Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 343 (2007) 228–237
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188

Madhuri Newa [a], Krishna Hari Bhandari [a], Dong Xun Li [a], Tae-Hyub Kwon [a], Jung Ae Kim [a], Bong Kyu Yoo [a], Jong Soo Woo [b], Won Seok Lyoo [c], Chul Soon Yong [a,*], Han Gon Choi [a,*]

[a] *College of Pharmacy, Yeungnam University, Gyongsan 712-749, South Korea*
[b] *Hanmi Pharmaceutical Company Limited, Hanmi Pharma Co., South Korea*
[c] *School of Textiles, Yeungnam University, Gyongsan 712-749, South Korea*

Received 24 January 2007; received in revised form 5 April 2007; accepted 17 May 2007
Available online 21 May 2007

Abstract

Ibuprofen–Poloxamer 188 (P 188) binary solid dispersions (SD) with different drug loadings were prepared, characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR), and evaluated for solubility, in vitro release, and oral bioavailability of ibuprofen in rats. Loss of their individual surface properties during melting and solidification as revealed by SEM micrographs indicated the formation of effective SDs. Absence or shifting towards the lower melting temperature of the drug peak in SDs and physical mixtures in DSC study indicated the possibilities of its interactions with P 188. However, no such interactions in the solid state were confirmed by FTIR spectra which showed the presence of drug crystalline in SDs. Immediate and complete release of ibuprofen from SDs might be because of the reduction in the drug crystalline due to eutectic formation, and their dosing to fasted rats resulted in a significant increase in the area under curve (AUC) of the plasma concentration versus time curve and the maximum plasma concentration (C_{max}), and a significant decrease in the time to reach C_{max} (T_{max}) over ibuprofen and physical mixtures.
© 2007 Elsevier B.V. All rights reserved.

Keywords: Ibuprofen; Solid dispersion; Poloxamer 188; Dissolution; Solubility; Bioavailability

1. Introduction

Ibuprofen (Fig. 1) is a non-steroidal anti-inflammatory drug that has been widely used in the treatment of mild to moderate pain and fever. Ibuprofen serum concentrations and its analgesic effect have been shown to be correlated. Therefore, the rapid ibuprofen absorption could be a prerequisite for the quick onset of its action. Because of high membrane permeability, extent of ibuprofen absorption approaches up to 100%. Dissolution thus becomes the rate limiting step for absorption and the quick release of ibuprofen in the gastrointestinal tract following oral administration is desirable (Laska et al., 1986; Levis et al., 2003; Matthias et al., 2005). Various formulations such as prodrugs (Murtha and Ando, 1994), inclusion complexes (Ghorab and Adeyeye, 2001), microcapsules (Adeyeye et al., 1994), etc. of ibuprofen were developed. However, the dissolution rate and the oral bioavailability of ibuprofen from these formulations differed widely, methods were time consuming and costly, and some formulations were bulky with poor flow characteristics and handling difficulties.

Solid dispersions (SDs) of many poorly water soluble drugs with hydrophilic carrier matrix have been formulated for improving drug dissolution rate, which can be further improved if such polymers have surface active properties (Serajuddin, 1999; Passerini et al., 2002; Seo et al., 2003). Moreover, SDs may improve the bioavailability of poorly soluble drugs by increasing the drug dissolution rate and their saturation solubility in the gastrointestinal fluids. However, the SDs prepared by high temperature melting, solvent or solvent-melting method, etc. might be problematic because the high melting temperatures could chemically decompose the drugs and/or carriers. Hardening of melts could cause difficulties in pulverization of SDs. Moreover, it may not always be easy to find a common solvent for both

* Corresponding authors. Tel.: +82 53 810 2813; fax: +82 53 810 4654.
E-mail addresses: csyong@ynu.ac.kr (C.S. Yong), hangon@ynu.ac.kr (H.G. Choi).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.05.031

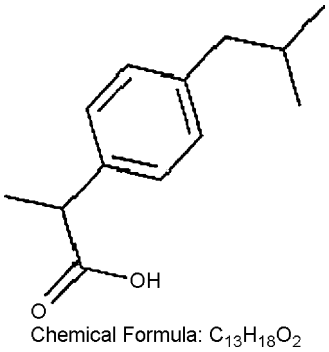

Fig. 1. Structure of ibuprofen.

hydrophobic drug and hydrophilic carrier, and large volumes of solvents and long duration of heating are required to enable complete dissolution of both components. Vacuum drying, spray drying, spraying on sugar beads using a fluidized bed coating system, lyophilization, etc. used for the removal of organic solvents from SDs make them more tedious and costly. Finally, most reports did not address the amount of residual solvents present in SDs when different solvents, carriers or drying techniques were used. They were also associated with various drawbacks such as environmental problems related to the solvents, manufacturing process, scale-up, reproducibility, etc. (Serajuddin, 1999). Therefore, it would be an advantage if the formation of SDs is achieved using a rapid, less expensive and reproducible process (Vilhelmsen et al., 2005).

Melt agglomerations using hot solution of meltable hydrophilic carriers such as polyethylene glycols (PEG), poloxamer 188 (P 188), etc. as a binding solution have been claimed to be advantageous industrially (Passerini et al., 2002; Seo et al., 2003; Vilhelmsen et al., 2005; Kinget and Kemel, 1985; Zhou et al., 1996; Voinovich et al., 2000). SDs by melt agglomeration in high shear mixers have been prepared by the addition of the molten binder containing the drug to the heated excipients (Seo et al., 2003; Kinget and Kemel, 1985) or of the molten binder to a heated mixture of drug and excipients (Passerini et al., 2002; Zhou et al., 1996) or by heating the mixture of the drug, binder and excipients to a temperature within or above the melting range of the binder (Seo et al., 2003; Voinovich et al., 2000). However, these approaches were also associated with many disadvantages. Separate melting of polymer with or without drug was an extra step that could make the process complicated and costly, and the entire amount of drug used in preparation was not always in the dissolved state in polymer solution or formulation mix. Moreover, the yield in many cases was low because of the polymer/drug loss while pouring into the powder mix, and the processes were very much similar to the wet granulation method used in tablet manufacturing process, thus making them relatively more expensive in terms of time and technology. Although drying was not needed, in many cases, the improvement in the drug dissolution was lower compared to SDs of similar composition prepared by the melting method. In addition, the use of inert fillers such as lactose, etc. might increase the bulk and price of the formulations (Passerini et al., 2002; Seo et al., 2003; Vilhelmsen et al., 2005; Kinget and Kemel, 1985; Zhou et al., 1996; Voinovich et al., 2000).

Poloxamers are polyoxyethylene–polypropylene block copolymer nonionic surfactants that have been widely used as wetting and solubilizing agents, and surface adsorption excipients (Collett and Popli, 2000). They have been employed to enhance the solubility, dissolution and bioavailability of many poorly water soluble drugs including ibuprofen using various techniques including melting agglomeration, and melting (Passerini et al., 2002; Seo et al., 2003; Chen et al., 2004; Rouchotas et al., 2000; Yu et al., 2007). For some drugs, the improvement in solubility using poloxamers was higher compared to the other meltable polymers such as PEGs or complex forming agents such as cyclodextrins (Chutimaworapan et al., 2000). P 188 is empirically selected to prepare SDs because of its low melting point (about 56–57 °C), surfactant properties and oral safety. In this study, low temperature melting method will be used to prepare immediate release ibuprofen–P 188 SDs, which will be evaluated for their in vitro and in vivo performances.

2. Materials and methods

2.1. Materials

Ibuprofen was supplied from Dong-A Pharm. Co. Ltd. (Anyang, South Korea) and P 188 was purchased from BASF Aktiengesellschaft (Ludwigshafen, Germany).

All other chemicals were of reagent grade and used without further purification.

2.2. Solubility of ibuprofen in molten polymer

Hot stage experiments were conducted to determine the solubility of ibuprofen in molten P 188. Fifty grams of P 188 was melted at its melting temperature (56–57 °C) in a glass beaker and 5 g ibuprofen at a time was added into it. The mixture was continuously stirred and the dissolution of ibuprofen in molten P 188 was visually recorded. When the earlier sample was completely dissolved, another 5 g ibuprofen was added and the procedure was repeated until any undissolved ibuprofen was visible.

2.3. Preparation of solid dispersions, and determination of drug content and percent yield

Ibuprofen and P 188 in 4:1, 2:1, 1:1, 1:3, 1:5, 1:7 and 1:10 weight ratios were mixed in a mortar and pestle to obtain a homogeneous physical mixture that was sieved through 40 mesh screen and transferred into a locally designed ointment formulation vessel (Fig. 2). Hot water (90–95 °C) was continuously circulated using a temperature controlled circulating water bath and the resulting clear molten solution was magnetically stirred at 700 rpm. After 10–15 min, the clear solution was cooled by circulating cold water (<4 °C) for about 1 h and the solidified SDs were then ground by using a mortar and pestle, sieved through a 40 mesh screen and stored in a screw capped vial at

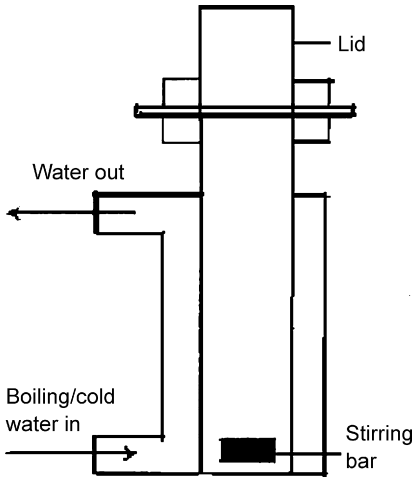

Fig. 2. Locally designed ointment formulation vessel.

room temperature for further use. Drug content was calculated by dissolving SDs equivalent to 20 mg ibuprofen in a suitable quantity of methanol, filtering (0.45 μm, Whatman), suitably diluting with methanol and analyzing by HPLC. Similarly, the percentage yield of each formulation was determined according to the total recoverable final weight of SDs and the total original weights of ibuprofen and P 188 used.

2.4. Scanning electron microscopy

The surface morphology of ibuprofen, P 188, physical mixtures and SDs were examined using a scanning electron microscope (S-4100, Hitachi, Japan). The powders were fixed on a brass stub using double-sided adhesive tape and made electrically conductive by coating in a vacuum ($6P_a$) with platinum (6 nm/min) using Hitachi Ion Sputter (E-1030) for 240 s at 15 mA.

2.5. Determination of solubility

Ibuprofen, physical mixtures or SDs equivalent to 250 mg of ibuprofen were added to 10 ml distilled water (pH adjusted to 6.8 using 20% (v/v) phosphoric acid or 10% (w/v) sodium hydroxide) in screw capped test tubes, vortexed for 2 min and shaken at 25 °C in a temperature controlled water bath (Shaking water bath KMC 12055 WI) for 24 h. Resultant samples containing undissolved SDs suspended in the test medium were centrifuged at 10,000 rpm for 5 min and the clear supernatants obtained were filtered (0.45 μm, Whatman), suitably diluted with distilled water of 25 °C and analyzed by HPLC.

2.6. In vitro ibuprofen release

In vitro release studies of ibuprofen, physical mixture and SDs (equivalent to 10 mg ibuprofen) were performed using United States Pharmacopeia (USP) model digital tablet dissolution test apparatus (Shinseang Instrument Co., South Korea) at the paddle rotation speed of 50 rpm in 900 ml distilled water (pH adjusted to 6.8 using 20% (v/v) phosphoric acid or 10% (w/v) sodium hydroxide) at 37 °C. At the specified times, 0.5 ml samples were withdrawn, filtered (0.45 μm, Whatman) and assayed for ibuprofen content by HPLC. 0.5 ml of fresh distilled water pre-warmed to 37 ± 0.5 °C was replaced into the dissolution medium after each sampling.

2.7. Solubility of ibuprofen in aqueous polymer solutions

To 10 ml of each of 6, 12, 24, 46, and 72 mg/ml solutions of P 188 in distilled water (pH adjusted to 6.8 using 20% (v/v) phosphoric acid or 10% (w/v) sodium hydroxide) in screw capped test tubes, 250 mg ibuprofen was added, vortexed for 2 min and shaken at 25 °C in a temperature controlled water bath for 120 h. This time was previously determined to achieve equilibrium. Resultant samples containing undissolved ibuprofen suspended in the test medium were centrifuged at 10,000 rpm for 5 min and the clear supernatants obtained were filtered (0.45 μm, Whatman), suitably diluted with corresponding P 188 solutions of 25 °C and analyzed by HPLC.

2.8. Differential scanning calorimetry

The DSC measurements were performed on a differential scanning calorimeter (DSC-6100, Seiko Instruments, Japan) with a thermal analyzer. Under nitrogen flow of 25 ml/min, approximately 2 mg of ibuprofen, P 188, their physical mixture, or SDs was placed in a sealed aluminum pan, and heated at a scanning rate of 5 °C/min from 20 °C to 100 °C. An empty aluminum pan was used as reference.

2.9. Fourier transform infrared spectroscopy

The Fourier transform infrared spectroscopy (FTIR) spectra were obtained using FTIR spectrometer-430 (Jasco, Japan). The samples (ibuprofen, P 188, physical mixtures or SDs) were previously ground and mixed thoroughly with potassium bromide, at 1:5 (sample:potassium bromide) weight ratio. The potassium bromide discs were prepared by compressing the powders at a pressure of 5 tonnes for 5 min in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 500 cm^{-1}.

2.10. Pharmacokinetic study

Animals care and the procedures were conducted according to the "Guiding Principles in the Use of Animals in Toxicology" as adopted by the "Society of Toxicology in 1989". The study protocol was approved by the Animal Care and Use Committee of the College of Pharmacy, Yeungnam University.

Twenty rats (250 ± 20 g) were divided into four groups, right femoral artery was cannulated using polyethylene tubing (PE-50, Intramedic®, Clay Adams, Parsi-ppany, NJ, USA) under light ether anesthesia, incisions were covered with wet cotton and the cannula was flushed with 0.1 ml of heparinized normal saline (80 U/ml) to prevent blood clotting. Hard gelatin capsules (Suheung capsule Co. Ltd., Seoul, South Korea) of ibuprofen powder, physical mixture of ibuprofen and P 188, and SDs with drug/polymer ratio of 2:1 and 1:1 equiva-

lent to 25 mg/kg ibuprofen were administered orally and at 0 (pretreatment), 10, 20, 30, 45, 60, 120, 240, and 480 min (post-administration), 0.2 ml of blood samples were collected into sodium EDTA anticoagulant tubes (K3 EDTA Vacutainer®, Becton Dickinson, Meylan, UK), thoroughly mixed and stored at 4 °C till the blood collection was completed. The plasma was separated by centrifuging the blood samples at 3000 rpm for 10 min (5415C, Eppendorf, USA) (Geisslinger et al., 1989).

Plasma (0.05 ml) was mixed with 0.4 ml of acetonitrile solution containing flufenamic acid (5 μg/ml) as an internal standard, centrifuged at 3000 rpm for 10 min to precipitate the proteins and the supernatant layer (0.4 ml) was evaporated in a rotary centrifugal vacuum evaporator. The residue was reconstituted in 50 μl mobile phase and 20 μl of the resulting solution was analyzed by HPLC (Canaparo et al., 2000).

The non-compartmental pharmacokinetic parameters, including AUC, were calculated using the WINNONLIN (Version 1.1, Scientific Consulting Inc., NC, USA) computer program. C_{max} and T_{max} were also obtained from plasma concentration–time profile data. The data from different formulations were compared for statistical significance by one-way analysis of variance (ANOVA). The statistical significance of means among different formulations was then compared by multiple range method of least significant difference (Gibaldi and Perrier, 1982).

2.11. Drug analysis

Ibuprofen concentrations were analyzed by Jasco P987 HPLC system equipped with a Jasco UV detector (UV-975), using Borwin program. HPLC separation was performed with 50 μl injection volume (pharmacokinetic study: 20 μl) on a reverse-phase C18 column (Inertsil GL Science column 5 μm particle size, 4.6 mm × 150 mm). The mobile phase was acetonitrile:phosphate buffer (pH 3.5) (6:4, v/v). The eluent was monitored at 220 nm with a flow rate of 1.2 ml/min (Canaparo et al., 2000).

3. Results

Intrinsic dissolution of ibuprofen in molten P 188 solution was low. However, upon stirring up to 50 g of ibuprofen could completely dissolve in it. This might be due to the viscous nature of the molten polymer and the stirring resulted into a thorough mixing of components. Ibuprofen assay in all SDs was almost 100% and the percentage yield was greater than 97% (data not shown). In scanning electron micrographs (Fig. 3),

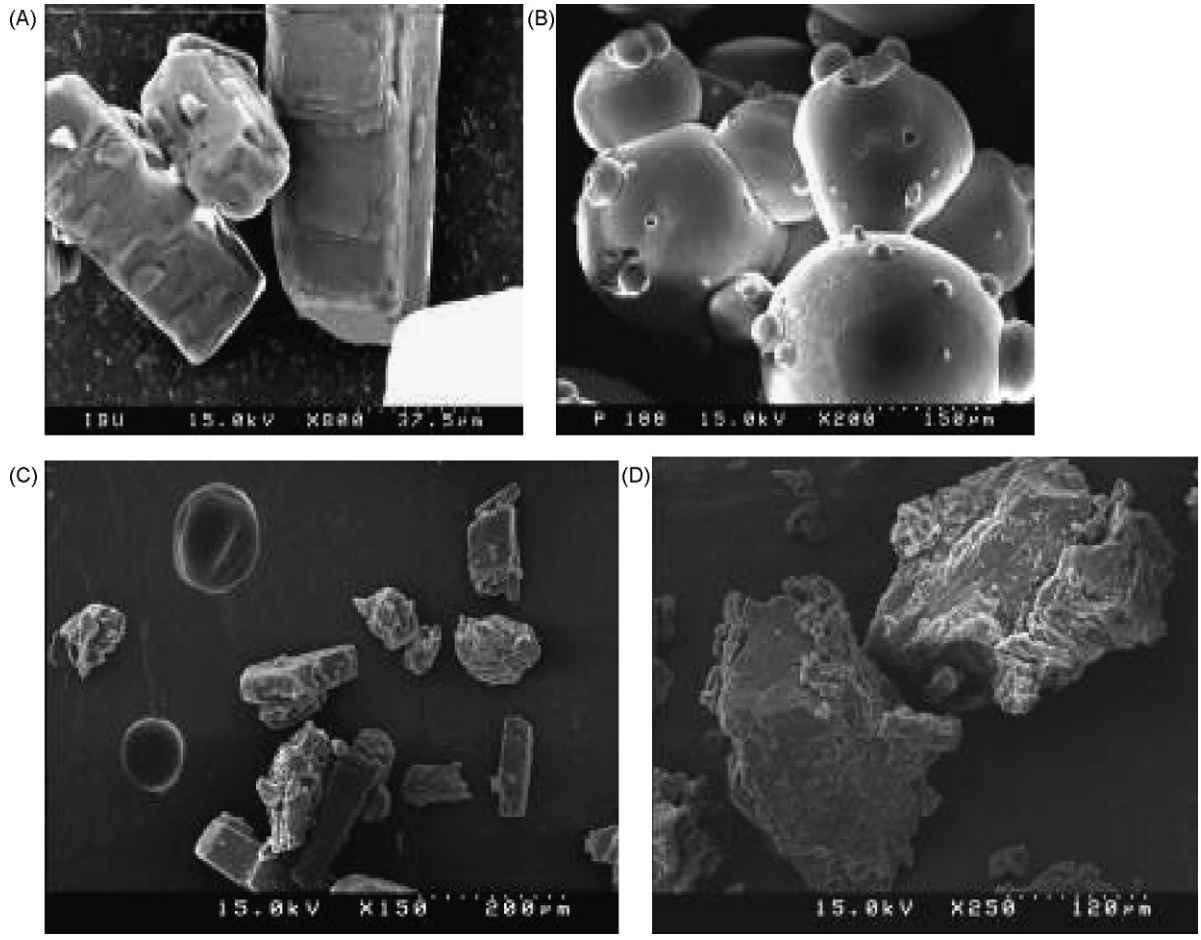

Fig. 3. Scanning electron micrographs: (A) ibuprofen, (B) poloxamer 188, (C) 1:10 (w/w) physical mixtures and (D) 1:10 (w/w) solid dispersions.

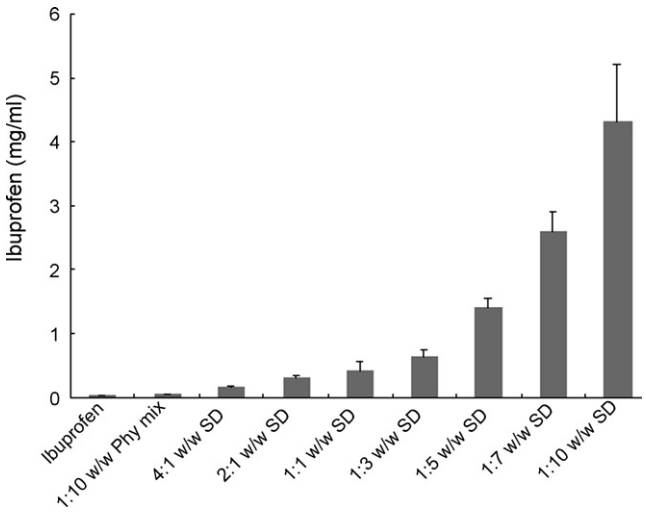

Fig. 4. Solubility of solid dispersions in distilled water (pH 6.8). Data are expressed as mean ± S.D. ($n = 3$).

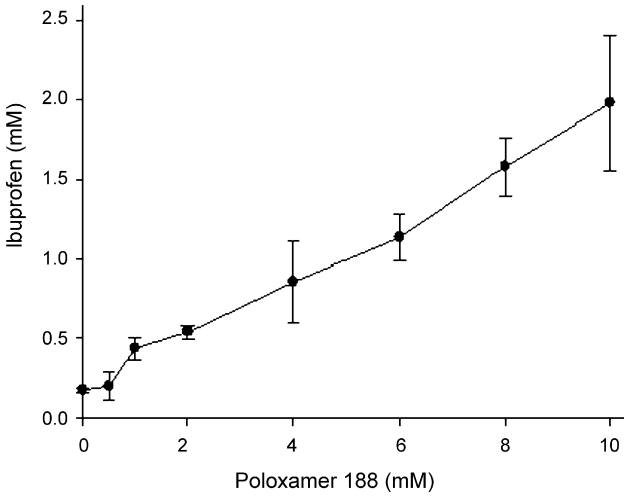

Fig. 6. Phase solubility behavior of ibuprofen at 25 °C in poloxamer 188 solutions in distilled water pH 6.8. Data are expressed as mean ± S.D. ($n = 3$).

ibuprofen appeared as smooth-surfaced rectangular crystalline structures (A) and P 188 as smooth-surfaced spherical particles (B). Physical mixtures contained individual ibuprofen and P 188 particles (C), and SDs appeared as uniform and homogeneously mixed mass with wrinkled surface (D). Preparation of SDs improved the solubility and dissolution rate of ibuprofen. Solubility increased with the increment in the ratio of P 188 in SDs. It was 0.057, 0.17, 0.41, 1.41 and 4.31 mg/ml for 1:10 (w/w) physical mixture, 4:1, 1:1, 1:5 and 1:10 (w/w) SDs, respectively (Fig. 4). Cumulative amount of ibuprofen dissolved from pure ibuprofen was lower compared to SDs and physical mixtures (Fig. 5). At the end of 5 min, approximately 10.28, 20.34, 45.35, 95.31, 99.76 and 99.84% of ibuprofen was released from ibuprofen, 1:10 (w/w) physical mixtures and 4:1, 1:1, 1:5 and 1:10 (w/w) SDs, respectively. Phase solubility study showed that the solubility of ibuprofen linearly increased as the concentration of P 188 increased ($R^2 = 0.9922$) (Fig. 6).

The DSC thermograms (Fig. 7) of ibuprofen showed apparent endothermic peak at 74.86 °C with enthalpy of fusion (ΔH)

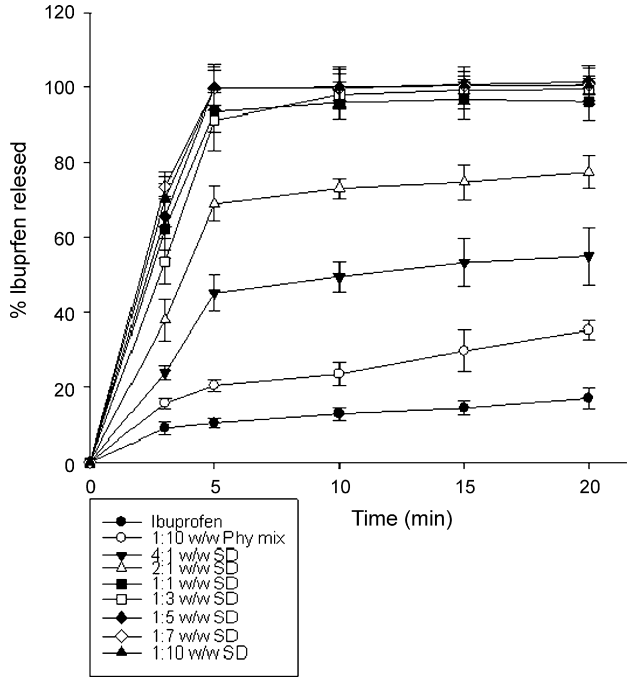

Fig. 5. Dissolution profiles of solid dispersions in distilled water (pH 6.8). Data are expressed as mean ± S.D. ($n = 3$).

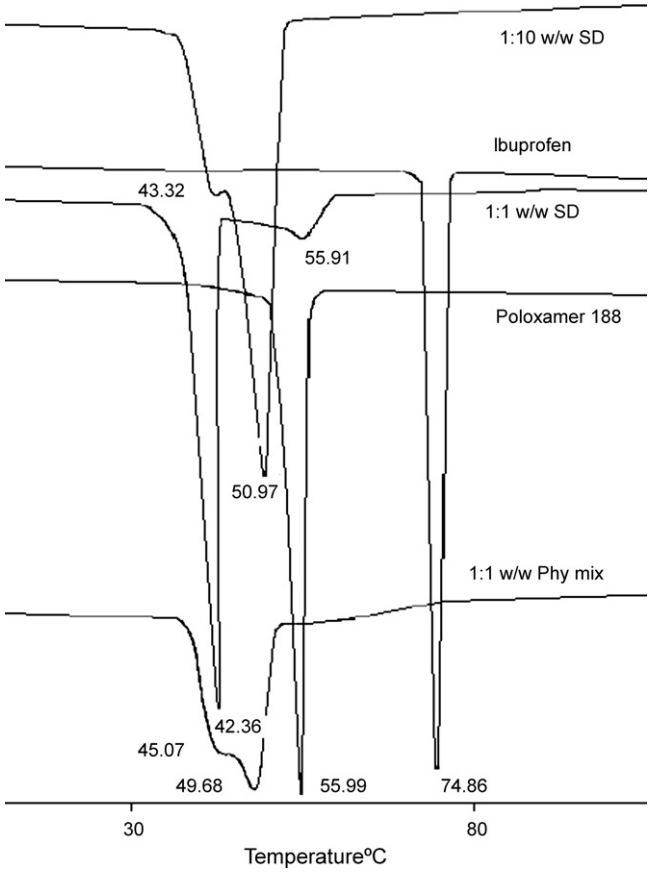

Fig. 7. Differential scanning calorimetric thermograms of ibuprofen, poloxamer 188, physical mixtures and solid dispersions.

129.0 J/g. Similarly, the melting peak of P 188 was observed at 55.99 °C. Sharp ibuprofen peaks as well as P 188 peaks were lost in SDs and physical mixtures. In 1:1 (w/w) SDs, a sharp peak was found at 42.36 °C with enthalpy of fusion (ΔH) 114.7 J/g. Similarly, another broad reduced endothermic peak was observed at 55.91 °C. In 1:10 (w/w) SDs, a small peak was observed at 43.32 °C and a sharp peak was observed at 50.97 °C with enthalpy of fusion (ΔH) 125.3 J/g. 1:1 (w/w) physical mixtures showed a broad peak at 45.07 °C and another sharp peak 49.68 °C with an enthalpy of fusion (ΔH) 93.11 J/g. In FTIR analysis (Fig. 8), the spectrum of pure ibuprofen showed an intense, well-defined infrared band at around 1721 cm^{-1} (carbonyl-stretching of isopropionic acid group) and another spectrum at around 3000 cm^{-1} whereas the P 188 showed characteristic spectra at around 3000 and 1100 cm^{-1}. Spectra of SDs were similar to the addition spectra of individual components. A decrease in the intensity of ibuprofen peak was observed with the increasing amount of P 188 in SDs.

Pharmacokinetic parameters are represented in Table 1 and Fig. 9. The total plasma concentrations of ibuprofen in SDs (in particular, the initial concentrations until 4 h) and physical mixtures were significantly higher compared with those in ibuprofen powder ($P < 0.0009$). Unlike 1:1 (w/w) SDs ($P < 0.002$), the T_{max} values of 2:1 (w/w) SDs and physical mixtures were not significantly different than that of ibuprofen ($P > 0.115$ and $P > 0.346$, respectively). But the AUC and C_{max} of ibuprofen from physi-

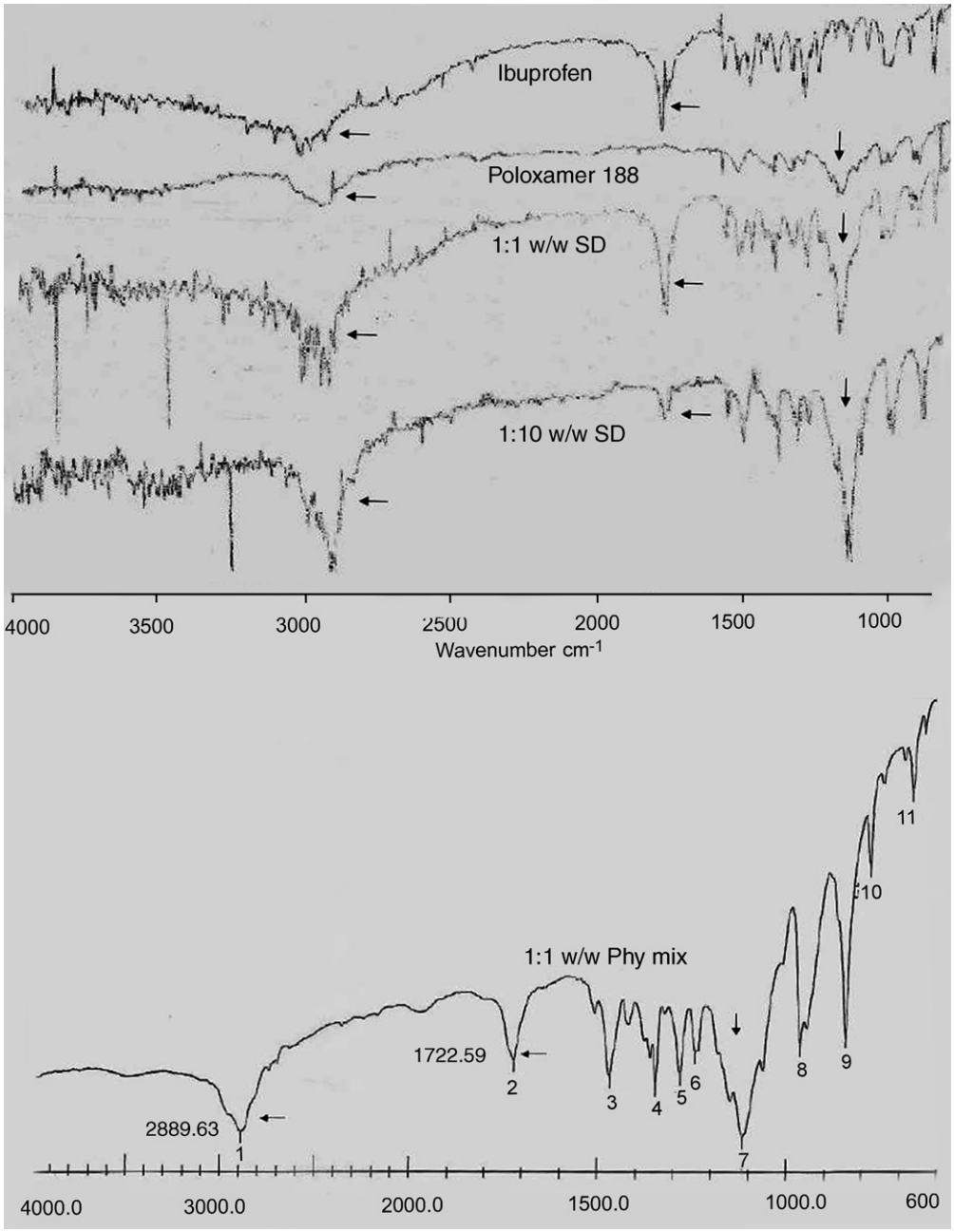

Fig. 8. Fourier transform infrared absorption spectra of ibuprofen, poloxamer 188, physical mixtures and solid dispersions.

Table 1
Pharmacokinetic parameters of ibuprofen delivered by ibuprofen powder, ibuprofen–poloxamer 188 solid dispersions and physical mixtures

Parameter	Ibuprofen	1:10 (w/w) PMs	2:1 (w/w) SD	1:1 (w/w) SD
AUC (h μg/ml)	12.38 ± 8.48	49.59 ± 7.49*	116.41 ± 33.38*	217.41 ± 82.25*
T_{max} (h)	0.749 ± 0.18	0.65 ± 0.14	0.533 ± 0.21	0.366 ± 0.07*
C_{max} (μg/ml)	5.31 ± 3.92	16.15 ± 1.65*	67.49 ± 22.62*	107.80 ± 45.04*
K_{el} (h^{-1})	0.229 ± 0.07	0.18 ± 0.02	0.38 ± 0.08*	0.3817 ± 0.12*
$T_{1/2}$ (h)	3.299 ± 1.01	3.97 ± 0.40	1.79 ± 0.30*	1.957 ± 0.57*

Data are expressed as mean ± S.D. ($n = 5$). Each value represents the mean ± S.D. ($n = 5$).
* P value <0.03, compared with ibuprofen powder.

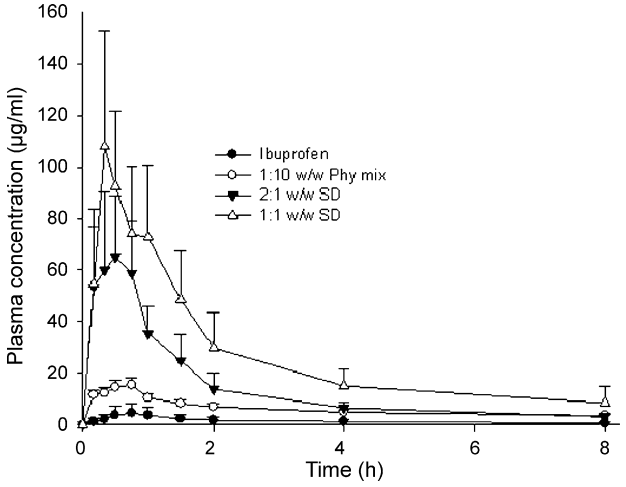

Fig. 9. Plasma concentration–time profiles of ibuprofen after oral administration of ibuprofen powder, physical mixtures, and solid dispersions equivalent to 25 mg/kg ibuprofen in rats. Data are expressed as mean ± S.D. ($n = 5$).

cal mixtures and SDs were significantly increased ($P < 0.001$). Similarly, the elimination rate constant (K_{el}) and half-life ($T_{1/2}$) values of ibuprofen from SDs were also significantly different compared to ibuprofen powder ($P < 0.05$).

4. Discussion

SD preparation was relatively simple and the cooled masses of SDs were frangible enough to be ground easily. This could be an advantage from industrial aspects because the pulverization of dispersions was one of the major problems encountered in melting, solvent and solvent-melting methods. Moreover, this method was relatively more feasible to prepare ibuprofen–P 188 SDs because of their low melting points, the ease in controlling the processing variables such as temperature and shearing rate, and the short duration of preparation (about 1–2 h). In addition, the results were reproducible with relatively higher percentage yields. Thus, this method avoids the disadvantages of other solid dispersion techniques described above for ibuprofen. The scale-up could possibly be carried out in a larger ointment formulation plant that could be designed in various ways. Water heating could be replaced by electric heating system and cooling step could be further simplified by making a provision for an extra valve on the bottom of the vessel so that the cold water could be circulated without detaching/changing the pipelines. Drug content analysis indicated that the ibuprofen was uniformly distributed in SDs and the higher yield showed relatively lower process loss. SEM pictures suggested that the individual surface properties of P 188 and ibuprofen were lost during melting and solidification indicating the formation of effective SD system. Hence, if the conversion of poorly water soluble ibuprofen into solubility improved granules of appropriate sizes is the sole aim, this method could possibly be relatively easy, simple, quick, inexpensive, and reproducible.

Enhanced solubility and dissolution rate of ibuprofen from physical mixtures could be correlated to the chemical structure of highly water soluble P 188. Arrangement of ethylene oxide (EO) and propylene oxide (PO) blocks in P 188 results in an amphiphilic structure, which has the properties to self-assemble into micelles in aqueous solution (Kabanov et al., 2002); the hydrophobic core (PO block) can act as reservoir for the drug, while the hydrophilic portion (EO) acts as interface between the aqueous medium and the drug. At low concentrations, approximating those at which more conventional nonionic detergents form micelles, the poloxamer monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentration, these monomolecular micelles associate to form aggregates of varying size, which have the ability to solubilize drugs and to increase the stability of solubilized agents (Jones and Leroux, 1999). Solubilization is likely to occur through the following mechanism. In the dry state, drug particles were in close contact or adhered to the polymer particles as a result of mixing (shown by SEM). When the mixture came in contact with water, the polymer particles might have hydrated rapidly into polymer solution solubilizing the adjacent drug particles and subsequently releasing the drug into the medium (Chen et al., 2004). This could also possibly explain the higher solubility of drug in phase solubility study where the ibuprofen particles were already dispersed in aqueous polymer solutions. Enhanced solubility and dissolution rate of ibuprofen from physical mixtures could possibly be because of the combined action of the surface activity, solubilization and wetting effect of P 188 (Passerini et al., 2002, 2006; Seo et al., 2003; Chen et al., 2004; Rouchotas et al., 2000; Yu et al., 2007; Chutimaworapan et al., 2000; Shin and Cho, 1997).

Many dissolution studies concerning ibuprofen have been performed using dissolution mediums containing a small amount of acids or surfactants which may accelerate its dissolution rate by their wetting, micellar solubilization, and/or deflocculation properties. But, the conclusion of its increased dissolution from improved formulations may not always be justified until its dissolution in pure water is carried out as a control.

It has also been reported that a biowaiver for immediate release ibuprofen solid oral dosage form is scientifically justified, provided that the dosage form is rapidly dissolving (85% in 30 min or less) in pH 6.8 (Potthast et al., 2005). Hence, the solubility and dissolution tests were performed in distilled water (pH adjusted to 6.8 using 20% (v/v) phosphoric acid or 10% (w/v) sodium hydroxide). In this study, immediate and complete release of ibuprofen was achieved at the paddle speed of 50 rpm in above dissolution medium.

Although the methods such as DSC, X-ray powder diffraction (XRD) or hot stage microscopy have been employed to answer how the drug is dispersed within the matrix, in most of the cases, it was difficult to say whether the drug was present as a molecular, a crystalline particulate or an amorphous particulate dispersion.

Techniques such as FTIR, Raman spectroscopy or solid state nuclear magnetic resonance (NMR) have been employed in addition to the DSC, XRD or hot stage microscopy to study the nature of the molecular interactions between the drug and the carrier systems (Matsumoto and Zografi, 1999; Forster et al., 2001; Craig, 2002). In this study, the characterization of SD was done by DSC and FTIR to understand the possible mechanisms of improved dissolution. Absence or shifting towards the lower melting temperature of the drug peak in SDs and physical mixtures in DSC study indicated the possibilities of interactions between ibuprofen and P 188. For a binary solid system such as a crystalline drug which usually has a higher melting temperature than a crystalline polymer, the drug must be soluble in the molten polymer at the melting temperature of the polymer or vice versa in order for the system to be eutectic (Carstensen, 2001). In order to have a high solubility for the drug in a molten polymer, the drug molecule should have a weak affinity to the crystalline drug and/or a strong affinity to the molten polymer. Solids with low melting temperatures have weak affinity in solid state. Therefore, a drug having low melting temperatures will have high solubility in the molten polymer. Consequently, this drug and the polymer will form a eutectic system (Sudha et al., 2007; Devalina et al., 2002). Because of low melting temperature, ibuprofen was highly soluble in molten P 188 at any given temperature and is expected to form a strong eutectic relative to other compounds having higher melting temperature. Ibuprofen has been reported to form eutectics with PEGs and P 188 (Passerini et al., 2002; Sudha et al., 2007; Devalina et al., 2002; Yong et al., 2005). According to Tamman's rule (Savchenko, 1959) at eutectic composition, the low melting component of a eutectic mixture forms the major phase. Moreover, it has been noted that when melts with eutectic composition are cooled, the two phases begin to crystallize spontaneously and proceeds with the minor phase of the eutectic growing in the interstitial spaces of the primary phase. This process leads to a marked reduction in particle size of the minor component (Podolinsky and Taran, 1981). A drug with lower melting temperature should have a higher eutectic composition and lower eutectic temperature. When the drug has the similar melting temperature as the polymer, the eutectic composition of the system approaches 50% (w/w) (Sudha et al., 2007). Many earlier studies have reported that ibuprofen forms eutectic composition with many polymers at around 35% (w/w) concentration in the mixture. The ibuprofen:poloxamer 188 ratio at eutectic composition was 35:65 (w/w) (Passerini et al., 2002). Hence, as long as the amount of ibuprofen in the dispersion is less than 35% (w/w) (as in the case of 1:10 (w/w) SD), all of it should be present as a eutectic mixture (the small peak at 43.32). The consistent dissolution profile obtained above or below the eutectic point (in 1:1–1:10 (w/w) SDs) implies that the eutectic point may not determine the upper limit for drug loading in ibuprofen–P 188 SDs prepared by this method. Since P 188 has a melting point lower than ibuprofen, it is likely that at the eutectic composition, P 188 is the major phase and P 188-ibuprofen eutectic crystallization have a well-defined microstructure with a reduction in drug particle size (Passerini et al., 2002; Devalina et al., 2003).

The DSCs of SDs and physical mixtures (PMs) exhibited two endothermic events. The peak at 42.36 °C of 1:1 (w/w) SD, at 45.07 °C of PMs and at 43.32 °C of 1:10 SDs is possibly the melting endotherm of eutectic. After the eutectic has melted, the solid phase suspended in the liquid melt might possibly be ibuprofen (whose concentration was above the eutectic composition in 1:1 (w/w) SDs and PMs), which melted to produce the second peak, the reduced broad fusion peaks at 55.91 in 1:1 (w/w) SD and 49.68 °C in PMs. The 1:10 (w/w) SDs the second peak at 50.97 °C could represent the melting of P 188, the major phase in this case (Bowden, 1938; Vasil'ev, 1964). Although the complete miscibility of ibuprofen and P 188 in the liquid phase indicates polymer–drug interaction at elevated temperatures and the ibuprofen can act as a hydrogen bond acceptor or donor, FTIR study showed no specific interactions between ibuprofen and P 188. Hence, the low melting points for ibuprofen could partially explain the formation of eutectics with P 188.

Since the principal aim of this work was to formulate fast releasing ibuprofen preparations and to evaluate their in vitro and in vivo performances, in-depth mechanism of eutectic formation was not studied and exact eutectic composition was not determined by constructing phase diagrams of ibuprofen–P 188 binary mixtures. The fact that ibuprofen–P 188 SD systems were completely miscible in the liquid state and immiscible in the solid state indicates that they might have crystallized out simultaneously as micro-fine crystals from the molten mixture resulting into increased ibuprofen surface area playing an important role for enhanced dissolution rate (Passerini et al., 2002; Seo et al., 2003; Bloch and Speiser, 1987). So, the enhancement of dissolution from the solid dispersions may be attributed partly to the reduction in particle size in ibuprofen crystalline due to the formation of eutectic system with P 188. The similarity in the dissolution profiles of 1:1–1:10 (w/w) SDs could indicate that along with eutectic formation, combination of other factors such as surface activity, wetting, solubilization effect of P 188 might have affected in ibuprofen solubilization and dissolution. In case of SDs where the drug concentration exceeded the eutectic composition, improved solubility and dissolution might be partly due to the enhanced dissolution of the non-eutectic portion of drug in the solid dispersion through mechanisms including reduced agglomeration, increased solubility and melting point depression of drug by the polymer, etc. In FTIR analysis, the absence

of major shift in the peak positions, retention of drug peak and the equivalent addition spectra (of ibuprofen and P 188) for SDs and physical mixtures suggested the absence of interactions in the solid state between P 188 and the ibuprofen. Presence of the stretching vibration of ibuprofen carbonyl peak at 1721 cm^{-1} in SDs and physical mixtures indicates that the drug crystalline form may not be altered during solid dispersion formation and its attenuated intensity could be due to the lower drug content. This observation fits well to the previous studies where poloxamers and ibuprofen were found to be primarily crystalline (Passerini et al., 2002; Vilhelmsen et al., 2005).

In pharmacokinetic study, ibuprofen was more readily available from SDs than from pure ibuprofen or physical mixtures containing high proportions of P 188. Since ibuprofen–P 188 simple physical mixtures showed remarkably improved water solubility, its pharmacokinetic profile was compared to that of SDs and pure ibuprofen. However, the ibuprofen being a high dose drug (200–600 mg), SDs with higher P 188 load would be impractical. Although the solubility of 1:1 (w/w) SD was lower than 1:10 (w/w) SDs, their dissolutions profiles were similar and the drug loading had no effect in ibuprofen dissolution above 1:1 (w/w) ratio. Hence, 1:1 and 2:1 (w/w) solid dispersion were compared with 1:10 (w/w) physical mixture to evaluate the effect of simple increment of P 188 (as a physical mixture) in formulation on pharmacokinetic profile of ibuprofen. Pharmacokinetic profiles of ibuprofen from 1:10 (w/w) physical mixtures implied that the absorption of ibuprofen from 1:1 (w/w) or 2:1 (w/w) physical mixtures would be further lower and hence were not included in pharmacokinetic study. Since the ibuprofen serum concentrations and its analgesic effect are correlated, rapid ibuprofen absorption is a prerequisite for the quick onset of its action. Because of its high membrane permeability, dissolution rate of ibuprofen formulation is the rate limiting step for ibuprofen absorption. The significantly higher AUC and C_{max}, and the earlier T_{max} for ibuprofen from SDs indicated the higher extent of absorption for SDs because of their improved dissolution rate in rat intestine.

5. Conclusion

Solubility and dissolution rate of ibuprofen were enhanced by preparing ibuprofen–P 188 SDs in relatively easy, simple, quick, inexpensive, and reproducible manner using low temperature melting method. Immediate release of free ibuprofen from SDs resulted into rapid absorption and improved bioavailability compared to pure ibuprofen. Preliminary results from this work suggested that the preparation of immediate release ibuprofen solid dispersion by low temperature melting method using poloxamer 188 as a meltable hydrophilic polymer carrier could be a promising approach to improve solubility, dissolution and absorption rate of ibuprofen.

Acknowledgements

This research was supported by the Regional R&D Cluster Project designated by the Ministry of Science and Technology & the Ministry of Commerce, Industry, and Energy (2006) and financially supported by the Ministry of Science and Technology (F104AA010008-06A0101-00810) in Korea.

References

Adeyeye, C.M., Price, J.C., 1994. Development and evaluation of sustained-release ibuprofen-wax microspheres. II. In vitro dissolution studies. Pharm. Res. 11, 575–579.

Bloch, D.W., Speiser, P.P., 1987. Solid dispersions—fundamentals and examples. Pharm. Acta Helv. 62, 23–27.

Bowden, S.T., 1938. The Phase Rule and Phase Reactions: Theoretical and Practical. Mac-Millan Press, London.

Canaparo, R., Muntoni, E., Zara, G.P., Della, P.C., Berno, E., Costa, M., Eandi, M., 2000. Determination of Ibuprofen in human plasma by high-performance liquid chromatography: validation and application in pharmacokinetic study. Biomed. Chromatogr. 14, 219–226.

Carstensen, J.T., 2001. Melting point diagrams and eutectics. In: Advanced Pharmaceutical Solids. Marcel Dekker Inc., New York, pp. 170–189.

Chen, Y., Zhang, G.G.Z., Neilly, J., Marsh, K., Mawhinney, D., Sanzgiri, Y.D., 2004. Enhancing the bioavailability of ABT-963 using solid dispersion containing pluronic F-68. Int. J. Pharm. 286, 69–80.

Chutimaworapan, S., Ritthidej, G.C., Yonemochi, E., Oguchi, T., Yamamoto, K., 2000. Effect of water soluble carriers on dissolution characteristics of nifedipine solid dispersions. Drug Dev. Ind. Pharm. 26, 1141–1150.

Collett, J.H., Popli, H., 2000. Poloxamer. In: Kibbe, A.H. (Ed.), Handbook of Pharmaceutical Excipients, 3rd ed. Pharmaceutical Press, London, pp. 385–388.

Craig, D.Q.M., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 231, 131–144.

Devalina, L., Weili, W., Eric, A.S., Yihong, Q., Steven, L.K., James, J.F., 2003. Properties of rapidly dissolving eutectic mixtures of poly(ethylene glycol) and fenofibrate: the eutectic microstructure. J. Pharm. Sci. 92, 505–515.

Devalina, L., Weili, W., Eric, A.S., Michelle, A.L., 2002. Prediction of poly(ethylene)glycol-drug eutectic compositions using an index based on the van't Hoff equation. Pharm. Res. 19, 315–321.

Forster, A., Hempenstall, J., Rades, T., 2001. Characterisation of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. J. Pharm. Pharmacol. 53, 57–66.

Geisslinger, G., Dietzel, K., Bezler, H., Nuernberg, B., Brune, K., 1989. Therapeutically relevant differences in the pharmacokinetical and pharmaceutical behavior of ibuprofen lysinate as compared to ibuprofen acid. Int. J. Clin. Pharmacol. Ther. Toxicol. 27, 324–328.

Ghorab, M.K., Adeyeye, M.C., 2001. Enhancement of ibuprofen, dissolution via wet granulation with beta-cyclodextrin. Pharm. Dev. Technol. 6, 305–314.

Gibaldi, M., Perrier, D., 1982. Pharmacokinetics, 2nd ed. Marcel Dekker Inc., New York.

Jones, M.C., Leroux, J.C., 1999. Polymeric micelles—a new generation of colloidal drug carriers. Eur. J. Pharm. Biopharm. 48, 101–111.

Kabanov, K.V., Batrakova, E.V., Alakhov, V.Y., 2002. Pluronic block copolymers as novel polymer therapeutics for drug and gene delivery. J. Contr. Rel. 82, 189–212.

Kinget, R., Kemel, R., 1985. Preparation and properties of granulates containing solid dispersions. Acta Pharm. Technol. 31, 57–62.

Laska, E.M., Sunshine, A., Marrero, I., Olson, N., Siegel, C., McCormick, N., 1986. The correlation between blood levels of ibuprofen and clinical analgesic response. Clin. Pharmacol. Ther. 40, 1–7.

Levis, K.A., Lane, M.E., Corrigan, O.I., 2003. Effect of buffer media composition on the solubility and effective permeability coefficient of ibuprofen. Int. J. Pharm. 6, 49–59.

Matsumoto, T., Zografi, G., 1999. Physical properties of solid molecular dispersions of indomethacin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-*co*-vinylacetate) in relation to indomethacin crystallization. Pharm. Res. 16, 1722–1728.

Matthias, K., Arne, R., Stefan, S., Dirk, T., Chris, S., Bernd, L., Gunther, B., 2005. Ibuprofen extrudate, a novel, rapidly dissolving ibuprofen formulation: relative bioavailability compared to ibuprofen lysinate and regular ibuprofen, and food effect on all formulations. J. Clin. Pharmacol. 45, 1055–1066.

Murtha, J.L., Ando, H.Y., 1994. Synthesis of the cholesteryl ester prodrugs cholesteryl ibuprofen and cholesteryl flufenamate and their formulation into phospholipid microemulsions. J. Pharm. Sci. 83, 1222–1228.

Passerini, N., Albertini, B., Perissutti, B., Rodriguez, L., 2006. Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel. Int. J. Pharm. 318, 92–102.

Passerini, N., Gonzalez-Rodriguez, M.L., Cavallari, C., Rodriguez, L., Albertini, B., 2002. Preparation and characterisation of ibuprofen–poloxamer 188 granules obtained by melt granulation. Eur. J. Pharm. Sci. 15, 71–78.

Podolinsky, V.V., Taran, Y.N., 1981. Influence of adsorption on structure formation in eutectic systems. J. Cryst. Growth 52, 82–87.

Potthast, H., Dressman, J.B., Junginger, H.E., Midha, K.K., Oeser, H., Shah, V.P., Vogelpoel, H., Barends, D.M., 2005. Biowaiver monographs for immediate release solid oral dosage forms: ibuprofen. J. Pharm. Sci. 94, 2121–2131.

Rouchotas, C., Cassidy, O.E., Rowley, G., 2000. Comparison of surface modification and solid dispersion techniques for drug dissolution. Int. J. Pharm. 195, 1–6.

Savchenko, P.S., 1959. The nature of eutectics. Russ. J. Inorg. Chem. 4, 186–189, 3.

Seo, A., Holm, P., Kristensen, H.G., Schæfer, T., 2003. The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. Int. J. Pharm. 259, 161–171.

Serajuddin, A.T.M., 1999. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci. 88, 1058–1066.

Shin, S.C., Cho, C.W., 1997. Physicochemical characterizations of piroxicam-poloxamer solid dispersion. Pharm. Dev. Technol. 2, 403–407.

Sudha, R.V., Zeren, W., Stefanie, H., Steven, L.K., 2007. Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. J. Pharm. Sci. 96, 294–304.

Vasil'ev, M.E., 1964. Classification of the phase diagrams of binary metallic systems according to atomic interaction forces. Russ. Phys. Chem. 38, 473–476.

Vilhelmsen, T., Eliasen, H., Schæfer, T., 2005. Effect of a melt agglomeration process on agglomerates containing solid dispersions. Int. J. Pharm. 303, 132–142.

Voinovich, D., Moneghini, M., Perissutti, B., Filipovic-Grcic, J., Grabnar, I., 2000. Preparation in high-shear mixer of sustained-release pellets by melt pelletisation. Int. J. Pharm. 203, 235–244.

Yong, C.S., Lee, M.K., Park, Y.J., Kong, K.H., Xuan, J.J., Kim, J.H., Kim, J.A., Lyoo, W.S., Han, S.S., Rhee, J.D., Kim, J.O., Yang, C.H., Kim, C.K., Choi, H.G., 2005. Enhanced oral bioavailability of ibuprofen in rats by poloxamer gel using poloxamer 188 and menthol. Drug Dev. Ind. Pharm. 31, 615–622.

Yu, H., Chun, M.K., Choi, H.K., 2007. Preparation and characterization of piroxicam/poloxamer solid dispersion prepared by melting method and solvent method. J. Kor. Pharm. Sci. 37, 1–5.

Zhou, F., Vervaet, C., Remon, J.P., 1996. Matrix pellets based on the combination of waxes, starches and maltodextrins. Int. J. Pharm. 133, 155–160.