Drug Development and Industrial Pharmacy, 34:1013–1021, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701744095

informa
healthcare

Enhanced Dissolution of Ibuprofen Using Solid Dispersion with Polyethylene Glycol 20000

Madhuri Newa, Krishna Hari Bhandari, Dong Xun Lee, Jung Hoon Sung, Jung Ae Kim, Bong Kyu Yoo, Jong Soo Woo, Han Gon Choi, and Chul Soon Yong
College of Pharmacy, Yeungnam University, Kyungsan, Kyungbuk, South Korea

To improve its dissolution, ibuprofen solid dispersions (SDs) were prepared in a relatively easy and simple manner, characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR), and evaluated for solubility and in vitro drug release. Loss of individual surface properties during melting and re-solidification as revealed by SEM micrographs indicated the formation of effective SDs. Absence or shifting toward the lower melting temperature of the drug peak in SDs in DSC study indicated the possibilities of drug–polymer interactions. FTIR spectra showed the presence of drug crystalline in SDs. The effect of improved dissolution on the oral absorption of ibuprofen in rats was also studied. Quicker release of ibuprofen from SDs in rat intestine resulted in a significant increase in AUC and C_{max}, and a significant decrease in T_{max} over pure ibuprofen. Preliminary results from this study suggested that the preparation of fast dissolving ibuprofen SDs by low-temperature melting method using polyethylene glycol 20000 as a meltable hydrophilic polymer carrier could be a promising approach to improve solubility, dissolution, and absorption rate of ibuprofen.

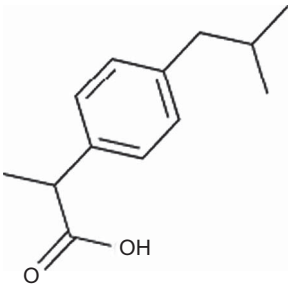
Keywords ibuprofen; solid dispersions; polyethylene glycol 20000; solubility; dissolution; bioavailability

INTRODUCTION

Ibuprofen (Figure 1) is a non-steroidal anti-inflammatory drug that has been widely used in the treatment of mild to moderate pain and fever. As its serum concentrations and pharmacological effect are correlated, rapid ibuprofen absorption is a prerequisite for the quick onset of its analgesic action. Because of its high membrane permeability, its dissolution from the dosage forms is the rate-limiting step for its absorption. However, ibuprofen dissolves slowly because of its low water solubility. Thus, the improvement of ibuprofen dissolution for its quicker release in its absorption site in the gastrointestinal tract following oral administration is desirable (Laska et al., 1986). Various formulations such as prodrugs (Murtha & Ando, 1994), inclusion complexes (Ghorab & Adeyeye, 2001), microcapsules (Adeyeye & Price, 1994) of ibuprofen were developed to improve its dissolution rate. 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 poorly water-soluble drugs in hydrophilic carrier matrix have been reported to improve their solubility and dissolution rate (Passerini, Gonzalez-Rodriguez, Cavallari, Rodriguez, & Albertini, 2002; Seo, Holm, Kristensen, & Schæfer, 2003; Serajuddin, 1999). However, ibuprofen SDs using solvent or solvent-melting method could be problematic because, it might not be always easy to find a common solvent, large volumes of solvents and long duration of heating might be necessary to enable complete dissolution of both components, and the common methods such as vacuum drying, spray-drying, spraying on sugar beads using a fluidized bed-coating system and lyophilization used for the removal of organic solvents from SDs could make the process relatively more complicated, tedious, and costly. In addition, they might also associate with the solvent-related environmental problems (Seo et al., 2003). Although SDs by melting could be problematic (for drugs with higher melting temperature) because of the possible thermal instability of the components, and the hardening of melts resulting in difficulties in the pulverization for subsequent formulation, in case of ibuprofen because of its low melting temperature, melting at lower temperature using meltable hydrophilic polymers might be feasible. However, the traditional melting methods have been reported to be associated with many processing difficulties such as the temperature and shear rate control, reproducibility, scalability. Although for many drugs including ibuprofen, SDs by melt agglomerations in high shear mixers using a hot solution of meltable hydrophilic carriers as a binding solution have been

Address correspondence to Han Gon Choi and Chul Soon Yong, College of Pharmacy, Yeungnam University, 214-1, Dae-Dong, Gyongsan 712-749, South Korea. E-mail: hangon@ynu.ac.kr; csyong@ynu.ac.kr



Chemical formula: $C_{13}H_{18}O_2$

FIGURE 1. Structure of ibuprofen.

claimed to be advantageous industrially (Passerini et al., 2002; Seo et al., 2003; Vilhelmsen, Eliasen, & Schæfer, 2005), they were also associated with many disadvantages such as separate melting of polymer with or without drug as an extra step that could make the process complicated and costly. In addition, the yield in many cases was low because of the polymer/drug loss while pouring into the powder mix. Also, the processes themselves were very much similar to the wet granulation method used in tablet-manufacturing process, thus making them relatively more demanding in terms of time and technology. Although the drying was not needed, in many cases, the improvement in the drug dissolution was lower compared with the SDs of equivalent composition prepared by melting method. In addition, the use of inert fillers such as lactose increased the bulk and the price of these formulations (Passerini et al., 2002; Seo et al., 2003; Vilhelmsen et al., 2005). Therefore, it would be an advantage if the formation of ibuprofen SDs could be achieved using a rapid, less-expensive, controllable, and reproducible process (Vilhelmsen et al., 2005).

PEGs are semicrystalline polymers that have been used extensively in the SD preparation for their wetting, solubilizing and surface-active properties (Craig, 1990). They have been reported to enhance the solubility, dissolution, and bioavailability of many poorly water-soluble drugs using various techniques including melting agglomeration, and melting. Although the polyethylene glycols are non-toxic and used in variety of oral products, the extent of their absorption appears to be dependent on the molecular weight, such that more complete absorption has been reported for the lower weight polyethylene glycols, whereas absorption is much more limited in the case of the higher molecular weight polyethylene glycols. In this study, low temperature melting method was used to prepare ibuprofen-polyethylene glycol 20000 (PEG 20000) SDs in a relatively easy, simple, quick, inexpensive, and reproducible manner, and SDs were evaluated for their in vitro and in vivo performances. PEG 20000 was empirically selected as a meltable polymer for its low melting point, surfactant properties, and oral safety (Craig, 1990; Passerini et al., 2002; Seo et al., 2003; Serajuddin, 1999; Vilhelmsen et al., 2005).

MATERIALS AND METHODS

Materials

Ibuprofen was supplied by Yuhan research Institute, South Korea, and PEG 20000 was purchased from Fluka Biochemika, Germany. All other chemicals were of reagent grade and used without further purification.

Solubility of Ibuprofen in Molten Polymer

About 50 g of PEG 20000 was melted (63–64°C) in a glass beaker and 5 g of ibuprofen at a time was added into it. The mixture was continuously stirred, and the dissolution of ibuprofen in molten PEG 20000 was visually recorded. When the earlier sample was completely dissolved, another 5 g of ibuprofen was added and the procedure was repeated until any undissolved ibuprofen was visible.

Preparation of SDs, and Determination of Drug Content and Percent Yield

Ibuprofen and PEG 20000 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 (PM) that was sieved through 40 mesh screens and transferred into a locally designed ointment formulation vessel (Figure 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 an hour and the solidified SDs were

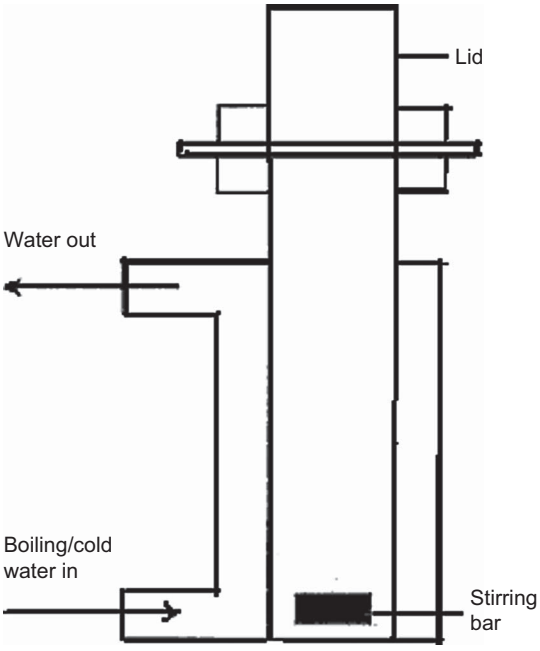


FIGURE 2. Locally designed formulation vessel.

then ground by using a mortar and pestle, sieved through a 40-mesh screen and stored in a screw-capped vial at room temperature for further use. Drug content was calculated by dissolving SDs equivalent to 20 mg ibuprofen in a suitable quantity of methanol, filtering (0.20 μm), suitably diluting with methanol, and analyzing using high-performance liquid chromatograph (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 PEG 20000 used.

Scanning Electron Microscopy

The surface morphology of Ibuprofen, PEG 20000, PMs, and SDs were examined using an SEM (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.

Determination of Solubility

Ibuprofen, PMs, or SDs equivalent to 250 mg of ibuprofen were added to 10 mL phosphate buffer pH 6.8 (PB) in test tubes, vortexed for 2 min, and shaken at 25°C (Shaking water bath KMC 12055 WI) for 24 h. Resultant samples containing undissolved SDs suspended in the test medium were centrifuged at 10,000 g for 5 min and the clear supernatants obtained were filtered (0.20 μm), suitably diluted with PB of 25°C and analyzed using HPLC.

In vitro Ibuprofen Release

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. Hence, the conclusion of its increased dissolution from improved formulations may not always be justified until its dissolution in 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 buffer (Potthast et al., 2005). Hence, the dissolution tests of ibuprofen, PM, and SDs (equivalent to 10 mg ibuprofen) were performed in 500 mL PB pH 6.8 (37 ± 0.5°C) devoid of surfactant, acids, and so forth, as the dissolution medium using United States Pharmacopeia (USP) model digital tablet dissolution test apparatus (Shinseang Instrument Co., Seoul, South Korea) at the paddle rotation speed of 50 rpm. At the specified times, 5 mL samples were withdrawn, filtered, and assayed for ibuprofen content using HPLC. Equivalent amount of fresh medium pre-warmed to 37 ± 0.5°C was replaced after each sampling.

Solubility of Ibuprofen in Aqueous Polymer Solutions

To 10 mL of each of 0.5, 1, 2, 4, 6, 8, and 10 mM solutions of PEG 20000 in PB in 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 g for 5 min and the clear supernatants obtained were filtered (0.20 μm), suitably diluted with corresponding polymer solutions of 25°C and analyzed using HPLC.

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, PEG 20000, their PM, or SDs was placed in a sealed aluminum pan, and heated at a scanning rate of 5°C/min. An empty aluminum pan was used as reference.

Fourier Transform Infrared Spectroscopy

The FTIR spectra were obtained using FTIR spectrometer-430 (Jasco, Japan). The samples (Ibuprofen, PEG 20000, PMs 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 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}.

Pharmacokinetic Study

Animal care and procedures were conducted according to the guidelines for animal use in toxicology (Society of Toxicology USP 1989), and the study protocol was approved by the Animal Care and Use Committee of the College of Pharmacy, Yeungnam University. Twenty male Sprague-Dawley rats (average weight 250 ± 20 g) were divided into four groups, right femoral artery was cannulated under light ether anesthesia and hard gelatin capsules (Suheung capsule Co. Ltd., Seoul, South Korea) of ibuprofen powder, PM or SDs equivalent to 25 mg/kg ibuprofen were administered orally. At predetermined time intervals, 0.2 mL of blood was collected and the plasma was separated by centrifuging at 3,000 g for 10 min (5415C, Eppendorf, Westbury, NY, USA) (Geisslinger, Dietzel, Bezler, Nuernberg, & Brune, 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 3,000 g 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 using HPLC (Canaparo et al., 2000). The non-compartmental pharmacokinetic parameters were calculated

using the WINNONLIN (Version 1.1, Scientific Consulting Inc., Gaithersburg, Maryland, USA) software program. 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.

Drug Analysis

Ibuprofen concentrations were analyzed using Jasco P987 HPLC system equipped with a Jasco UV detector (UV-975). 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 × 150 mm). The mobile phase was acetonitrile: phosphate buffer (pH 3.5) (6:4 vol/vol). The eluent was monitored at 220 nm with a flow rate of 1.2 mL/min (Canaparo et al., 2000).

RESULTS AND DISCUSSION

Preparation of SDs, and Determination of Drug Content and Percent Yield

SD preparation was relatively simple and the cooled masses of SDs were frangible enough to be ground easily. Ibuprofen assay in all SDs was almost 100%, and the percentage yield was greater than 97% (data not shown). This method was relatively more feasible to prepare ibuprofen-PEG 20000 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. Drug content analysis indicated that the ibuprofen was uniformly distributed in SDs, and the higher yield showed relatively lower process loss.

Scanning Electron Microscopy

In scanning electron micrographs (Figure 3), ibuprofen appeared as smooth-surfaced rectangular crystalline structures (A) and PEG 20000 too as a smooth-surfaced mass (B). PMs contained individual ibuprofen and PEG 20000 particles (C) and 1:1 wt/wt SD appeared as uniform and homogeneously mixed mass having porous rough surface (D). Similarly, the 1:10 wt/wt SD appeared as uniform and homogeneously mixed mass with smooth surface containing small flakes (E). SEM pictures showed that the individual surface properties of PEG 20000 and ibuprofen were lost during melting and solidification indicating the formation of effective SD systems. Surface morphology of SDs showed that ibuprofen was homogeneously dispersed into the polymer.

Solubility, Dissolution, and Phase Solubility

Solubility and dissolution of ibuprofen increased with the increment in the ratio of PEG 20000 in SDs (Figures 4 and 5).

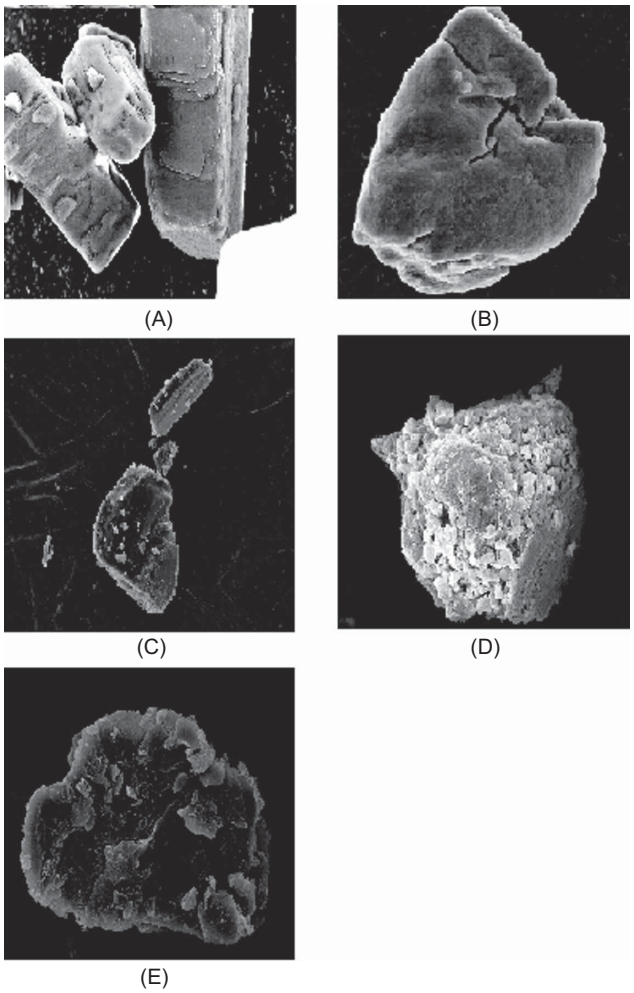


FIGURE 3. Scanning electron micrographs. (A) Ibuprofen, (B) Polyethylene glycol 20000, (C) 1:1 wt/wt Physical mixtures, (D) 1:1 wt/wt Solid dispersions and (E) 1:10 wt/wt Solid dispersions.

Phase solubility study showed that the solubility of ibuprofen almost linearly increased as the concentration of P 407 increased (R^2 = .88) (Figure not shown). In the dry state, drug particles were in close contact with the polymer particles (shown by SEM). When the mixture came in contact with water, the polymer particles hydrated rapidly (because of the high hydrophilic potency of PEG 20000) into polymer solution contributing to the increased wettability of the drug particles (Craig, 2002; Mura, Manderioli, Bramanti, & Ceccarelli, 1996). This could also possibly explain the higher solubility of drug in phase solubility study where the ibuprofen particles were dispersed in aqueous polymer solutions. Enhanced solubility and dissolution of ibuprofen from PMs could thus be related to the surface activity, wetting effect which may lead to reduced agglomeration and hence increased surface area, and solubilizing effect of PEG 20000 (Corrigan, 1985; Craig, 1990; Craig, 2002; Law et al., 2003; Mura et al., 1996; Seo et al., 2003; Sudha, Zeren, Stefanie, & Steven, 2007; Verheyen,

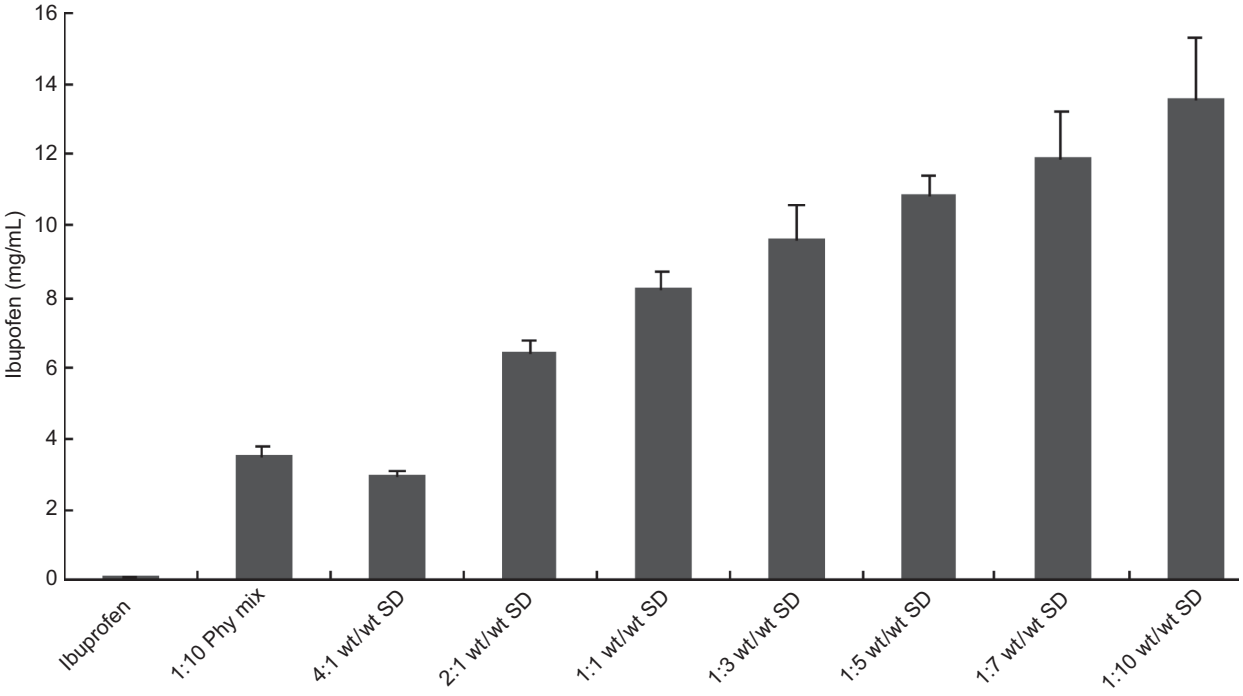


FIGURE 4. Solubility of solid dispersions in phosphate buffer (pH 6.8). Data are expressed as $M \pm SD$ ($n = 3$).

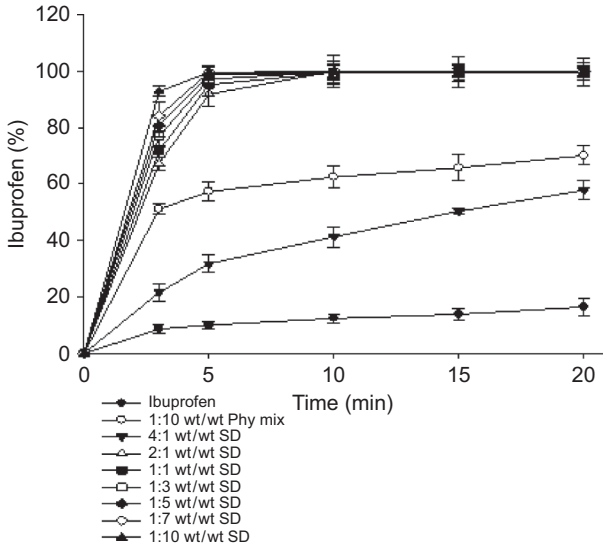


FIGURE 5. Dissolution profiles of solid dispersions in phosphate buffer (pH 6.8). Data are expressed as $M \pm SD$ ($n = 3$).

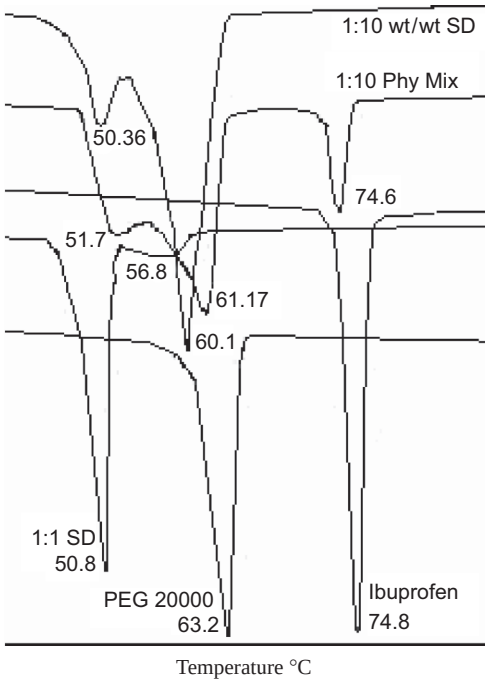


FIGURE 6. Differential scanning calorimetric thermograms of ibuprofen, polyethylene glycol 20000, physical mixtures, and solid dispersions.

Blaton, Kinget, & Mooter, 2002; Vilhelmsen et al., 2005; Zerrouk, Chemtob, Arnaud, Toscani, & Dugue, 2002).

DSC and FTIR

To understand the possible mechanisms of improved dissolution, we characterized SDs by DSC and FTIR. The DSC thermograms (Figure 6) of Ibuprofen and PEG 20000 showed apparent endothermic peak at 74.86°C with enthalpy of fusion (ΔH) 129.0 J/g and 63.28°C with enthalpy of fusion (ΔH)

183.8 J/g, respectively. In 1:1 wt/wt SDs, a sharp peak was found at 50.81°C with enthalpy of fusion (ΔH) 143.5 J/g. Similarly, another broad reduced endotherm was observed at 56.89°C. In 1:10 wt/wt SDs, a sharp small peak was observed at 46.61°C and another sharp peak was observed at 50.36°C with enthalpy of fusion (ΔH) 179.9 J/g. In addition to a small endotherm at 51.76°C with an enthalpy of fusion (ΔH) 160.5 J/g and another endotherm at 61.17°C, PMs showed characteristic ibuprofen peak at 74.65°C.

Absence or shifting toward the lower melting temperature of the drug peak in SDs indicated the possibilities of interactions between ibuprofen and PEG 20000. Because of low melting temperature, ibuprofen was soluble in molten PEG 20000 at any given temperature. In a binary solid system such as a crystalline drug and a crystalline polymer, if the drug is soluble in the molten polymer at the melting temperature of the polymer or vice versa, then this drug and the polymer form a eutectic system (Carstensen, 2001; Law, Wang, Schmitt, & Michelle, 2002; Sudha et al., 2007). PEGs are known to form eutectic systems with negligible solid solution (Anastasiadou, Henry, Legendre, Souleau, & Duchene, 1983; Ford & Rubeinstein, 1978; Law et al., 2001; Law et al., 2002; Law et al., 2003; Zerrouk et al., 2002). However, the amount of drug at eutectic composition differed widely. For example, the concentration of drug at eutectic composition with PEGs was 25% for fenofibrate with PEG 8000 (Law et al., 2001), 17% for diazepam with PEG 4000 (Anastasiadou et al., 1983), 15% for indomethacin with PEG 6000 (Ford et al., 1978), 35 and 33% for flurbiprofen with PEG 4000 and 6000 (Lacoulonche, Chauvet, Masse, Egea, & Garcia, 1998), and 15% for tamazepam with PEG 6000 (Moter, Augustijns, Blaton, & Kinget, 1998). PEG-drug eutectics belong to a category that exhibits complete miscibility in the liquid state and complete immiscibility in the solid state (Vasil'ev, 1964). In this category, the liquid phase interactions between unlike components are expected to be stronger than those between like components. The lattice mismatch between PEGs and small organic molecules makes the formation of PEG–drug solid solution difficult and the liquid phase PEG–drug miscibility leads to simple binary eutectic systems (Law et al., 2001). The complete miscibility of ibuprofen and PEG 20000 in the liquid phase indicates polymer–drug interaction at elevated temperatures, and the recognition that there would be negligible polymer–drug interaction in the solid state (as showed by FTIR) imposes a significant constraint on drug loading at the solid solution limit. Ibuprofen has been reported to form eutectics with PEG 8000 and its concentration at eutectic composition was 35% wt/wt (Law et al., 2002). Because the earlier studies showed that the PEG-drug phase diagrams are not sensitive to the PEG molecular weight (Lacoulonche, Manderioli, Bramanti, & Ceccarelli, 1996; Lacoulonche et al., 1998) and because the ibuprofen was highly soluble in molten PEG 20000 at any given temperature, it is expected to form a eutectic with PEG 20000 (Law et al., 2002).

As the melt of any composition other than that corresponding to the eutectic is cooled, one component will progressively solidify, thereby rendering the remaining liquor richer in the other component until the eutectic composition is reached, and at that point, the remaining liquid will solidify as a fine dispersion. According to the Tamman's rule, PEG 20000 (the lower melting component—the major phase)–ibuprofen eutectic crystallization have well-defined microstructure with a reduction in drug particle size (Passerini et al., 2002; Podolinsky & Taran, 1981). The DSCs of 1:1 and 1:10 wt/wt dispersions and PMs exhibited two endothermic events. The peaks at 50.81°C of 1:1 wt/wt SD, at 50.36°C of 1:10 wt/wt SDs, and at 51.76°C of PMs are the melting endotherm of eutectic. After the eutectic has melted, the solid phase suspended in the liquid melt might be ibuprofen (whose concentration might have exceeded the eutectic composition), which melted to produce the second peak, the reduced broad fusion peaks at 56.89°C in 1:1 wt/wt SD. Similarly, in 1:10 wt/wt SDs, the second peaks at 60.10°C might represent the melting of PEG 20000 (Bowden, 1938; Vasil'ev, 1964). Presence of three peaks in PM was interesting, because it contained separate ibuprofen and PEG 20000 (as seen in SEM picture), upon heating in the DSC study, ibuprofen particles which were in immediate contact with PEG 20000 formed eutectic (peak at 51.76°C), the peak at 61.17°C might correspond to the melted PEG 20000 containing some amount of dissolved ibuprofen which might have caused its melting point depression, and the separate ibuprofen peak was because of the viscosity of the molten mass in which the ibuprofen was soluble only upon stirring. However, in 1:1 SDs as the ibuprofen and PEG 2000 were in a homogenously mixed condition and as they were melted and resolidified mass, all the PEG 20000 might have formed eutectic.

In FTIR analysis (Figure 7), the spectrum of pure ibuprofen showed an intense, well-defined infrared band at around 1,721 cm^{-1} (carbonyl-stretching of isopropionic acid group) and another spectrum at around 3,000 cm^{-1} whereas the PEG 20000 showed a characteristic broad spectra of O–H stretching vibration from 3,300 to 3,600 cm^{-1}, C–H stretching of OC_2H_5 groups from 2,800 to 2,900 cm^{-1}, and C–O stretching from 1,000 to 1,200 cm^{-1}. SDs showed IR spectra almost similar to those of their corresponding PMs. Presence of the stretching vibration of ibuprofen carbonyl peak in SDs and PMs indicates that the drug crystalline form was not completely lost during SD formation and its attenuated intensities with the increasing amount of PEG 20000 in SDs could be due to the lower drug content. This observation fits well to the previous studies where ibuprofen was found to be primarily crystalline (Passerini et al., 2002; Vilhelmsen et al., 2005). Although the complete miscibility of ibuprofen and PEG 20000 in the liquid phase indicates polymer–drug interaction at elevated temperatures and also the ibuprofen can act as a hydrogen bond acceptor or donor, the absence of major shift in the peak positions, retention of drug peak, and the almost equivalent addition spectra (of ibuprofen and PEG 20000) for SDs and PMs

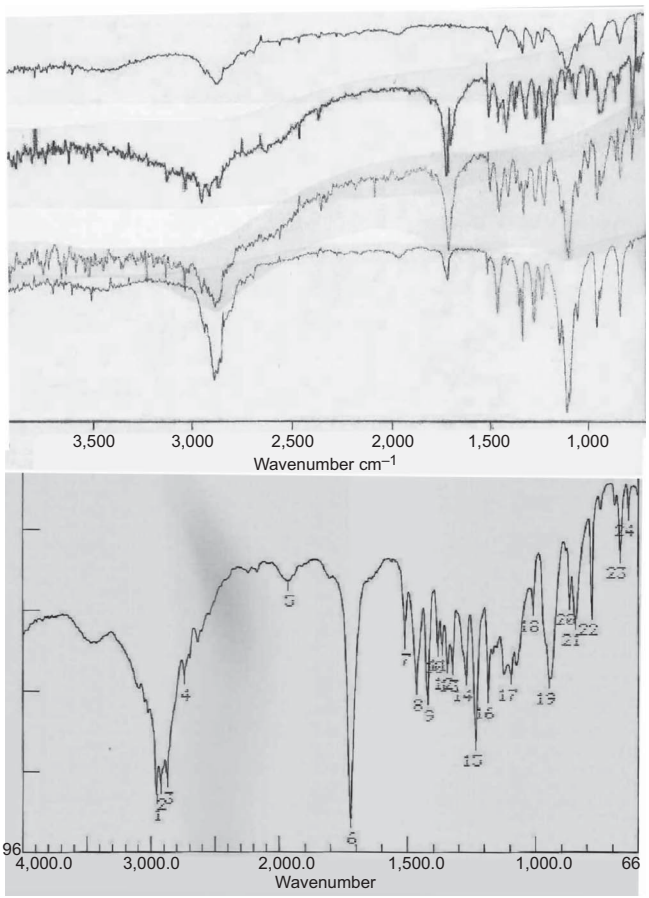


FIGURE 7. Fourier transform infrared absorption spectra of polyethylene glycol 20000, ibuprofen, 1:1 wt/wt solid dispersions, 1:10 wt/wt solid dispersions, and 1:1 wt/wt physical mixtures (top to bottom).

suggested the absence of interactions in the solid state between PEG 20000 and the ibuprofen. Thus, the PEG 20000–ibuprofen eutectics belong to a category that exhibits complete miscibility in the liquid state and complete immiscibility in the solid state (Vasil'ev, 1964).

Because the principal aim of this work was to formulate fast-dissolving ibuprofen SDs and to evaluate their in vitro and in vivo performances, DSC or FTIR study was not performed and compared for other SDs and PMs, and the phase diagrams were not constructed to understand the mechanism of eutectic formation. The fact that ibuprofen- PEG 20000 SD systems were completely miscible in the liquid state and immiscible in the solid state indicates that they crystallized out simultaneously as micro-fine crystals from the molten mixture resulting in increased ibuprofen surface area that might have played an important role for enhanced dissolution rate (Passerini et al., 2002; Seo et al., 2003). So, the enhancement of solubility and the dissolution from the SDs may be attributed partly to the reduction in particle size in ibuprofen crystalline because of the formation of eutectic system with PEG 20000. The similarity in the dissolution profiles of 1:1 to 1:10 wt/wt SDs implies that the eutectic point may not determine the upper limit for drug loading in ibuprofen-PEG 20000 SDs prepared by this method, and along with eutectic formation, combination of other factors such as surface activity, wetting, solubilization effect of PEG 20000 affected ibuprofen solubilization and dissolution. In case of SDs where the drug concentration exceeded the eutectic composition (1:1 SD), improved solubility and dissolution could partly be due to the enhanced dissolution of the non-eutectic portion of drug in the SD through mechanisms including reduced agglomeration, increased solubility, and melting point depression of drug by the polymer, and so forth. Particle size reduction and improved wetting may lead to reduced agglomeration and hence increased surface area (Zerrouk et al., 2002). The differences in the dissolution pattern of PMs and the corresponding SDs might be attributed to a significant reduction of the drug particle size in the carrier matrix (Rabasco, Ginés, Fernández-Arévalo, & Holgado, 1991).

Pharmacokinetic Study

The effect of improved dissolution on the oral absorption of ibuprofen in rats is shown in Table 1 and Figure 8. The total plasma concentrations of ibuprofen in SDs and PMs were

TABLE 1
Pharmacokinetic Parameters of Ibuprofen After Oral Administration of Ibuprofen Powder, 1:10 wt/wt PMs, and 2:1 and 1:1 wt/wt Ibuprofen : Polyethylene Glycol 20000 Solid Dispersions Equivalent to 25 mg/kg Ibuprofen in Rats. Data are Expressed as $M \pm SD$ ($n = 5$)

Parameter	Ibuprofen	1:10 Phy Mix	2:1 *SD*	1:1 *SD*
T_{max} (h)	0.75 ± 0.18	0.58 ± 0.23	0.59 ± 0.14	0.37 ± 0.07*
C_{max} (μg/mL)	5.32 ± 3.92	18.04 ± 8.54*	59.24 ± 30.49*	112.7 ± 42.88*
AUC (h μg/mL)	12.41 ± 8.56	61.21 ± 14.08*	146.05 ± 5.14*	303.78 ± 7.97*
$T½$ (h)	3.25 ± 1.01	4.05 ± 1.59	3.75 ± 0.86	3.34 ± 0.62
K_{el} (h^{-1})	0.23 ± 0.67	0.31 ± 0.23	0.19 ± 0.05	0.23 ± 0.03

Each value represents the $M \pm SD$ ($n = 5$).
*p-value < .017, compared with powder ibuprofen.

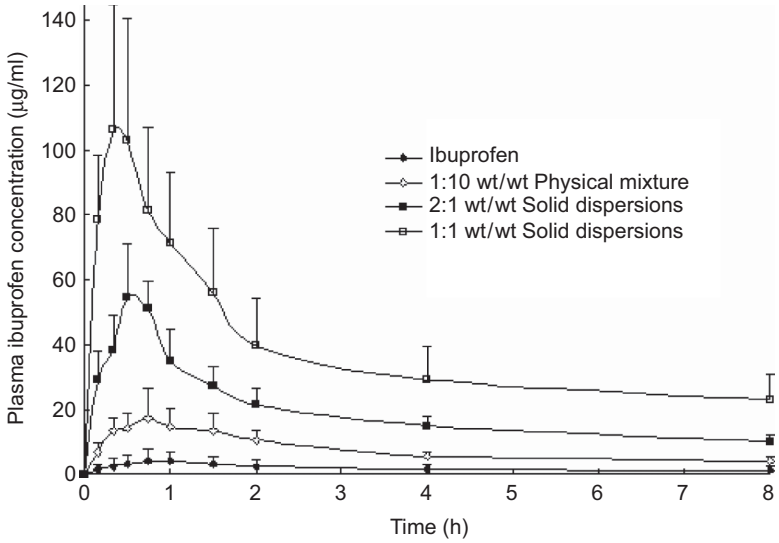


FIGURE 8. Plasma concentration-time profiles of ibuprofen after oral administration of ibuprofen powder, physical mixtures, and solid dispersions equivalent to 25 mg/kg ibuprofen in rats. Data are expressed as $M \pm SD$ ($n = 5$).

significantly higher compared with those in ibuprofen powder ($p < .017$). Unlike 1:1 wt/wt SDs ($p < .002$), the T_{max} values of 2:1 wt/wt SDs ($p > .13$) and PMs ($p > .23$) were not significantly different than that of ibuprofen. But the AUC and C_{max} of Ibuprofen from PMs and SDs were significantly increased ($p < .017$). However, the elimination rate constant (K_{el}) and half-life ($T_{1/2}$) values of ibuprofen from PMs and SDs were not significantly different compared with ibuprofen powder ($p > .34$). 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. In summary, the SDs resulted in much higher bioavailability compared with ibuprofen as reflected by both AUC and C_{max} values. These results showed that the ibuprofen was more readily available from SDs than from pure ibuprofen or a simple PM containing high proportion of PEG 20000. Taken together, the fast and complete dissolution resulting from improved solubility of the ibuprofen was responsible for its enhanced oral absorption.

CONCLUSION

In this study, rapid release of ibuprofen was achieved in a relatively easy, simple, quick, inexpensive, and reproducible manner. Quicker dissolution of SDs in rat intestine resulted in its rapid absorption and improved bioavailability compared with pure ibuprofen. Preliminary results from this work suggested that the preparation of ibuprofen SD using PEG 20000 as a meltable hydrophilic polymer carrier could be a promising approach to improve its dissolution and hence its oral absorption rate.

ACKNOWLEDGMENT

This work was supported by Korea Research Foundation Grant (KRF-2004-005-E00003).

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.

Anastasiadou, C., Henry, S., Legendre, B., Souleau, C., & Duchene, D. (1983). Solid dispersions: Comparison of prepared melts and coprecipitates of diazepam and polyoxyethylene glycol 4000. *Drug Dev. Ind. Pharm., 9*, 103–115.

Bowden, S. T. (1938). *The phase rule and phase reactions: Theoretical and practical*. London: Macmillan Press.

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. *Advanced pharmaceutical solids* (pp. 170–189). New York: Marcel Dekker Inc.

Corrigan, O. I. (1985). Mechanisms of dissolution of fast release solid dispersions. *Drug Dev. Ind. Pharm., 11*, 697–724.

Craig, D. Q. M. (1990). Polyethylene glycols and drug release. *Drug Dev. Ind. Pharm., 16*, 2501–2506.

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

Ford, J. L., & Rubeinstein, M. J. H. (1978). Phase equlibria and dissolution rates of indomethacin-polyethylene glycol 6000 solid dispersions. *Pharm. Acta Helv., 53*, 93–98.

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.

Lacoulonche, F., Chauvet, A., Masse, J., Egea, M. A., & Garcia, M. L. (1998). An investigation of FB interactions with poly(ethylene glycol) 6000, poly(ethylene glycol) 4000 and poly-epsilon-caprolactone by thermoanalytical and spectroscopic methods and modeling. *J. Pharm. Sci., 87*, 543–551.

Lacoulonche, F., Manderioli, A., Bramanti, G., & Ceccarelli, L. (1996). Properties of solid dispersions of naproxen in various polyethylene glycols. *Drug Dev. Ind. Pharm., 22*, 909–916.

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.

Law, D., Krill, S. L., Schmitt, E. A., Fort, J. J., Qiu, Y., Wang, W., & Porter, W. R. (2001). Physicochemical considerations in the preparation of amorphous ritonavir/PEG 8000 solid dispersions. *J. Pharm. Sci., 90*, 1015–1025.

Law, D., Wang, W., Schmitt, E. A., & 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.

Law, D., Wang, W., Schmitt, E. A., Qiu, Y., Steven, L. K., & Fort, J. J. (2003). Properties of rapidly dissolving eutectic mixtures of poly(ethylene glycol) and fenofibrate: The eutectic microstructure. *J. Pharm. Sci., 92*, 505–515.

Moter, G. V., Augustijns, P., Blaton, N., & Kinget, R. (1998). Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. *Int. J. Pharm., 164*, 67–80.

Mura, P., Manderioli, A., Bramanti, G., & Ceccarelli, L. (1996). Properties of solid dispersions of naproxen in various polyethylene glycols. *Drug Dev. Ind. Pharm., 22*, 909–916.

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., 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. (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.

Rabasco, A. M., Ginés, J. M., Fernández-Arévalo, M., & Holgado, M. A. (1991). Dissolution rate of diazepam from polyethylene glycol 6000 solid dispersions. *Int. J. Pharm., 67*, 201–205.

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.

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.

Verheyen, S., Blaton, N., Kinget, R., & Mooter, G. V. (2002). Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions. *Int. J. Pharm., 249*, 45–58.

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

Zerrouk, N., Chemtob, C., Arnaud, P., Toscani, S., & Dugue, J. (2002). In vitro and in vivo evaluation of carbamazepine-PEG 6000 solid dispersions. *Int. J. Pharm., 225*, 49–62.