Thus, decreasing pH_M could increase the dissolution rate of a weakly basic drug like IDP.

Fig. 2 showed that all acidifiers significantly decreased pH_M meanwhile the pH_M of the reference tablets (without pH modifiers) was approximately 5.0. At 5 min, the pH_M was not varied by the preparation method. PM or ternary SD with acidifier also gave almost constant surface and inner core pH_M. Furthermore, the initial pH_M of surface and core tablet was almost identical although the surface pH_M was slightly lower. Specifically, fumaric acid, malic acid and glycolic acid had almost identical pH_M (2.7–3), whereas citric acid gave the lowest pH_M at 2.3. This result matched the solubility data, with citric acid the highest solubility (see Table 2).

However, the pH_M gradually increased to 3.5–4 after 10 and 15 min except fumaric acid in SD, which constantly maintained pH_M around 3.0. Interestingly, the SD was more efficient for decreasing pH_M than the PM. These results indicated that fumaric acid was more efficient for modulating pH_M during dissolution than other acidifiers.

3.3. Structural characterization

We analyzed the crystalline structure of pure drug, PVP, amorphous binary SD without pH modifiers, and ternary SDs with pH

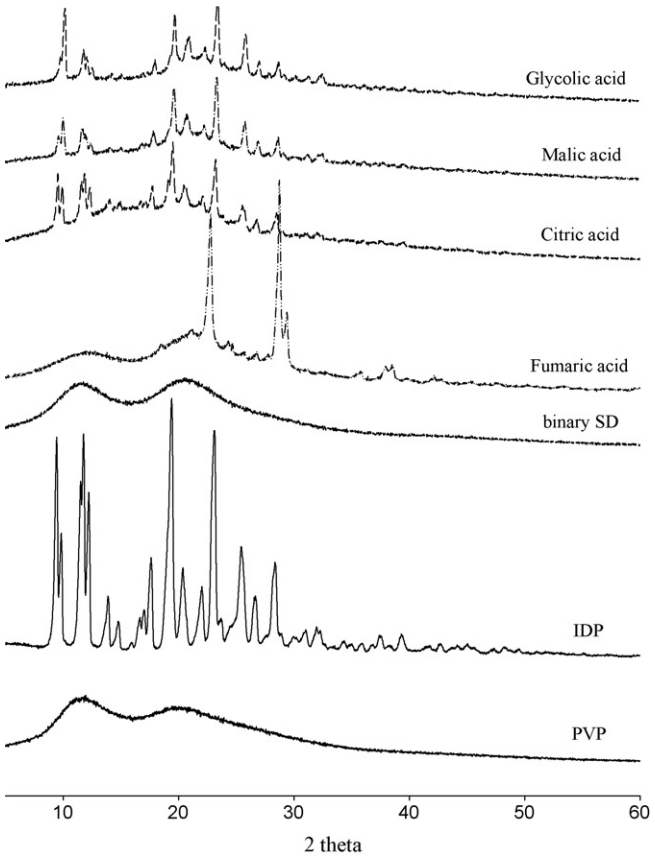

Fig. 4. PXRD patterns of pure drug, PVP, binary SD and ternary SD with acidifiers.

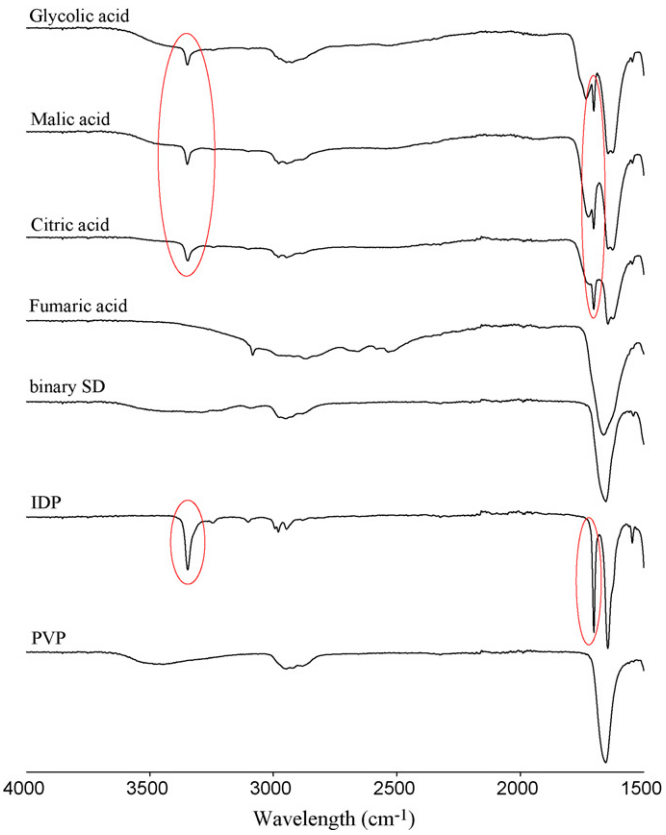

Fig. 5. FT-IR spectra of pure drug, PVP, binary SD and ternary SD with acidifiers.

modifiers using DSC (Fig. 3) and PXRD (Fig. 4), respectively. The pure drug had a distinct melting peak at 169 °C, whereas PVP itself has an amorphous structure. Binary SD and the ternary SD system with fumaric acid did not have a drug melting peak, indicating that the drug had an amorphous structure. On the other hand, citric acid and glycolic acid showed some transitions of temperature and reduced peak intensity of the distinct drug melting point, implying their crystalline structure. Particularly, malic acid showed a slight transition temperature with a broad peak, suggesting a partially amorphous structure. As mentioned previously, the enhanced dissolution rate of binary SD could be partially attributed to the amorphous nature of the PVP carrier. Although polymer can affect solubility, recrystallization (Konno et al., 2008), viscosity (Tantishaiyakul et al., 1999), particle size distribution and molecular interactions in SD (Karavas et al., 2007), the binary SD only showed about 45% dissolution rate.

With PXRD, IDP is naturally crystalline whereas PVP showed an amorphous state. PVP altered IDP structure in binary SD into a totally amorphous form. Ternary SDs showed different diffractograms of drug crystallinity based on the pH modifier. Likewise DSC, fumaric acid maintained the drug in an amorphous structure, but citric acid, malic acid, and glycolic acid did not. Fewer and less intense drug peaks were present from drug recrystallization. In particular, fumaric acid did not show any drug peaks, suggesting it did not interfere with the amorphous IDP structure and produced the best dissolution rate.

3.4. Molecular interactions of pH modifiers

We then measured the FT-IR spectra of pure drug, PVP, binary SD and ternary SD with pH modifiers (Fig. 5). IDP has two noticeable functional peaks at 3346 cm^{-1} for the N–H bond and 1701 cm^{-1} for the C=O bond and PVP also has a C=O peak at 1653 cm^{-1}. However, the NH and C=O peaks of IDP disappeared in amorphous binary SD, indicating that a molecular interaction between PVP and IDP occurred. Hydrogen bonding between a proton donor (NH group) and acceptor (C=O) is readily available (Karavas et al., 2007). Meanwhile, only fumaric acid produced a similar lack of NH and C=O peaks but other acidifiers did not. Thus, FTIR together with DSC and PXRD studies pointed out that fumaric acid did not affect the amorphous formation of IDP and PVP. For this reason, fumaric acid showed the best dissolution among acidifiers (Fig. 6) although all of them could create an acidic micro-environment. Generally, the

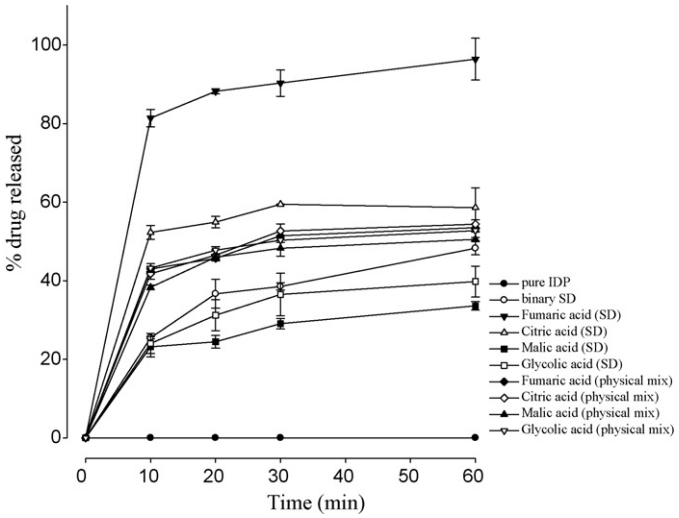

Fig. 6. Dissolution rates of pure IDP and compressed tablet containing binary SD or ternary SD and PM with acidifiers in simulated intestinal fluid (pH 6.8).

Table 3
The final pH of dissolution media after 1 h dissolution test.

pH modifier	pH
Without pH modifier	6.84 ± 0.01
Fumaric acid	6.82 ± 0.01
Citric acid	6.82 ± 0.01
Malic acid	6.83 ± 0.01
Glycolic acid	6.84 ± 0.01

enhancement of IDP dissolution rate was attributed to the ability of fumaric acid in the ternary SD to modulate pH_M and prevent crystallization.

3.5. Drug dissolution

The dissolution profiles of pure IDP and tablets containing binary SD or ternary SD and PM containing acidifiers in simulated intestinal fluid (pH 6.8) are shown in Fig. 6. The results reflected those above mechanism as indispensable consequences. In general, pH modifiers enhanced IDP dissolution compared to the pure drug no matter what the method of sample preparation (PM vs. SD) was. However, only fumaric acid in the ternary-SD tablet could remarkably increased IDP dissolution by almost 100%. In case of ternary SD-bearing tablet, dissolution enhancement was highly dependent on the type of pH modifiers and consistent with the solubility study. Fumaric acid and citric acid were more efficient than other acidifiers such as glycolic acid and malic acid. Fumaric acid remarkably increased IDP dissolution by almost 100%. Although citric acid showed the highest drug solubility, the dissolution profile (about 60%) was worse than fumaric acid. It was reasonable that fumaric acid in SD could maintain inside tablets and provide a favorable environment to modulate pH_M, structural amorphousness and intermolecular hydrogen bonding between drug and PVP, leading to the best dissolution of drug without drug recystallization compared to other acidifiers. In contrast, a high solubility of citric acid can cause its faster release from the tablet and result in losing its capability of pH_M modulation and intermolecular interaction. Furthermore, citric acid changed the drug structure into a partially crystalline form whereas only fumaric acid could maintain drug at totally amorphous structure unlike the other acidifiers. Unexpectedly, the simple amorphous binary SD without pH modifiers showed a much greater dissolution than acidifiers like malic acid and glycolic acid but was not satisfactory. PVP is a water-soluble polymer that can inhibit drug crystallinity and increase drug release rates (Cao et al., 2003; Sethia and Squillante, 2004; Zhang et al., 2008).

On the other hand, the PM-bearing tablet of fumaric acid or citric acid showed lower IDP dissolution as compared to ternary SD. In contrast, malic acid and glycolic acid in SD-bearing tablet were not efficient as compared to PM. Preparation method and acidifier type could function in SD differently but complete dissolution was not reached except ternary SD with fumaric acid. Interestingly, PM of fumaric acid with binary SD did not completely increase IDP dissolution as compared to ternary SD. Thus, separate addition of acidifiers including fumaric acid to the binary SD was not a way to increase IDP dissolution. It is essential to add fumaric acid to the internal structure of SD (ternary SD) and subsequently compressed into tablet for 100% IDP dissolution. Otherwise, the fumaric acid in PM released rapidly and the modulation of pH_M was not efficient.

The final pH of the dissolution media (pH 6.8) after the 1 h test was also determined to see if the pH modifiers changed the dissolution media pH (Table 3). The pH of dissolution media was almost constant at pH 6.8. The enhancement of IDP dissolution was not simply caused by the varying pH of dissolution media by dissolving the pH modifiers. The dissolution fluid from non-nanoemulsifying SD was very transparent. It indicated that the acidic micro-environment surrounding drug particles was modulated by acidifiers.

In summary, dissolution rate of IDP from ternary SDs-bearing tablets were in a decreased order: fumaric acid, citric acid, glycolic acid and malic acid. However, pH_M effective for enhancing dissolution rate at the first stage (5 min) were in a increasing order of citric acid, glycolic acid, malic acid and fumaric acid. Thus, dissolution rate of IDP from citric acid-bearing SD tablet was much higher as compared to glycolic or malic acid-bearing SD tablet. However, due to the lack of maintaining structural amorphousness of the PVP-based SD as shown in PXRD diffractogram, the citric acid-bearing SD tablet could not bring optimal dissolution rate of IDP compared to fumaric-bearing SD tablet. Furthermore, the release rate of citric acid, glycolic acid and malic acid from SD-loaded tablet was quite rapid, leading to higher pH_M after 15 min while fumaric acid released in the slowest manner and maintained pH_M.

4. Conclusions

PVP produced an amorphous IDP structure, but the dissolution rate of drug in binary PVP-based SD without acidifier was not satisfactory regardless of structural amorphousness. The acidifiers in an amorphous SD enhanced dissolution rate of drug by changing release rate of acidifier, pH_M and the changes of drug crystallinity in a different extent. A simple physical mixture of acidifier with PVP was not efficient. Among four pH modifiers, fumaric acid could maximize drug dissolution without recrystallization via slower release rate and modulation of pH_M for an extended period of time as well as maintenance of structural amorphousness via intermolecular interactions. This work provides clear insights in the dissolution-controlling mechanisms of pH-dependent poorly water-soluble drug how the pH modifiers can function in solid dosage forms.

Acknowledgements

This work was supported by the Korea Science and Engineering Foundation (KOSEF: R01-2008-000-11777-0). We would like to thank the Central Research Laboratory for the use of the DSC, PXRD, and FTIR, and the Research Institute of Pharmaceutical Sciences, Kangwon National University, for the use of their HPLC systems.

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