Enhancement of Solubility, Dissolution and Bioavailability of Ibuprofen in Solid Dispersion Systems

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Received March 20, 2007; accepted January 11, 2008

To improve its solubility, dissolution, and bioavailability; Ibuprofen–polyethylene glycol 8000 (PEG 8000) solid dispersions (SDs) with different drug loadings were prepared, characterized by scanning electron microscopy (SEM) and differential scanning calorimetry (DSC), and evaluated for solubility, *in-vitro* release, and oral bioavailability of ibuprofen in rats. Loss of 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 drug–polymer interactions. 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 of this study suggested that the preparation of ibuprofen SDs using PEG 8000 as a meltable hydrophilic polymer carrier could be a promising approach to improve solubility, dissolution and bioavailability of ibuprofen.

Key words ibuprofen; solid dispersion; polyethylene glycol 8000; solubility; dissolution; bioavailability

Ibuprofen 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 analgesic effect are correlated, 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.[1] Various formulations such as prodrugs,[2] inclusion complexes,[3] microcapsules,[4] *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 poorly water soluble drugs in hydrophilic carrier matrix have been reported to improve their solubility and dissolution rate.[5—7] Moreover, they are also proven to enhance their bioavailability by increasing their saturation solubility in gastrointestinal fluids. 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, lyophilization etc 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.[7] Although, SDs by melting could be problematic (for drugs with higher melting temperature) because of the possible thermal unstability of the components, and the hardening of melts resulting into 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 *etc.* 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 claimed to be advantageous industrially,[6—8] they were also associated with many disadvantages, *e.g.* separate melting of polymer with or without drug was an extra step that could make the process complicated and costly, the yield in many cases was low because of the polymer/drug loss while pouring into the powder mix, and 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. Though the drying was not needed, in many cases, the improvement in drug dissolution was lower compared to the SDs of equivalent composition prepared by melting method. In addition, use of inert fillers such as lactose *etc.* might increase the bulk and the price of these formulations.[6—8] Therefore, it would be an advantage if the formation of ibuprofen SDs could be achieved using a rapid, less expensive, controllable and reproducible process.[8]

Polyethylene glycols (PEGs) are semicrystalline polymers that have been used extensively in the SDs preparation for their wetting, solubilizing and surface active properties.[9] 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. Extent of their absorption appears to be dependent on their molecular weights and the more complete absorptions have been reported for PEGs with lower molecular weights. But the absorption is much more limited in the case of PEGs with higher molecular weights. Hence, the polyethylene glycol 8000 (PEG 8000) was empirically selected as a meltable polymer for its low melting point, surfactant properties and oral safety. In this study, to improve its solubility, dissolution and bioavailability, low melting temperature of

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ibuprofen will be utilized to make SDs with PEG 8000 in a relatively simple manner using a locally designed formulation plant.

Experimental

Materials Ibuprofen was supplied by Yuhan Research Institute South Korea, and PEG 8000 was purchased from Fluka Biochemika, Germany. All other chemicals were of reagent grade and used without further purification.

Solubility of Ibuprofen in Molten Polymer Hot stage experiments were conducted to determine the solubility of ibuprofen in molten PEG 8000 at its melting temperature (59—61 °C). Fifty gram of PEG 8000 was melted 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 8000 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 Solid Dispersions, and Determination of Drug Content and Percent Yield Ibuprofen and PEG 8000 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 formulation vessel (Fig. 1). 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 room temperature for further use. Drug content was calculated by dissolving SDs equivalent to 20 mg ibuprofen in a suitable quantity of methanol, filtering (Minisart RC 4, 0.20 μm, Satorious, Germany), 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 PEG 8000 used.

Scanning Electron Microscopy (SEM) The surface morphology of ibuprofen, PEG 8000, physical mixtures and SDs were examined using a 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, physical mixtures 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 10000 rpm for 5 min and the clear supernatants obtained were filtered (0.20 μm), suitably diluted with PB of 25 °C and analyzed by 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.[10] Hence, the solubility and dissolution tests were performed in PB pH 6.8 without any exogenous surfactants. Based on these facts, dissolution tests of ibuprofen, physical mixture and SDs (equivalent to 10 mg ibuprofen) were performed in 500 ml PB pH 6.8 (37±0.5 °C) devoid of surfactant, acids *etc.* as the dissolution medium using United States Pharmacopoeia (USP) model digital tablet dissolution test apparatus (Shinseang Instrument Co., South Korea) at the paddle rotation speed of 50 rpm. At the specified times, 0.5 ml samples were withdrawn, filtered and assayed for ibuprofen content by HPLC. Equivalent amount of fresh medium pre-warmed to 37±0.5 °C was replaced after each sampling.

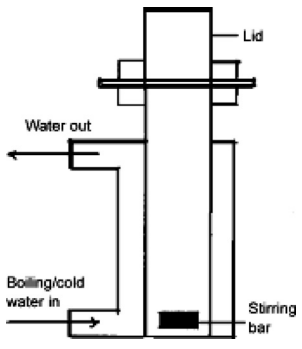

Fig. 1. Locally Designed Formulation Vessel

Solubility of Ibuprofen in Aqueous Polymer Solutions To 10 ml of each of 5, 10, 20, 40, 60, 80 and 100 mM solutions of PEG 8000 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 10000 rpm for 5 min and the clear supernatants obtained were filtered (0.20 μm), suitably diluted with corresponding polymer solutions of 25 °C and analyzed by HPLC.

Differential Scanning Calorimetry (DSC) 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 8000, their physical mixture, 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.

Pharmacokinetic Study Animals 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, 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, physical mixture 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 3000 rpm for 10 min (5415C, Eppendorf, U.S.A.).[11]

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.[12] The non-compartmental pharmacokinetic parameters were calculated using the WINNONLIN (Version 1.1, Scientific Consulting Inc., NC, U.S.A.) 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 by 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 v/v). The eluent was monitored at 220 nm with a flow rate of 1.2 ml/min.[12]

Results and Discussion

Preparation of Solid Dispersions, 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 98% (data not shown). This method was relatively more feasible to prepare ibuprofen-PEG 8000 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.

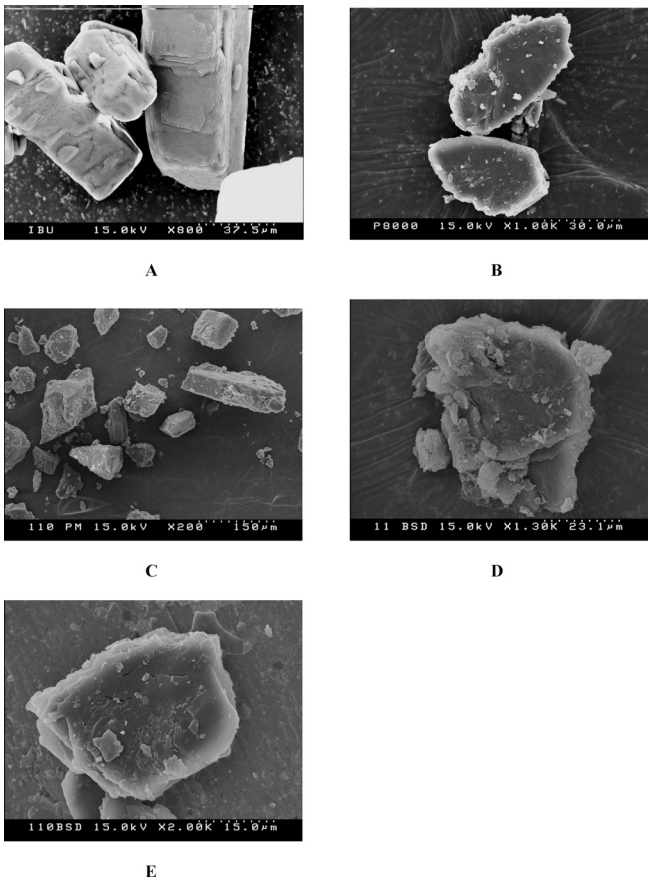

Fig. 2. Scanning Electron Micrographs

(A) Ibuprofen, (B) polyethylene glycol 8000, (C) 1 : 10 w/w physical mixtures, (D) 1 : 1 w/w solid dispersions and (E) 1 : 10 w/w solid dispersions.

Scanning Electron Microscopy In scanning electron micrographs (Fig. 2), ibuprofen appeared as smooth-surfaced rectangular crystalline structures (A) and PEG 8000 as smooth-surfaced irregular particles (B). Physical mixtures contained individual ibuprofen and PEG 8000 particles (C) and 1 : 1 w/w SD (D) and 1 : 10 w/w SD (E) appeared as smooth scaly surfaced uniform and homogeneously mixed mass. The surface morphology of SDs almost resembled to that of pure PEG 8000, indicating that ibuprofen was adsorbed into the PEG 8000 and homogeneously dispersed into the polymer. SEM pictures suggested that the individual surface properties of PEG 8000 and ibuprofen were lost during melting and solidification indicating the formation of effective SD systems.

Solubility, Dissolution and the Solubility of Ibuprofen in Aqueous Polymer Solutions Solubility and dissolution of ibuprofen increased with the increment in the ratio of PEG 8000 in SDs. Solubility value for 1 : 10 w/w physical mixture, 4 : 1, 1 : 1, 1 : 5 and 1 : 10 w/w SDs was 2.93, 2.09, 6.03, 10.14 and 12.81 mg/ml, respectively (Fig. 3). Cumulative amounts of ibuprofen dissolved from pure ibuprofen, SDs and physical mixtures (Fig. 4) at the end of 5 min were approximately 10.01, 51.93, 32.05, 84.21, 94.27 and 96.53% respectively for ibuprofen, 1 : 10 w/w physical mixtures, and 4 : 1, 1 : 1, 1 : 5 and 1 : 10 w/w SDs. In phase solubility study the solubility of ibuprofen in aqueous polymer solutions increased as the concentration of PEG 8000 increased (Fig. 5). Enhanced solubility and dissolution of ibuprofen from physical mixtures could be related to the surface activity, wetting effect which may lead to reduced agglomeration and hence increased surface area, and solubilizing effect of PEG 8000.[7—9,13—19] 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 (because of the high hydrophilic potency of PEG 8000) into polymer solution contributing to the increased wettability of the drug particles and to the local enhancement of the drug solubility at the diffusion layer surrounding the particles and subsequently releasing the drug into the medium.[16,17] This could also possibly explain the higher solubility of drug in phase solubility study where the ibuprofen particles were dispersed in aqueous polymer solutions.

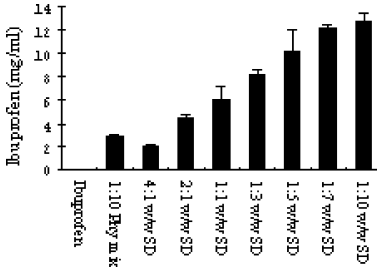

Fig. 3. Solubility Profiles of Solid Dispersions in Distilled Water at 25 °C

Data are expressed as mean±S.D. (n=3).

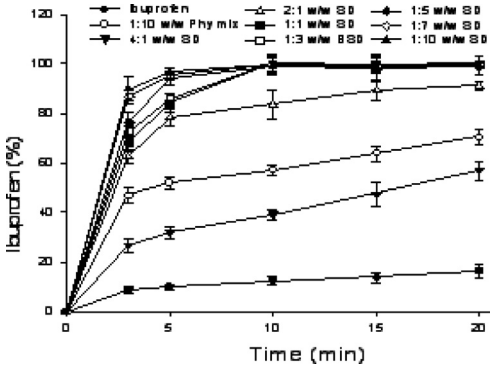

Fig. 4. Dissolution Profiles of Solid Dispersions and Physical Mixtures

Data are expressed as mean±S.D. (n=3).

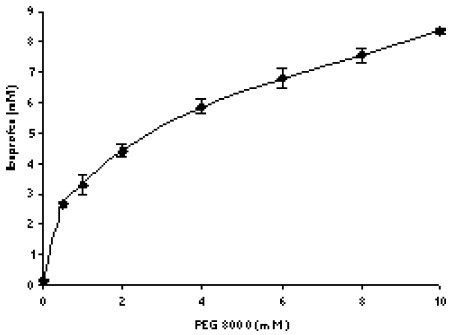

Fig. 5. Phase Solubility Behavior of Ibuprofen at 25 °C in Polyethylene Glycol 8000 Solutions in Distilled Water

Data are expressed as mean±S.D. (n=3).

Differential Scanning Calorimetry The DSC thermograms (Fig. 6) of ibuprofen showed an apparent endothermic

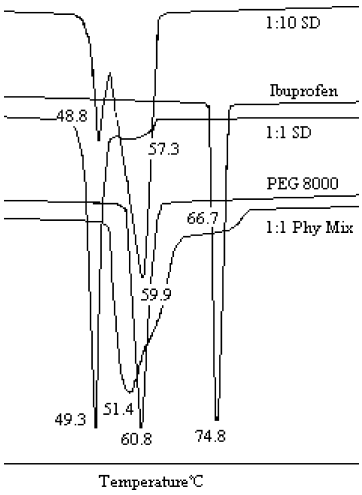

Fig. 6. Differential Scanning Calorimetric Thermograms of Ibuprofen, Polyethylene Glycol 8000, Physical Mixtures and Solid Dispersions

peak at 74.86 °C with enthalpy of fusion (ΔH) 129.0 J/g. Similarly, the melting peak of PEG 8000 was observed at 60.89 °C with enthalpy of fusion (ΔH) 197.8 J/g. Sharp ibuprofen peak was lost in SDs and physical mixtures. In 1 : 1 w/w SDs, a sharp peak appeared at 49.38 °C with enthalpy of fusion (ΔH) 143.8 J/g, and a broad reduced endotherm was observed at 57.38 °C. In 1 : 10 w/w SDs, a sharp small peak was observed at 48.89 °C and another sharp peak appeared at 59.97 °C with an enthalpy of fusion (ΔH) 176.5 J/g. Similarly, 1 : 1 w/w physical mixtures showed a sharp peak at 51.48 °C with an enthalpy of fusion (ΔH) 150.7 J/g and another broad endotherm at 66.79 °C.

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 PEG 8000. 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 the systems could be eutectic.[20] In order to have a high solubility in the 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.[13]

PEGs are known to form eutectic systems with negligible solid solution.[14,15,21—27] However, the amount of drug at eutectic composition differed widely. For example, the concentration of drug at eutectic composition with PEGs was, 25% fenofibrate for with PEG 8000,[21] 17% for diazepam with PEG 4000,[23] 15% for indomethacin with PEG 6000,[24] 35 and 33% for flurbiprofen with PEG 4000 and 6000,[25] 15% for tamazepam with PEG 6000.[26] PEG–drug eutectics belong to a category that exhibits complete miscibility in the liquid state and complete immiscibility in the solid state.[17] 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.[22] Since the melted PEG 8000 solution was viscous, stirring might have caused a thorough mixing and ibuprofen was soluble in molten PEG 8000 up to 50% w/w. However, they were miscible at any proportion at the temperature used in the SD preparation (90—95 °C). Because of low melting temperature, ibuprofen was highly soluble in molten PEG 8000 at any given temperature and is thus expected to form a strong eutectic relative to other compounds having higher melting temperature. Ibuprofen has been reported to form eutectics with PEG 8000 and its concentration at eutectic composition was 35% w/w.[21]

When the melts with eutectic composition are cooled, the two phases begin to crystallize spontaneously, and the eutectic crystallization rate accelerates at the contact between the two phases, 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. According to the Tamman's rule, the lower melting component (PEG) is the major phase in the eutectic mixture and PEG–drug eutectic crystallization will have a well defined microstructure with a reduction in drug particle size.[14,28] The complete miscibility of ibuprofen and PEG 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 (due to lattice mismatch) imposes a significant constraint on drug loading at the solid solution limit.[14]

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–ibuprofen eutectic crystallization might have well defined microstructure with a reduction in drug particle size.[14,16] As long as the amount of ibuprofen in the dispersion is less than the eutectic composition *e.g.* 1 : 10 w/w SDs, all of it would be present as a eutectic mixture (the small peak at 48.89 °C). The consistent dissolution profile obtained above or below the eutectic point (in 1 : 1 to 1 : 10 w/w SDs) implies that the eutectic point may not determine the upper limit for drug loading in ibuprofen–PEG 8000 SDs prepared by this method.[21] The DSCs of SDs and physical mixtures (PMs) exhibited two endothermic events. The peaks at 49.38 °C of 1 : 1 w/w SD, at 51.48 °C of PMs and at 48.89 °C of 1 : 10 w/w SDs were 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 57.38 °C in 1 : 1 w/w SD and 66.79 °C in PMs. Similarly, in 1 : 10 w/w SDs, the second peaks at 59.97 °C might represent the melting of PEG 8000.[27,30] Difference between the DSC curves of 1 : 1 w/w SD and PMs was as expected. 1 : 1 w/w SD was two component system—eutectic mixture and remaining ibuprofen. However, 1 : 1 PM was three component system—small amount eutectic mixtures formed possibly due to the heat of friction during physical mixing by grinding in mortar, and free PEG and ibuprofen as evidenced by SEM. During DSC

Table 1. Pharmacokinetic Parameters of Ibuprofen after Oral Administration of Ibuprofen Powder, 1 : 10 w/w Physical Mixtures, and 2 : 1 and 1 : 1 w/w Ibuprofen : Polyethylene Glycol 8000 Solid Dispersions Equivalent to 25 mg/kg Ibuprofen in Rats

Parameter	Ibuprofen	Phy Mix	2 : 1 SD	1 : 1 SD
T_{max} (h)	0.75±0.18	0.53±0.21	0.43±0.15*	0.37±0.07*
C_{max} (μg/ml)	5.32±3.92	15.24±5.87*	53.25±35.19*	103.16±43.62*
AUC (h·μg/ml)	12.41±8.46	57.04±13.99*	126.67±71.35*	330.10±121.55*
$T_{1/2}$ (h)	3.25±1.01	3.76±1.17	3.37±0.62	3.46±0.67
K_{el} (h^{-1})	0.23±0.67	0.20±0.047	0.21±0.04	0.21±0.04

Each value represents the mean±S.D. (n=5). * p value <0.0165 (compared with powder ibuprofen).

study, the eutectic mixture melted first followed by PEG. Although the presence of PEG decreased the melting point of ibuprofen and the ibuprofen was soluble in melted PEG, it dissolved slowly because of the viscosity. This type of sequential melting of three components in 1 : 1 w/w PMs might be responsible for the broad curve.

The fact that ibuprofen–PEG 8000 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 that might have played an important role for enhanced dissolution rate.[6,7] 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 PEG 8000. The similarity in the dissolution profiles of 1 : 1 to 1 : 10 w/w SDs could indicate that along with eutectic formation, combination of other factors such as surface activity, wetting, solubilization effect of PEG 8000 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.* Particle size reduction and improved wetting may lead to reduced agglomeration and hence increased surface area.[15] Since the physical mixture of the same composition dissolved more slowly than the solid dispersions, the intrinsic effect of PEG 8000 might have also had an important role to increase the dissolution rate of ibuprofen. Such 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.[30]

As the principal aim of this work was to enhance the solubility, dissolution and bioavailability of ibuprofen in SD systems, and also, the earlier studies reported the existence of ibuprofen–PEG 8000 eutectics; SEM and DSC study was not performed and compared for other SDs and physical mixtures, and the phase diagrams were not constructed to understand the mechanism of eutectic formation. However, subsequent studies will be done in future to evaluate the mechanism of enhanced solubility, dissolution and bioavailability by characterizing these SDs in detail using various techniques.

Pharmacokinetic Study The total plasma concentrations of ibuprofen in SDs and physical mixtures were significantly higher compared with those in ibuprofen powder (p<0.0165) (Table 1, Fig. 7). Unlike 1 : 1 and 2 : 1 w/w SDs

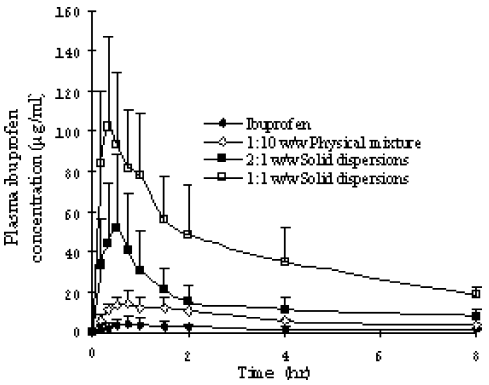

Fig. 7. Plasma Concentration–Time Profiles of Ibuprofen after Oral Administration of Ibuprofen Powder, Physical Mixtures, and Solid Dispersions Equivalent to 25 mg/kg Ibuprofen in Rats

Data are expressed as mean±S.D. (n=5).

(p<0.0154), the T_{max} values of physical mixtures (p>0.116) were not significantly different than that of ibuprofen. But the *AUC* and C_{max} of ibuprofen from physical mixtures and SDs were significantly increased (p<0.006). However, the elimination rate constant (K_{el}) and half-life ($T_{1/2}$) values of ibuprofen from physical mixtures and SDs were not significantly different compared to ibuprofen powder (p>0.18). The significantly higher (p<0.0164) *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 physical mixture containing high proportion of PEG 8000. Taken together, the fast and complete dissolution resulting from improved solubility of the ibuprofen was responsible for its enhanced oral absorption.

Conclusion

As the serum concentrations and analgesic effects of ibuprofen are correlated, rapid ibuprofen absorption could be a prerequisite for the quick onset of its action. Dissolution thus becomes the rate limiting step for the ibuprofen absorption, and the quick release of ibuprofen in the gastrointestinal tract following oral administration is desirable. In this study, rapid release of ibuprofen was achieved in a relatively easy and simple manner. Quicker dissolution of SDs in rat intestine resulted into its rapid absorption and improved bioavailability compared to pure ibuprofen. Preliminary results from this work suggested that the preparation of ibuprofen solid

dispersion using PEG 8000 as a meltable hydrophilic polymer carrier could be a promising approach to improve solubility, dissolution and bioavailability 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 (2007) and financially supported by the Ministry of Science and Technology (M10414030001-05N1403-00140) in South Korea.

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