European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 83–90

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Dissolution-modulating mechanism of alkalizers and polymers in a nanoemulsifying solid dispersion containing ionizable and poorly water-soluble drug

Thao Truong-Dinh Tran, Phuong Ha-Lien Tran, Beom-Jin Lee *

National Research Laboratory for Bioavailability Control, Kangwon National University, Chuncheon, Republic of Korea

ARTICLE INFO

Article history:
Received 12 June 2008
Accepted in revised form 15 December 2008
Available online 25 December 2008

Keywords:
Dissolution-modulating mechanism
Nanoemulsifying solid dispersion
Alkalizers
Crystalline structure
Microenvironmental pH
Spring-like precipitation

ABSTRACT

We investigated the dissolution-modulating mechanism of alkalizers and polymers in nanoemulsifying Gelucire 44/14 (GUC)-based solid dispersions (SDs) for controlled release. Aceclofenac (AFC), an ionizable and poorly water-soluble drug, was chosen because of its extremely low solubility at low pH. Nanoemulsifying SD systems containing alkalizers and/or polymers were prepared by the melting method. Drug crystallinity, microenvironmental pH (pH_M), dissolution rate, and droplet size in the media from nanoemulsifying SD were then characterized. Ternary SD containing alkalizers, mainly Na_2CO_3 and $NaHCO_3$, enhanced the initial release rate of AFC in simulated gastric fluid (pH 1.2), but resulted in spring-like precipitation. However, adding a secondary polymer, Poloxamer 407, prevented precipitation in the quaternary SD system. Poloxamer 407 and alkalizer (Na_2CO_3) facilitated nanoemulsion formation (80–140 nm) with a smaller droplet size in a medium of pH 1.2 as visualized by TEM. The surface and inner pH_M were also modulated by the alkalizers, but not by the polymers. The drug's crystalline structure was further changed to partially or almost amorphous form by the alkalizers and polymers in SD as characterized by instrumental analysis. The synergistic effects of alkalizers and secondary polymers in SD on reduction of drug crystallinity and modulation of pH_M via molecular interactions could modulate dissolution rates of ionizable and poorly water-soluble model drug without spring-like precipitation by providing more favorable nanoemulsion-forming environment.

1. Introduction

Poorly water-soluble drugs have limited dissolution rates due to their highly ordered crystalline structures. Solid dispersions (SDs) are effective for enhancing their dissolution rate via structural changes of crystalline drugs into amorphous forms [1–3]. However, the solubilization capacity of SD systems is limited in many cases, resulting in recrystallization or precipitation in a spring-like manner upon exposure to an aqueous solution. Therefore, pharmaceutical strategies require more detailed dissolution-controlling mechanisms of SDs.

One solution is to utilize a self-emulsifying carrier when exposed to aqueous media. Gelucire 44/14 (GUC), a solid waxy amphiphilic material with a melting point of 44 °C and an HLB value of 14, is used as an SD carrier [4]. Gelucire 44/14 was used in an SD formulation as a carrier to improve the solubility of poorly water-soluble drugs, due to its surface-active and self-emulsifying properties upon contact with aqueous fluid [5,6].

Alternatively, incorporation of pH modifiers is a common strategy to enhance the dissolution rate of weakly acidic or basic drugs if the solubility of the drug is dependent on pH. These pH modifiers can alter the microenvironmental pH (pH_M) within and surrounding a dissolving solid to an optimal pH for controlled solubility [7–13]. Finally, secondary pharmaceutical excipients, such as surfactants and polymers, can be simultaneously combined and incorporated in SD systems for the complete solubilization of poorly water-soluble drugs by limiting spring-like precipitation in solution [1].

We recently reported that incorporating pH modifiers, mainly alkalizers in non-emulsifying polyethylene glycol 6000-based SD, could readily modify drug crystallinity and pH_M [14]. However, there have been no detailed studies for dissolution-modulating mechanisms and on how these pH modifiers and/or secondary pharmaceutical excipients in a nanoemulsifying SD can modulate drug crystallinity, pH_M and the molecular interactions of ionizable and poorly water-soluble drug. This information may provide basic solution for pharmaceutical scientists to solubilize many ionizable and poorly water-soluble drugs from a SD system at early formulation stages.

The objective of this study was to investigate dissolution-controlling mechanisms of alkalizers and/or polymers in nanoemulsifying GUC-based SD systems containing ionizable and poorly water-soluble drug. Aceclofenac (AFC), a weakly acidic drug (pK_a = 4–5), was chosen as a model drug. AFC is used for the relief

* Corresponding author. National Research Laboratory for Bioavailability Control, College of Pharmacy, Kangwon National University, Chuncheon 200-701, Republic of Korea. Tel.: +82 33 250 6919; fax: +82 33 242 3654.
E-mail address: bjl@kangwon.ac.kr (B.-J. Lee).

0939-6411/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2008.12.009

of pain and inflammation in osteoarthritis and rheumatoid arthritis. AFC exhibits extremely low solubility in water and acidic pH conditions, but high solubility in high pH solutions [15,16]. Nine commonly used alkalizers, Na_2CO_3, $NaHCO_3$, meglumine, arginine, MgO, $CaCO_3$, bentonite, Na_2HPO_4, and K_2HPO_4, were selected as pH modifiers. Three polymers: Poloxamer 407, PEG 6000, and Cremophor RH40, were also chosen as secondary pharmaceutical excipients. Drug crystallinity, pH_M, dissolution rate, and droplet size in media from nanoemulsifying SD were characterized to elucidate dissolution-modulating mechanisms. Drug crystallinity was studied by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). Fourier transform infrared (FTIR) spectroscopy was used to study the molecular interactions of functional groups between the drug, pH modifiers and excipients. Dissolution rate was investigated in simulated gastric fluid (pH 1.2). Droplet size and nanoemulsion images were characterized by laser light scattering and transmission electron microscopy (TEM), respectively.

2. Materials and methods

2.1. Materials

AFC was obtained from Dae Woong Pharmaceutical Co. Ltd., (Seoul, Korea). Gelucire 44/14 and Cremophor RH40 were purchased from Gatteffosse (France). Poloxamer 407 (Pluronic F-127) was purchased from BASF (Germany). PEG 6000 was purchased from Yakuri Pure Chemicals Co., Ltd., (Osaka, Japan); magnesium oxide (MgO) was purchased from Junsei Chemical Co., Ltd., (Japan); sodium bicarbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3), arginine, meglumine, and calcium carbonate ($CaCO_3$) were purchased from (Sigma–Aldrich, USA); bentonite was purchased from Mineral and Pigment Solutions, Inc., (USA); and disodium hydrogen phosphate (Na_2HPO_4) and dipotassium hydrogen phosphate (K_2HPO_4) were purchased from Showa Chemical Co., Ltd., (Japan). The solvents used were of 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. HPLC analysis

AFC concentration was determined by HPLC system (Water, USA) with Luna 5μ C_{18} analytical column (150 × 4.6 mm). A mobile phase of methanol and 0.02 M potassium dihydrogen phosphate (65:35 v/v) was used at a flow rate of 1.2 ml/min. The UV detector was set at 282 nm to analyze the column effluent. The entire solution was filtered through a 0.45 μM membrane filter (Millipore Corp., Bedford) and was degassed prior to use. Twenty microliters of samples were injected into HPLC system for analysis.

2.2.2. Solubility studies of AFC with various alkalizers

An excess amount of AFC was added to snap-cap Eppendorf tubes (Hamburg, FRG) containing 1 ml of various media (deionized water; pH 1.2; pH 6.8 or 1% (w/v) alkalizer in deionized water) according to the method reported previously [14]. All the solutions prepared in the whole study were surely degassed prior to use. The resulting mixture was shaken in a shaking water bath at 37 °C (100 rpm) for 24 h. Tubes were centrifuged at 15,000 rpm for 10 min. The supernatant was adjusted with a proper dilution and injected for the determination of drug concentration by HPLC.

2.2.3. Preparation of GUC-based SD

GUC-based SD was prepared by the melting method in an oil bath. First, the carrier (70 mg) was melted at 60 °C and then the drug (70 mg) was incorporated. The resulting binary mixtures were constantly stirred with a glass agitator for 15 min until a uniform mixture was obtained. Alkalizer (Na_2CO_3, $NaHCO_3$, meglumine, arginine, MgO, $CaCO_3$, bentonite, Na_2HPO_4, or K_2HPO_4) and/or secondary polymer (Poloxamer 407, PEG 6000, or Cremophor RH40) was then added to obtain a uniform ternary or quaternary SD. The melted mixture was homogeneously mixed with a glass agitator for 15 min and poured into a hard gelatin capsule equivalent to 70 mg AFC. The weight ratio of the drug, GUC, and alkalizer used to prepare ternary SD was kept at 70:70:28. The quaternary SD consisted of drug, GUC, Na_2CO_3 and polymer at a weight ratio of 70:70:28:70 (or 100 for Poloxamer 407). A binary SD consisting of drug (70 mg) and GUC (35, 70, or 115 mg) in weight ratios (1:0.5, 1:1, or 1:1.5) was also prepared to investigate drug/carrier ratio effects as a reference for comparison. Codes in this paper are named according to the type of alkalizer or polymer in the SD formulation.

2.2.4. Dissolution test

The GUC-based SD in a No. 1 hard gelatin capsule equivalent to 70 mg AFC was exposed to dissolution media. Dissolution tests were performed in triplicate with a DST-810 dissolution tester (Labfine, Seoul, Korea) in 900 ml simulated gastric (pH 1.2) or intestinal fluid (pH 6.8) at 37 °C using the paddle method at a rotation speed of 100 rpm according to the USP 26 pharmacopoeia [14]. At 5, 10, 15, 30, 45, 60, 90, and 120 min, samples were withdrawn and replaced with an equal volume of dissolution media. The aliquot was immediately filtered through 0.45 μm membrane (regenerated cellulose) and was immediately diluted with the mobile phase for the prevention of drug precipitation. The drug concentration was then determined by HPLC.

2.2.5. Thermal analysis (DSC)

The raw materials of AFC, GUC, binary SD (GUC:AFC = 1:1) and ternary and quaternary SD containing alkalizer and/or polymer were analyzed by DSC (TA Instruments, Model 2910, USA). An approximate sample (0.2–0.5 mg) was weighed in a standard open aluminum pan. An empty pan of the same type was used as a reference. Dry nitrogen was used as purge gas. Samples were heated from 20 to 200 °C at a heating rate 10 °C/min. Calibration of temperature and heat flow was performed with indium.

2.2.6. Powder X-ray diffraction (PXRD)

All the samples characterized by DSC were also investigated for their crystallinity by PXRD. The technique could be described briefly as follows: the samples were scanned in steps of 0.02° from 5° to 60° (diffraction angle 2θ) at a rate of 1 s per step, using a zero background sample holder through a D5005 diffractometer (Bruker, Germany) using Cu-K radiation at a voltage of 40 kV, 50 mA.

2.2.7. Fourier transform infrared (FTIR) spectroscopy

The spectra of the raw materials of AFC, GUC, binary SD (GUC:AFC = 1:1), and ternary and quaternary SD containing alkalizer and/or secondary polymer by using an FTIR spectrophotometer (Model Excalibur Series UMA-500, Bio-Rad, USA). The wavelength was set from 500 to 4000 cm^{-1} were recorded with a resolution of 2 cm^{-1} to characterize KBr pellets which had been prepared by gently mixing 1 mg of the sample with 200 mg KBr.

2.2.8. Measurement of pH_M

GUC-based SD systems in a hard gelatin capsule were used to investigate the effect of pH_M. The non-disintegrated capsule was removed from the dissolution media at 5 min (or 15 min in case of quaternary SD containing Poloxamer 407) and was frozen immediately at −40 °C in a deep freezer for 30 min. The surface

and inner pH_M of the capsule were then determined potentiometrically using a surface pH electrode (Metoxy pH Meter HM-17MX, DKK-TOA Corp., Japan). In the case of quaternary SD containing Poloxamer 407, pH_M was measured at 5, 10, and 15 min.

2.2.9. Particle size measurement in dissolution media

To identify the formation of nanoemulsion, GUC-based ternary and quaternary SD containing alkalizer and/or polymer were exposed to gastric fluid of pH 1.2 for 2 h, and then about 3 ml of the sample was withdrawn. The droplet sizes were analyzed by Electrophoretic Light Scattering 8000 (Photal Otsuka Electronics, Japan). All measurements were performed in triplicate with a He–Ne laser light source (5 mW) at a 90° angle.

2.2.10. Transmission electron microscopy (TEM)

Transmission electron microscopy (LEO 912AB-100, Carl Zeiss, Korea Basic Science Institute, Chuncheon) was used to investigate the formation of self-nanoemulsion from quaternary SD containing Poloxamer 407. Samples were placed onto a copper grill covered with nitrocellulose. They were dried at room temperature and then examined using a transmission electron microscope without being negative stained.

3. Results and discussion

3.1. Drug solubility in different alkaline solutions

In theory, a weakly acidic drug shows low solubility in an acidic medium but has a good solubility in a basic medium. Based on the degree of AFC ionization (pK_a = 4–5), it could be deprotonated at a high pH, resulting in the formation of a soluble compound. The pH modifiers can modulate AFC solubility and produce a much higher dissolution rate. The solubility of weakly acidic AFC was dependent on pH, being highly soluble in basic conditions but relatively insoluble in deionized water and acidic pH conditions (Table 1). These results were also matched with those of a previous report [17]. Interestingly, incorporating 1% alkalizers in deionized water greatly increased drug solubility. Moreover, among alkalizers, Na_2CO_3 showed the best enhancement. For this reason, Na_2CO_3 was chosen to be the model alkalizer in the SD formulations.

3.2. Dissolution modulation by formulation parameters

In preliminary studies, dissolution rates of the pure AFC were determined in simulated gastric (pH 1.2) and intestinal fluid (pH 6.8). The release of AFC, a weakly acidic drug, was 100% at pH 6.8 after 15 min, but was almost negligible for 2 h in gastric fluid (pH 1.2). Therefore, dissolution-modulating behaviors were further investigated in gastric fluid.

Table 1
Solubility of AFC at 37 °C in gastric and intestinal fluid, deionized water, and 1% (w/v) solution of pH modifiers.

Media	Solubility of AFC in media (μg/ml)
Deionized water	55.46 ± 0.14
Gastric fluid (pH 1.2)	11.77 ± 0.64
Intestinal fluid (pH 6.8)	4962.00 ± 4.54
1% Na_2CO_3 in deionized water	46538.05 ± 0.28
1% $NaHCO_3$ in deionized water	20385.24 ± 2.95
1% bentonite in deionized water	876.48 ± 0.29
1% arginine in deionized water	19271.42 ± 0.32
1% K_2HPO_4 in deionized water	13794.03 ± 0.36
1% Na_2HPO_4 in deionized water	16634.14 ± 0.28
1% MgO in deionized water	1242.82 ± 0.22
1% $CaCO_3$ in deionized water	638.47 ± 3.10
1% meglumine in deionized water	19042.06 ± 3.45

In general, drug dissolution rates and crystallinity of SD can be governed by the carrier-to-drug ratio. The more the amount of carrier added, the more the drug's structure was changed into amorphous form, resulting in increased dissolution rate of drug [18]. For weakly acidic AFC, effect of drug and carrier ratio affected dissolution rate of SD-loaded capsule in gastric fluid (Fig. 1). The enhancing effect of carrier was maximized around 12–15% release at drug to carrier ratio (1:1.5). Addition of more carriers was not efficient and would rather inhibit initial release. Dissolution enhancement of binary SD by itself was unsatisfactory. To modulate these dissolution behaviors, nine alkalizers were selected according to their basic strength and were combined in binary SD to modulate the pH dependency of AFC. Except for bentonite, the incorporation of alkalizers in SD enhanced drug release rates in gastric fluid, but the extent of this enhancement depended on the type of alkalizer (Fig. 2). The addition of Na_2CO_3 led to the highest drug release, followed by $NaHCO_3$, meglumine, $CaCO_3$, and the others, which had almost the same influence on the drug release rate. In general, Na_2CO_3 showed the greatest potential in increasing AFC release rates.

However, the enhanced dissolution by alkalizers rapidly decreased due to spring-like precipitation in gastric fluid. For this rea-

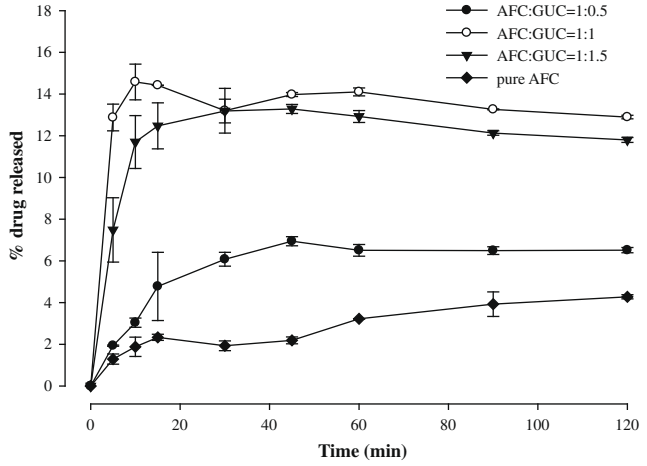

Fig. 1. Effect of drug and carrier ratio on drug dissolution rate of binary SD-loaded capsule in gastric fluid.

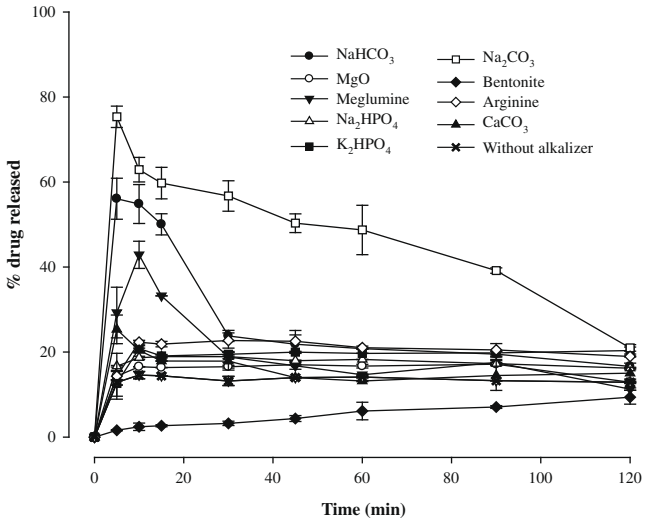

Fig. 2. Effect of alkalizers on drug dissolution rate of ternary SD-loaded capsule in gastric fluid.

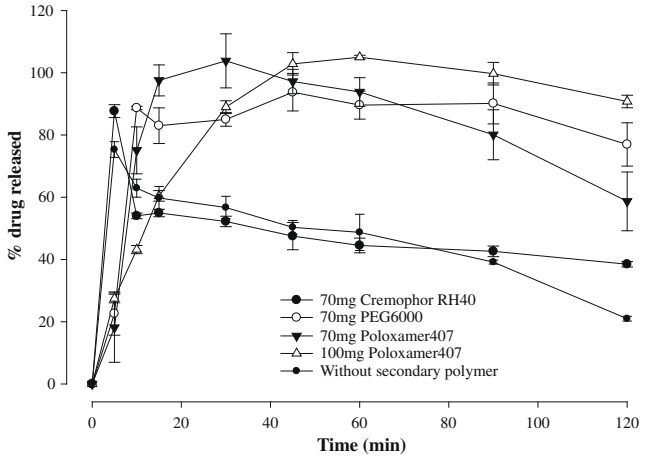

Fig. 3. Effect of secondary polymers on drug dissolution rate of quaternary SD-loaded capsule containing Na_2CO_3.

son, secondary polymers were incorporated in the GUC-based ternary SD system containing Na_2CO_3 to prevent spring-like precipitation. The incorporation of a secondary polymer in the formulation containing surfactant may help prevent precipitation [19]. Three polymers, Cremophor RH40, PEG 6000, and Poloxamer 407, were incorporated in the ternary SD containing Na_2CO_3 to see whether they would improve AFC dissolution rates as well as prevent spring-like drug precipitation. Cremophor RH40 and Poloxamer 407 are non-ionic solubilizing and emulsifying agents, and PEG 6000 is composed of hydrophilic polymers. They have been widely used to enhance poorly soluble drugs in SD systems [20–22].

In general, when using the same amount of drug, the addition of a secondary polymer to ternary SD containing Na_2CO_3 significantly improved the drug dissolution rate (Fig. 3). The maximum drug release obtained was approximately 90%, or even 100% in the case of Poloxamer 407, and the minimum amount of drug dissolved after precipitation was about 60%. Meanwhile, SD alone without secondary polymers had about 75% maximum and 20% minimum drug releases. Specifically, Cremophor RH40 enhanced the drug release rate up to 90% within 5 min, but it decreased to 40% after 2 h due to spring-like precipitation. In the case of PEG 6000, drug release reached 90% within 5 min and was sustained over 2 h with slight (10%) precipitation. Poloxamer 407 (70 mg or 100 mg) also improved AFC dissolution with a release rate over 100%, but it was not as effective in preventing precipitation at 70 mg loading. Surprisingly, as the amount of Poloxamer 407 increased to 100 mg, the drug release rate increased gradually up to 100%, with negligible precipitation. For this reason, we evaluated the detailed dissolution-modulating mechanisms of alkalizer and secondary polymers in the nanoemulsifying SD system, and how pH_M, drug crystallinity, and nanoemulsion formation are correlated with drug dissolution without showing spring-like precipitation.

3.3. Measurement of microenvironmental pH (pH_M)

The modulation of pH_M for SD incorporated with alkalizers is a factor in enhancing dissolution rates of weakly acidic AFC. Effect of alkalizers on pH_M of SD-loaded capsule is shown in Fig. 4. The pH_M of the SD capsule without alkalizer was also determined for comparison. Because the SD-loaded capsules completely disintegrated after 5 min, we determined the surface and inner pH_M at 5 min. In contrast, the pH_M of the SD-loaded capsules containing Poloxamer 407 was measured for 15 min because capsules could stand their form until 15 min. The SD-loaded capsule without alkalizers showed a pH_M around 5 and 5.5 on the surface and inside of the

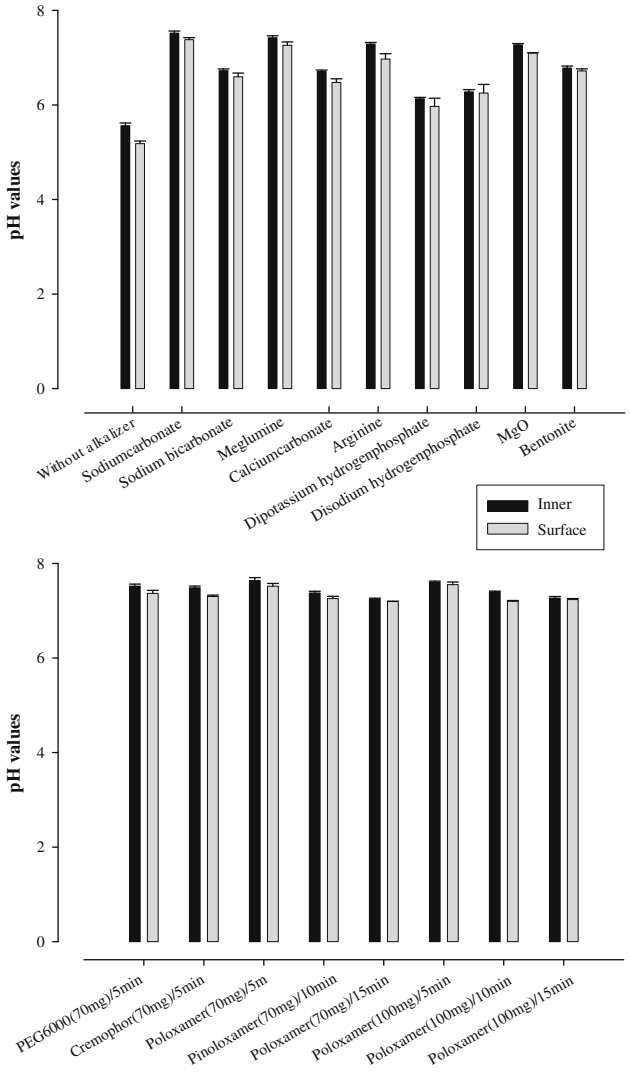

Fig. 4. Surface and inner pH_M of SD-loaded capsule. Top: binary SD (AFC:GUC = 1:1) and ternary SD containing alkalizer; bottom: quaternary SD containing AFC, GUC, Na_2CO_3 and polymer.

capsules, respectively, indicating that GUC alone had no effect on modulating pH_M. The presence of an alkalizer consistently increased the pH_M. As the dissolution fluid penetrated into the SD-loaded capsules, alkalizers leached out and increased the pH_M of the vicinity of drug particles. However, the loss of alkalizers on the surface and the effect of the pH in the bulk medium resulted in slightly decreased pH_M of the surface of capsules as compared to the inner distance, except for Na_2HPO_4 and bentonite. The modulating power of pH_M by these alkalizers was in the following decreasing order: Na_2CO_3, meglumine, arginine, and MgO. Na_2CO_3 led to the highest pH_M of 7.38 and 7.52 on the surface and the inside of the SD-loaded capsules, respectively, which corresponded to the highest dissolution profile. The pH_M of $CaCO_3$, Na_2HPO_4, K_2HPO_4, and bentonite did not create a basic environment and remained around 6.5 or less. Therefore, their effects on drug dissolution rates were almost negligible. Interestingly, the incorporation of secondary polymers such as PEG 6000, Poloxamer 407, or Cremophor RH40 in SD-loaded capsules containing Na_2CO_3 gave almost identical pH_M. The pH_M decreased slightly as a function of increased time, but changes were almost negligible.

Alkalizers incorporated in ternary SD produced a more basic pH_M, increasing the initial dissolution rates of AFC at pH 1.2 but then immediately decreasing in a spring-like manner. The dissolu-

tion rates of quaternary SD-loaded capsules containing Na_2CO_3 and secondary polymers could be improved without showing spring-like precipitation (see Fig. 3). We therefore performed instrumental analysis to characterize the molecular interactions and to investigate drug crystallinity.

3.4. DSC thermograms

DSC thermograms of various SD systems incorporated with alkalizer and secondary polymer are shown in Fig. 5. The DSC curves of GUC and pure AFC exhibited their single endothermic peaks at 44 °C and 153 °C, respectively, which corresponded to their intrinsic melting points. The characteristic melting point peak of GUC existed in all the cases, but varied via its molecular interaction with other components. In the binary SD system, no AFC peak was observed, indicating that AFC existed in an amorphous form. Moreover, most of the SDs containing alkalizer and/or polymer had no distinct AFC melting peak and changed the drug's crystalline structure into an amorphous form, except for meglumine, which was shifted left at 138 °C in the ternary SD. The enhanced AFC dissolution rate seemed to result from this transformation of drug's crystalline structure. However, these DSC thermograms could not completely explain the differences in drug dissolution.

3.5. PXRD diffractograms

PXRD diffractograms of various SD systems incorporated with alkalizer and secondary polymer were investigated (Fig. 6). The PXRD diffractogram of pure AFC was highly crystalline, with many

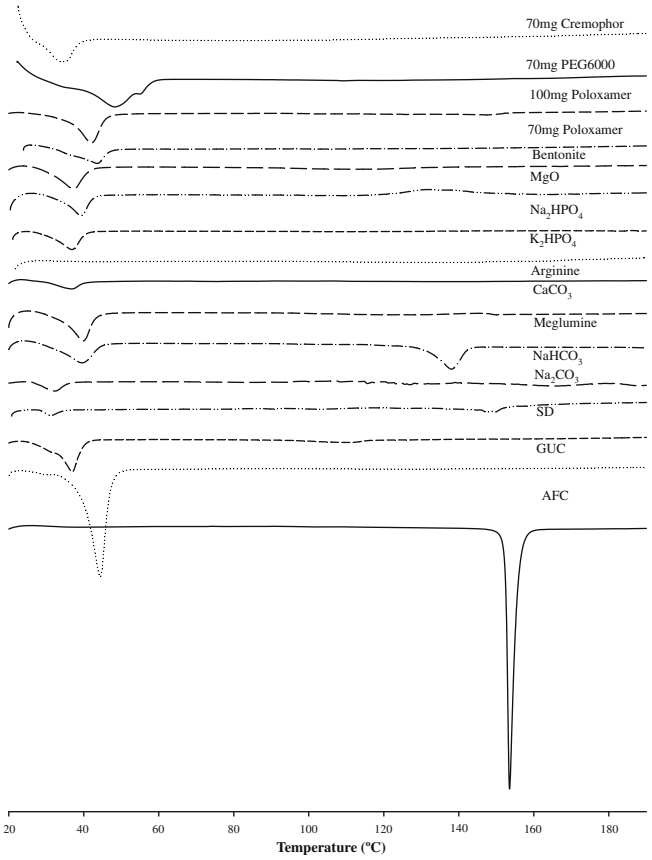

Fig. 5. DSC thermograms. From the bottom: pure drug, GUC, binary SD (AFC and GUC), ternary SDs (AFC, GUC and an alkalizer in the following order: Na_2CO_3, $NaHCO_3$, meglumine, $CaCO_3$, arginine, K_2HPO_4, Na_2HPO_4, MgO, bentonite), and quaternary SDs (AFC, GUC, Na_2CO_3 and polymer in the following order: 70 mg Poloxamer, 100 mg Poloxamer, 70 mg PEG 6000, 70 mg Cremophor).

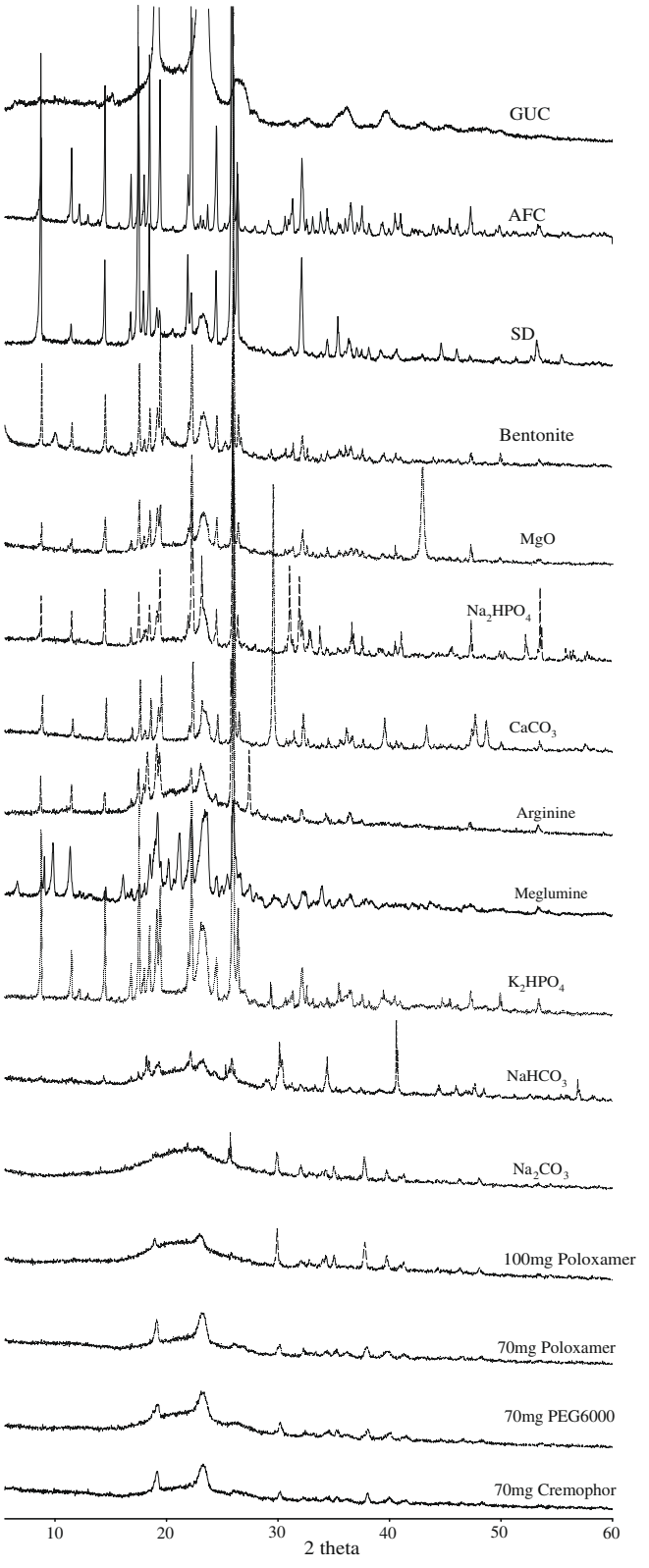

Fig. 6. PXRD patterns. From the top: GUC, pure drug, binary SD (AFC and GUC), ternary SDs (AFC, GUC and an alkalizer in the following order: bentonite, MgO, Na_2HPO_4, $CaCO_3$, arginine, meglumine, K_2HPO_4, $NaHCO_3$, Na_2CO_3), and quaternary SDs (AFC, GUC, Na_2CO_3 and polymer in the following order: 100 mg Poloxamer, 70 mg Poloxamer, 70 mg PEG 6000, 70 mg Cremophor).

characteristic peaks. The incorporation of GUC as a carrier with AFC in the binary SD decreased some of these peaks, indicating that the drug's crystalline structure was changed into a partially crystalline

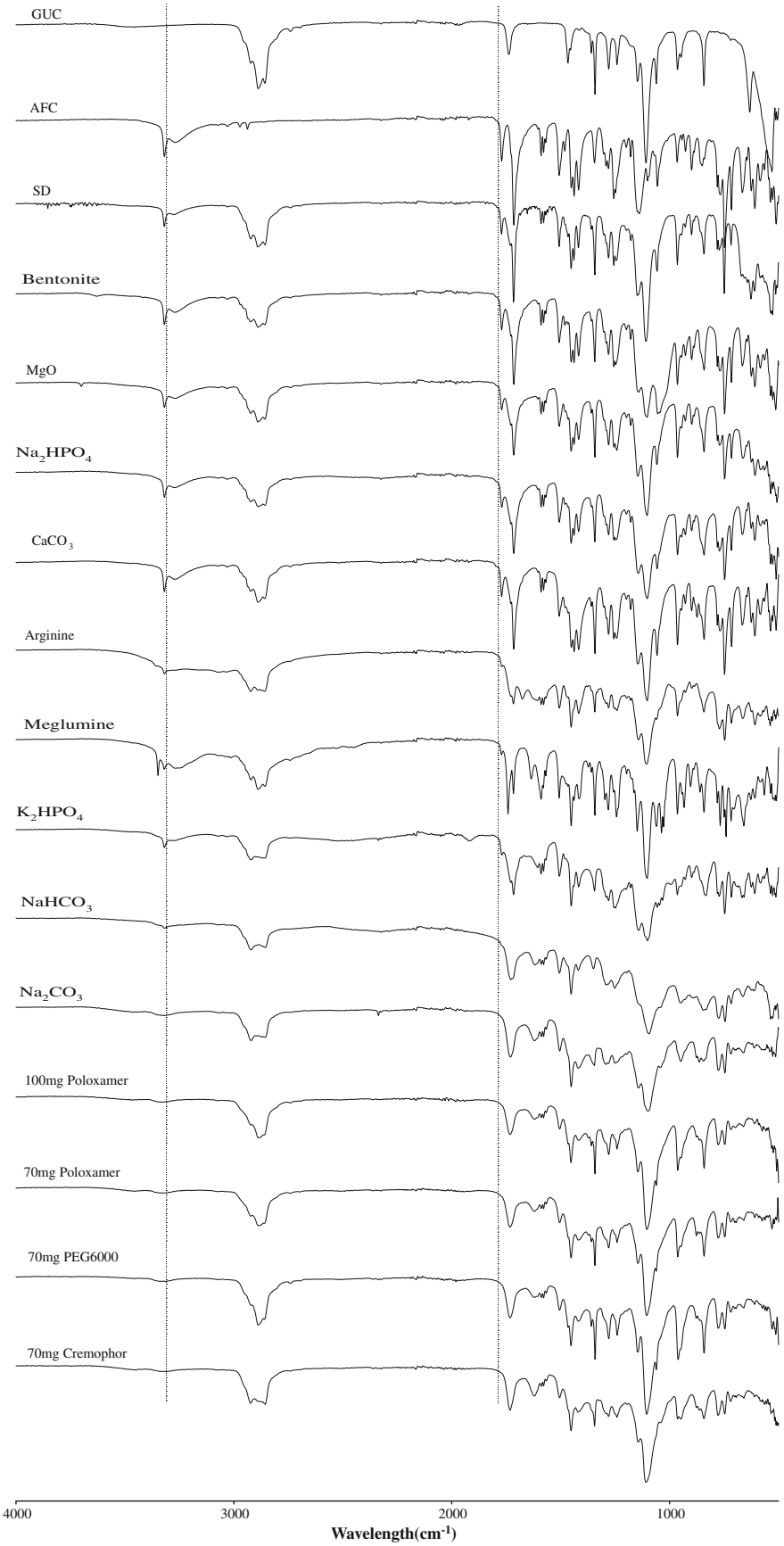

Fig. 7. FTIR spectra. From the top: GUC, pure drug, binary SD (AFC and GUC), ternary SDs (AFC, GUC and an alkalizer in the following order: bentonite, MgO, Na_2HPO_4, $CaCO_3$, arginine, meglumine, K_2HPO_4, $NaHCO_3$, Na_2CO_3), and quaternary SDs (AFC, GUC, Na_2CO_3 and polymer in the following order: 100 mg Poloxamer, 70 mg Poloxamer, 70 mg PEG 6000, 70 mg Cremophor).

form. Furthermore, ternary SDs, including bentonite, MgO, Na_2HPO_4, K_2HPO_4, $CaCO_3$, and arginine, also changed the drug's crystalline structure into a partially amorphous form. The drug peaks at 8.75°, 12.19°, and 12.97° disappeared or peak intensity decreased. Moreover, the number of peaks in the range between 30° and 40° decreased, indicating an amorphous state [23]. In contrast, the ternary SDs incorporating meglumine, $NaHCO_3$, and Na_2CO_3 and quaternary SD systems containing Na_2CO_3 and polymers showed that AFC existed in an almost totally amorphous form. Most of AFCs characteristic peaks disappeared, although there were peaks at 25.95° and a few peaks between 30° and 40°. These peaks decreased in intensity and even disappeared at 25.95° when the secondary polymers were incorporated.

The binary SD based only on GUC could slightly enhance the AFC release rate due to changing of the AFC structure into a partially amorphous form. Incorporation of an alkalizer further induced structural changes into a partially amorphous form. Na_2CO_3 promoted the strongest structural changes among alkalizers, resulting in the best enhancement of drug dissolution. Furthermore, these PXRD diffractograms clearly elucidated the roles of the secondary polymers in changing the drug's crystalline structure into an almost totally amorphous form, improving the drug dissolution rate without showing spring-like precipitation.

3.6. FTIR characterization

We measured FTIR spectra to investigate the molecular interactions among functional groups (Fig. 7). Structural changes and the lack of a crystal structure can lead to changes in the molecular bonding energy between functional groups which can be detected by FTIR spectroscopy [24].

The spectrum of pure AFC showed a distinct absorption band for the carbonyl group C═O at 1716.64 cm^{-1} and the O–H, N–H band at 3265.47 cm^{-1}. These positions were observed throughout all the spectra. The spectra of binary and ternary SDs, including the alkalizers, bentonite, MgO, Na_2HPO_4, $CaCO_3$, arginine, meglumine, and K_2HPO_4, still showed these distinct absorption bands. Interestingly, C═O, N–H, and O–H bands in the spectra of ternary SDs incorporated with $NaHCO_3$ and Na_2CO_3 and quaternary SDs containing Na_2CO_3 and polymers disappeared, indicating an interaction between drug and alkalizers that enhanced drug dissolution rate. The disappearance of the carboxylic acid O–H peak indicated that it could be deprotonated by some alkalizers via a Bronsted acid–base interaction [25]. FTIR spectra showed a molecular interaction between AFC and alkalizers, resulting in changes in pH_M, drug crystallinity, and dissolution.

3.7. Droplet size in dissolution media

In addition to pH_M and changes in drug crystallinity, nanoemulsion formation in SD systems might affect how the alkalizer and secondary polymer enhance dissolution rates and prevent spring-like drug precipitation. GUC itself creates a self-emulsifying system, which can improve the solubility of poorly water-soluble drugs [4]. Moreover, a self-emulsifying system should form an emulsion upon dilution in aqueous media to allow distribution of droplet size [26]. In this study, GUC alone was not efficient due to its limited solubilization capacity.

Droplet size of dissolution fluid from SD-loaded capsules containing Na_2CO_3 and secondary polymers was measured by dynamic light scattering method (Electrophoretic Light Scattering 8000) in a range of nanoscale (Fig. 8a). The increasing order of droplet size was Cremophor RH40 (101 nm), Poloxamer 407 (125 nm), ternary SD without polymers (138 nm), and PEG 6000 (144 nm). In case of Poloxamer 407, the droplet size further decreased (about 85 nm) as the amount increased from 70 mg to 100 mg. Images of nanoemulsion were also observed by TEM (Fig. 8b). These nanoemulsion droplets were attributed to the exposure of the ternary and quaternary SD systems upon aqueous fluid. However, these differences in droplet size of the nanoemulsions did not predict the best dissolution of AFC for Poloxamer 407.

In quaternary SD system, Cremophor RH40 and Poloxamer 407 function as co-surfactants, while PEG 6000 acts as a hydrophilic co-solvent. Poloxamer and Cremophor RH40 have hydrophilic–lipophilic balance (HLB) values of 22 and 14, respectively. HLB describes the relative composition of a hydrophilic group and a lipophilic group within an emulsifier. Hence, a higher HLB of a secondary polymer could lead to a higher solubility of the formulation in aqueous phase, which forms micelles or nanoemulsion from the quaternary SD system to maintain the drug in a soluble form [27,28]. It may explain the reason why Cremophor RH40 with relatively lower HLB did not produce dissolution as efficiently as Poloxamer 407. PEG 6000 showed better dissolution rates than Cremophor RH40 due to its high hydrophilicity despite the larger droplet size. Poloxamer 407 produced the best modulation of dissolution rates due to its high HLB and surface-active properties, and this explains why the AFC dissolution profile was more pronounced as the concentration of Poloxamer increased (see Fig. 3). The increased surfactant concentration also decreased interfacial tension and droplet size [29].

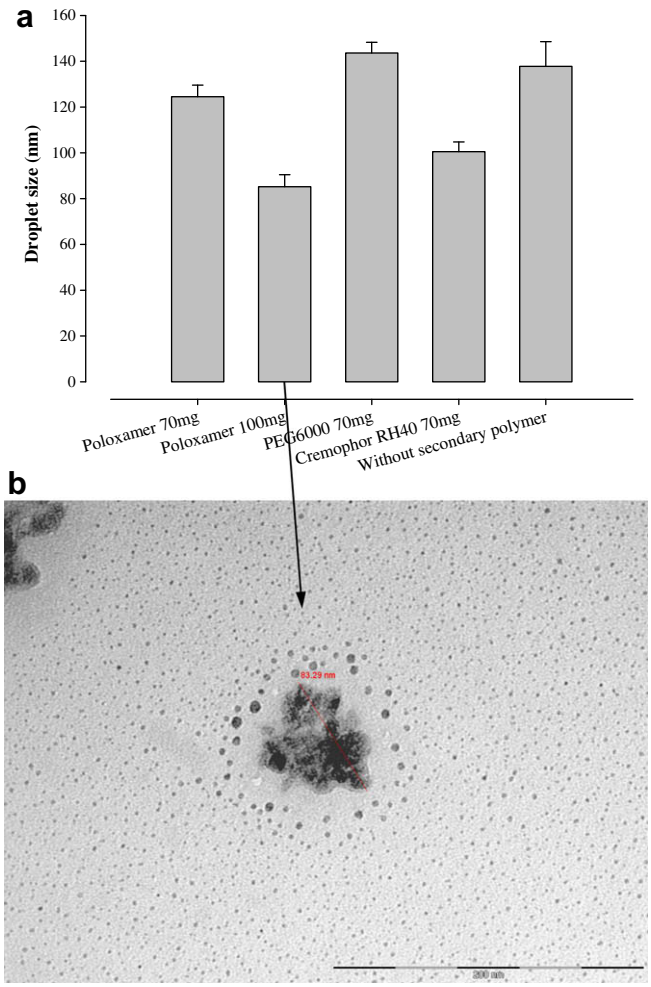

Fig. 8. Droplet size of dissolution fluid from quaternary SD-loaded capsule containing Na_2CO_3 and polymers. (a) Average droplet size; (b) TEM image of quaternary SD-loaded capsule containing Na_2CO_3 and 100 mg poloxamer.

4. Conclusions

Modulation of pH_M and changes of drug crystallinity into an amorphous form by alkalizers enhanced the dissolution rate of weakly acidic drug such as AFC in SD systems. Furthermore, incorporation of secondary polymers combined with alkalizer could increase these efficiencies and maintain the drug in solubilized nanoemulsion droplets without spring-like precipitation. Among the SD systems, the incorporation of Na_2CO_3 combined with Poloxamer 407 gave the highest potentials, and was a promising approach for AFCs dissolution enhancement. The current SD systems containing pH modifiers and polymers can enhance dissolution rates of ionizable and poorly water-soluble drugs by the three major mechanisms: modulating pH_M, changing drug crystallinity into an amorphous form via molecular interactions and providing more favorable nanoemulsion-forming environment in solution.

Acknowledgements

This work was supported by the Korea Science and Engineering Foundation KOSEF: RO1-2008-000-11777-0, Korea. We also thank the Central Research Laboratory for the use of the DSC, PXRD, and FTIR and the Research Institute of Pharmaceutical Sciences for allowing the use of their HPLC systems in the Kangwon National University.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejpb.2008.12.009.

References

[1] M.-Y. Heo, Z.-Z. Piao, T.-W. Kim, Q.-R. Cao, A. Kim, B.-J. Lee, Effect of solubilizing and microemulsifying excipients in polyethylene glycol 6000 solid dispersion on enhanced dissolution and bioavailability of ketoconazole, Arch. Pharm. Res. 28 (2005) 604–611.
[2] A.T.M. Serajuddin, Solid dispersion of poorly water-soluble drugs: early promises, subsequents problems, and recent breakthroughs, J. Pharm. Sci. 88 (1999) 1058–1066.
[3] H.N. Joshi, R.W. Tejwani, M. Davidovich, V.P. Sahasrabudhe, M. Jemal, M.S. Bathala, S.A. Varia, A.T.M. Serajuddin, Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol–polysorbate 80 mixture, Int. J. Pharm. 269 (2004) 251–258.
[4] N. Yüksel, A. Karataş, Y. Özkan, A. Savaşer, S.A. Özkan, T. Baykara, Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: in vitro and in vivo evaluation, Eur. J. Pharm. Biopharm. 56 (2003) 453–459.
[5] F. Damian, N. Blaton, L. Naesens, J. Balzarini, R. Kinget, P. Augustijnsa, G.V.d. Mooter, Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14, Eur. J. Pharm. Sci. 10 (2000) 311–322.
[6] D. Yang, R. Kulkarni, R.J. Behmeb, P.N. Kotiyanl, Effect of the melt granulation technique on the dissolution characteristics of griseofulvin, Int. J. Pharm. 329 (2007) 72–80.
[7] C. Doherty, P. York, Microenvironmental pH control of drug dissolution, Int. J. Pharm. 50 (1989) 223–232.
[8] S. Siepe, B. Lueckel, A. Kramer, A. Ries, R. Gurny, Strategies for the design of hydrophilic matrix tablets with controlled microenvironmental pH, Int. J. Pharm. 316 (2006) 14–20.
[9] R. Espinoza, E. Hong, L. Villafuerte, Influence of admixed citric acid on the release profile of pelanserin hydrochloride from HPMC matrix tablets, Int. J. Pharm. 201 (2000) 165–173.
[10] A. Streubel, J. Siepmann, A. Dashevsky, R. Bodmeier, pH-independent release of a weakly basic drug from water-insoluble and -soluble matrix tablets, J. Control. Release 67 (2000) 101–110.
[11] H. Kranz, C. Guthmannb, T. Wagner, R. Lipp, J. Reinhard, Development of a single unit extended release formulation for ZK 811 752, a weakly basic drug, Eur. J. Pharm. Sci. 26 (2005) 47–53.
[12] M.V.S. Varma, A.M. Kaushal, S. Garg, Influence of micro-environmental pH on the gel layer behavior and release of a basic drug from various hydrophilic matrices, J. Control. Release 103 (2005) 499–510.
[13] T. Riis, A. Bauer-Brandl, T. Wagner, H. Kranz, pH-independent drug release of an extremely poorly soluble weakly acidic drug from multiparticulate extended release formulations, Eur. J. Pharm. Biopharm. 65 (2007) 78–84.
[14] P.H.L. Tran, H.T.T. Tran, B.-J. Lee, Modulation of microenvironmental pH and crystallinity of ionizable telmisartan using alkalizers in solid dispersions for controlled release, J. Control. Release 129 (2008) 59–65.
[15] A. Alvarez-Laurena, J.F. Piniella, E. Carrasco, A. Ginebreda, S. Yulia, G. Germain, Crystal structure and spectroscopy study of 2-[(2,6-dichlorophenyl) amino]phenylacetoxyacetic acid (aceclofenac), J. Crystallogr. Spectrosc. Res. 22 (1992) 323–328.
[16] B.-J. Lee, H. Jung, Enhanced bioavailability of poorly water-soluble aceclofenac using PEG-based solid dispersion in rats, beagle dogs and human subjects, AAPS Annual Meeting, New Orleans, LA, USA, 1999, pp. 14–18.
[17] S. Mutalik, P. Anju, K. Manoj, A.N. Usha, Enhancement of dissolution rate and bioavailability of aceclofenac: a chitosan-based solvent change approach, Int. J. Pharm. 350 (2008) 279–290.
[18] V. Tantishaiyakul, N. Kaewnopparat, S. Ingkatawornwong, Properties of solid dispersions of piroxicam in polyvinylpyrrolidone, Int. J. Pharm. 181 (1999) 143–151.
[19] T. Vasconcelos, B. Sarmento, P. Costa, Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs, Drug Discov. Today 12 (2007) 1068–1075.
[20] G. Dumortier, J.L. Grossiord, F. Agnely, J.C. Chaumeil, A review of poloxamer 407 pharmaceutical and pharmacological characteristics, Pharm. Res. 23 (2006) 2709–2728.
[21] M. Grove, A. Müllertz, J.L. Nielsen, G.P. Pedersen, Bioavailability of seocalcitol. II: Development and characterisation of self-microemulsifying drug delivery systems (SMEDDS) for oral administration containing medium and long chain triglycerides, Eur. J. Pharm. Sci. 28 (2006) 233–242.
[22] A. Fini, J.R. Moyano, J.M. Ginés, J.I. Perez-Martinez, A.M. Rabasco, Diclofenac salts. II: Solid dispersions in PEG 6000 and Gelucire 50/13, Eur. J. Pharm. Biopharm. 60 (2005) 99–111.
[23] J. Hu, K.P. Johnston, R.O. Williams III, Spray freezing into liquid (SFL) particle engineering technology to enhance dissolution of poorly water soluble drugs: organic solvent versus organic/aqueous co-solvent systems, Eur. J. Pharm. Sci. 20 (2003) 295–303.
[24] C. Leuner, J. Dressman, Improving drug solubility for oral delivery using solid dispersions, Eur. J. Pharm. Biopharm. 50 (2000) 47–60.
[25] N. Song, Z.Y. Wang, Synthesis, characterization, and multilayer assemblies of acid and base polyimides, Macromolecules 36 (2003) 5885–5890.
[26] C.J.H. Porter, C.W. Pouton, J.F. Cuine, W.N. Charman, Enhancing intestinal drug solubilisation using lipid-based delivery systems, Adv. Drug Deliv. Rev. 60 (2008) 673–691.
[27] S. Shafiq, F. Shakeel, S. Talegaonkar, F.J. Ahmad, R.K. Khar, M. Ali, Development and bioavailability assessment of ramipril nanoemulsion formulation, Eur. J. Pharm. Biopharm. 66 (2007) 227–243.
[28] S. Ren, M.-J. Park, H. Sah, B.-J. Lee, Effect of pharmaceutical excipients on aqueous stability of rabeprazole sodium, Int. J. Pharm. 350 (2008) 197–204.
[29] M. Porras, C. Solans, C. González, A. Martínez, A. Guinart, J.M. Gutiérrez, Studies of formation of W/O nano-emulsions, Colloids Surf. A 249 (2004) 115–118.