International Journal of Pharmaceutics 404 (2011) 301–307

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Pharmaceutical Nanotechnology

Dry elixir formulations of dexibuprofen for controlled release and enhanced oral bioavailability

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ARTICLE INFO

Article history:
Received 20 September 2010
Received in revised form 29 October 2010
Accepted 11 November 2010
Available online 18 November 2010

Keywords:
Dexibuprofen
Dry elixir
Coated dry elixir
Bioavailability

ABSTRACT

The objective of this study was to achieve an optimal formulation of dexibuprofen dry elixir (DDE) for the improvement of dissolution rate and bioavailability. To control the release rate of dexibuprofen, Eudragit® RS was employed on the surface of DDE resulting in coated dexibuprofen dry elixir (CDDE). Physicochemical properties of DDE and CDDE such as particle size, SEM, DSC, and contents of dexibuprofen and ethanol were characterized. Pharmacokinetic parameters of dexibuprofen were evaluated in the rats after oral administration. The DDE and CDDE were spherical particles of 12 and 19 μm, respectively. The dexibuprofen and ethanol contents in the DDE were dependent on the amount of dextrin and maintained for 90 days. The dissolution rate and bioavailability of dexibuprofen loaded in dry elixir were increased compared with those of dexibuprofen powder. Moreover, coating DDE with Eudragit® RS retarded the dissolution rate of dexibuprofen from DDE without reducing the bioavailability. Our results suggest that CDDE may be potential oral dosage forms to control the release and to improve the bioavailability of poorly water-soluble dexibuprofen.

1. Introduction

Dexibuprofen, S(+)-ibuprofen, is a pharmacologically active enantiomer and is more potent than ibuprofen, which has equal quantities of R(−)- and S(+)-enantiomers (Adams et al., 1976). The racemic mixture of ibuprofen shows an unusual metabolic fate because the inactive R(−)-enantiomer undergoes a unidirectional enzymatic chiral conversion to the S(+)-form. This conversion of racemic ibuprofen to the active dexibuprofen may contribute to variability in analgesia, including delayed onset of activity and may explain the poor relationship observed between plasma concentrations of ibuprofen and clinical response for acute pain and rheumatoid arthritis (Grennan et al., 1983; Laska et al., 1986). Furthermore, R(−)-ibuprofen might contribute to adverse effects such as gastrointestinal toxicities. Thus, it is thought that the use of pure dexibuprofen may be more advantageous. However, the bioavailability of dexibuprofen is relatively low due to the limited solubility in acidic media.

Until now, few formulations have been applied to improve the solubility and bioavailability of dexibuprofen (Yi et al., 2008; Balakrishnan et al., 2009), whereas numerous studies were reported on ibuprofen (Li et al., 2008; Park et al., 2009; Valot et al., 2009). There have been many attempts to increase the solubility of poorly water soluble drugs, which included cosolvent (Kawakami et al., 2006), inclusion complexation (Kim et al., 2010), crystal modification (Cho et al., 2010), prodrug formation (Stella and Nti-Addae, 2007) and microparticle system (Wischke and Schwendeman, 2008). Of these formulations, microparticles have been widely used to enhance therapeutic efficacy while reducing the adverse effects, to regulate the dissolution rate and bioavailability of hydrophilic compounds by dispersing them in water-insoluble polymers, and to improve the dissolution of poorly water-soluble drugs using water-soluble carriers (Wischke and Schwendeman, 2008; Mora-Huertas et al., 2010). The microparticles are usually prepared by the solvent evaporation technique, either freeze dry or spray dry (Lee et al., 2001; Konan et al., 2002; Anhorn et al., 2008). To prepare microparticulate systems, the spray drying can be applicable to either heat resistant or heat sensitive drugs, and to either water soluble or water insoluble drugs. This spray drying technique was applied for the preparation of powder alcohol in wall-forming materials (Kim et al., 1995; Lee et al., 1999; Li et al., 2008).

Previously, our group developed a rapidly absorbed dosage form for poorly water-soluble drugs termed a 'dry elixir' (Kim et al., 1994). Dry elixir is a solid form of microcapsules containing ethanol and drug in water-soluble polymer shell. The active ingredients and excipients in dry elixir are dissolved or suspended in ethanol–water

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doi:10.1016/j.ijpharm.2010.11.020

mixtures. The poorly soluble drugs encapsulated in the dry elixir are readily dispersed and dissolved in aqueous media on account of the cosolvent effect of ethanol and rapid dissolution of amorphous dexibuprofen, leading to raising dissolution rate and bioavailability. Dry elixir was successfully applied to several poorly water-soluble drugs; indomethacin, ketoprofen and ibuprofen appeared to have a considerably fast dissolution rate by incorporation in dry elixir (Kim et al., 1994). It was also represented that dry elixir formulations incorporating digoxin (Kim and Yoon, 1995), flurbiprofen (Kim et al., 1995), ketoprofen (Ahn et al., 1998) or cyclosporin A (Lee et al., 2001) showed remarkably higher bioavailability than drug powder.

However, since dry elixir tends to result in fast initial dissolution, which might induce an adverse effect of drug with narrow therapeutic range, the coating of tablet or microparticle is necessary to prepare the controlled-release oral pharmaceutical forms. As a coating material of tablet and microparticle, commonly used polymer is Eudragit® RS, which is a copolymer of poly(ethylacrylate, methyl-methacrylate and chlorotrimethylammonio-ethyl methacrylate) containing an amount of quaternary ammonium groups between 4% and 8%. This composition makes the Eudragit® RS polymer insoluble at physiologic pH values but able to swell and become permeable to water, which is a good material for the controlled oral administration of drugs (Esposito et al., 2002; Ubrich et al., 2005; Trapani et al., 2007). Therefore, coated dry elixir with Eudragit® RS which retards the dissolution rate of drug from dry elixir might be useful reducing initial burst with bioavailability enhancement.

Here, we prepared the dexibuprofen dry elixir (DDE) for improving the dissolution rate and bioavailability of dexibuprofen. By extension, the coated dexibuprofen dry elixir (CDDE) were prepared with Eudragit® RS to reduce the initial burst of dexibuprofen from DDE and to maintain the effective plasma level over a longer period by controlling the release rate of dexibuprofen from CDDE. Finally, *in vitro* dissolution and *in vivo* bioavailability of dexibuprofen in the DDE or CDDE were compared with those of dexibuprofen powder.

2. Materials and methods

2.1. Materials

Dexibuprofen (S-(+)-ibuprofen) was kindly supplied by Enzychem Co. (Seoul, Korea). Dextrin and sodium lauryl sulfate (SLS) were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). Acrylic acid–methacrylic acid copolymer (Eudragit® RS) was obtained from Röhm Pharma GmBH (Weiterstadt, Germany). Ethanol and acetonitrile used as mobile phase in high performance liquid chromatography (HPLC) were purchased from Merck (Darmstadt, Germany) and Burdick & Jackson (Muskegon, MI, USA), respectively. All other chemicals were reagent grade and used without further purification.

2.2. Preparation of dry elixir and coated dry elixir

2.2.1. Preparation of dexibuprofen dry elixir (DDE)

Dexibuprofen dry elixir (DDE) was prepared by a spray drying technique described previously with minor modification (Kim et al., 1995). A laboratory scale spray drying was carried out using the Büchi mini spray dryer B-190 (Büchi Laboratory-Techniques, Flawil, Switzerland) with a standard nozzle (0.7 mm diameter). Table 1 shows the compositions of spraying solution for DDE. Dexibuprofen was dissolved in ethanol, while dextrin and SLS were dissolved in distilled water. Each solution was prewarmed to 55–60 °C and then blended. SLS was employed to prevent spray-dried particles from attaching to the inner wall of spray-drying chamber, to produce free-flowing powder, to handle with easy and to increase the encapsulation of ethanol in the dry elixir (Lee et al., 1999). The final solution was delivered to spray dryer under the following operation conditions: inlet air temperature (95 ± 2 °C), outlet air temperature (70 ± 2 °C), spray flow control (800 NL/h), pump setting at feed spray rate (5 ml/min) and aspirator level (10). The DDE was collected in cyclone separator and stored in a conical tube.

Table 1
Composition of spraying solution for DDE preparation.

Formulation	Composition (g)				
	Dextrin	Dexibuprofen	SLS	Water	Ethanol
DDE-1	5	2	0.2	25	20
DDE-2	10	2	0.2	25	20
DDE-3	20	2	0.2	25	20

2.2.2. Preparation of coated dexibuprofen dry elixir (CDDE)

Eudragit® RS was employed to prepare a coated dexibuprofen dry elixir (CDDE). DDE-3 formulation was chosen because of high ethanol content and improved dissolution rate in aqueous media. Compositions of spraying solution for the preparation of coated dexibuprofen dry elixir (CDDE) are shown in Table 2. Eudragit® RS was dissolved in ethanol and the DDE-3 was dispersed in the ethanol solution. The final solution was delivered to spray dryer under the following operation conditions; inlet air temperature 120 ± 2 °C, outlet air temperature 85 ± 2 °C with continuous stirring. The CDDE was collected in cyclone separator and stored in the conical tube.

2.3. Characterization of dexibuprofen-loaded formulations

2.3.1. Particle shape and size measurements of dexibuprofen microcapsules

Particle shape of DDE and CDDE was observed using scanning electron microscopy (SEM, JSM-5310LV, Jeol, Tokyo, Japan). The samples were mounted on a double-faced adhesive tape, sputtered with platinum using ion coater. An accelerating voltage of 15 kV was used. The particle size and size distribution of microcapsules were measured using a Mastersizer-scirocco 2000 (Malvern instruments Ltd., Malvern, UK) after dispersing them in air flow. All results were recorded as volume distributions. The width of the particle size distribution was expressed by the SPAN value: 10% volumetric $d(v, 0.1)$; median $d(v, 0.5)$; 90% volumetric $d(v, 0.9)$ diameters.

$$\text{SPAN} = \frac{d(v, 0.9) - d(v, 0.1)}{d(v, 0.5)}$$

2.3.2. Differential scanning calorimetry (DSC)

Thermal characteristics of dexibuprofen powder, dextrin, Eudragit® RS, the physical mixture, DDE and CDDE were investigated by a differential scanning calorimeter (DSC, DSC Q-1000, TA Instrument, Leatherhead, UK). Aliquots (5–10 mg) of samples were placed in an aluminum pan and crimped with an aluminum lid. DSC analyses were carried out with a nitrogen flow of 20 ml/min at

Table 2
Composition of spraying solution for CDDE preparation.

Formulation	Composition (g)		
	Eudragit® RS	DDE-3	Ethanol
CDDE-1	0.5	5	45
CDDE-2	1	5	45
CDDE-3	2	5	45

a heating rate of 10 °C/min from 30 to 200 °C temperature range. Indium (99.98%, melting point 156.65 °C, Aldrich Chemical Co., Milwaukee, WI, USA) was used as standard for calibrating the temperature.

2.3.3. Determination of ethanol content in dexibuprofen microcapsules

The ethanol content in DDE and CDDE was determined by gas chromatography. Briefly, 0.5 g of spray dried particles were dissolved in 50 ml of purified water and 125 μl of internal standard (IS, pyridine 10%, v/v) was spiked. The prepared samples were assayed for concentration of ethanol by Hewlett-Packard 5890 Series II gas chromatograph equipped with a flame ionization detector. Ethanol standard solutions containing 0.01, 0.05, 0.1, 0.2, 0.5 and 1% (v/v) were prepared to obtain a calibration curve. The analysis was carried out using a HP 101 column (25 m × 0.32 mm, 0.3 μm, methyl silicone fluid, Hewlett–Packard, Palo Alto, CA, USA) at a detector and injection temperature of 170 °C. The oven temperature was maintained at 80 °C.

2.3.4. Determination of drug content in dexibuprofen microcapsules

The drug content in DDE and CDDE was determined spectrophotometrically. Stock solution of dexibuprofen was prepared as 1 mg/ml in methanol. Standard solutions containing 5, 10, 20, 50 and 100 μg/ml were prepared using serial dilution for calibration curves. Exactly weighed amounts of DDE and CDDE were completely dissolved in 0.1 N NaOH and methanol–water cosolvent solution (50%, v/v), respectively. Then, the mixtures were sonicated for 10 min to destroy any agglomerates. The concentration of dexibuprofen was determined using a Beckman DU-600 UV/VIS spectrophotometer (Beckman Instruments, Fullerton, CA, USA) at a wavelength of 225 nm.

2.3.5. Stability test

Stability of DDE and CDDE was evaluated by changes in drug and ethanol contents. The DDE and CDDE were stored at room temperature (25 ± 5 °C) in sealed bottle for 90 days. At predetermined intervals, the contents of drug and ethanol were determined. The loss of encapsulated ethanol and drug were observed for 90 days.

2.4. In vitro dissolution study

In vitro dissolution of dexibuprofen from various formulations was investigated at 37 ± 0.5 °C at a stirring rate of 100 rpm using paddle method described in USP XXIII. As dissolution mediums, distilled water and simulated gastric fluid without pepsin (SGF, pH 1.2) consisting of 7 ml c-HCl and NaCl (2 g/l) were used. In each dissolution test, dexibuprofen powder, DDE or CDDE containing 80 mg dexibuprofen was placed in 900 ml of dissolution medium. Aliquots (3 ml each) were withdrawn at 5, 10, 15, 30, 45, 60, 90 and 120 min for DDE and at 15, 30, 45, 60, 90, 120, 150, 180, 240 and 300 min for CDDE by replacing an equal volume of fresh medium to compensate volume. The released amount of dexibuprofen was determined by UV spectroscopy at 225 nm.

2.5. In vivo study

2.5.1. In vivo bioavailability study

In vivo pharmacokinetic studies were carried out in male Sprague–Dawley rats (Samtako Bio Korea, Seoul, Korea) weighing between 300 and 330 g. The animals were housed at 25 °C and fed with commercial rodent chow (Samyang Co., Seoul, Korea) and tap water. A 12/12-h light/dark cycle was maintained throughout the study period. The rats were divided into 5 animals per group and had been fasted for 12 h with free access to water.

After anesthesia with diethylether during surgery, femoral vein was cannulated with a 23-gauge polyethylene tube. The other end of the tube was fitted with 1 ml syringe which was filled with heparinized normal saline (80 units/ml). All of the incisions were covered with wet cotton and the cannula was flushed with 0.2 ml heparinized normal saline to prevent blood clotting. After recovery from anesthesia, dexibuprofen as powder, DDE and CDDE were orally administered to rats at dose of 10 mg/kg as dexibuprofen. The formulations were dispersed in 1 ml of 0.5% tween 80 solution by simple vortexing for 10 s immediately prior to dosing. Five hundred microliters of blood were withdrawn at designated time intervals (0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6 and 8 h) and centrifuged at 10,000 rpm for 10 min. Plasma was thereafter obtained and stored under −70 °C until analysis. All animal care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted in 1989, revised in 1999 and amended in 2008 by the Society of Toxicology (SOT, 2008). Furthermore, the protocols for the animal studies were approved by the Institute of Laboratory Animal Resources of Seoul National University.

2.5.2. Determination of dexibuprofen in rat plasma

Concentration of dexibuprofen in rat plasma was determined using high performance liquid chromatography with UV detector as previously reported with slight modification (Sochor et al., 1995). Ten μl of IS was spiked into 150 μl of plasma and vortex-mixed. For deproteinization, 200 μl of 1 N HCl and 500 μl of methyl *tert*-butyl ether (MTBE) were added and vortex-mixed for 20 s. After centrifugation for 10 min at 4000 rpm, organic phase was taken and evaporated to dryness. The residue was redissolved in 150 μl of mobile phase (acetonitrile:distilled water adjusted to pH 2.5 with orthophosphoric acid = 60:40, v/v). Then, 50 μl of aliquot was injected into a high performance liquid chromatographic system. All experiments were performed using an automated Hitachi HPLC system (Hitachi, Tokyo, Japan) consisting of a model L-4200 UV-VIS detector, an L-6200 pump and an L-7200 autosampler. The column inlet filter (3 mm × 0.5 μm, Shiseido, Tokyo, Japan) was used to remove plasma protein. The signals were processed by dsChrom2000 (Donam, Seoul, Korea). The plasma samples were separated by isocratic elution with the mobile phase on the Luna 5 μm C18 column (4.6 mm × 250 mm, 5 μm, Phenomenex, Torrance, CA, USA) at a flow rate of 1 ml/min at 25 °C. The eluates were monitored with an UV detector at 225 nm.

2.5.3. Pharmacokinetic analysis

The area under the plasma concentration–time curve from time 0 to 8 h ($AUC_{0-8\,h}$) was calculated using the trapezoidal rule method. The peak plasma concentration (C_{max}), time to reach a C_{max} (t_{max}) and elimination half-life ($t_{1/2}$) were calculated using the Bioavailability Calculator 2002 (BA Calc 2002) program (Seoul, Korea).

3. Results and discussion

3.1. Physicochemical characterization

3.1.1. Particle shape and size of dexibuprofen dry elixir formulations

From the SEM images of the dexibuprofen powder, DDE-3 and CDDE-2 represented in Fig. 1, it was found that dexibuprofen powder was white crystalline in shape, whereas both DDE and CDDE were spherical shape with a smooth nonporous surface but partly distorted. There was no notable morphological difference between DDE-3 and CDDE-2. The particle size and size distribution (SPAN value) are summarized in Table 3. The particle sizes of DDE and CDDE were about 12 and 19 μm, indicating that the CDDE-2 had a slightly larger mean diameter than DDE-3. It was supposed that the difference in particle size between the DDE-3 and the CDDE-2 might

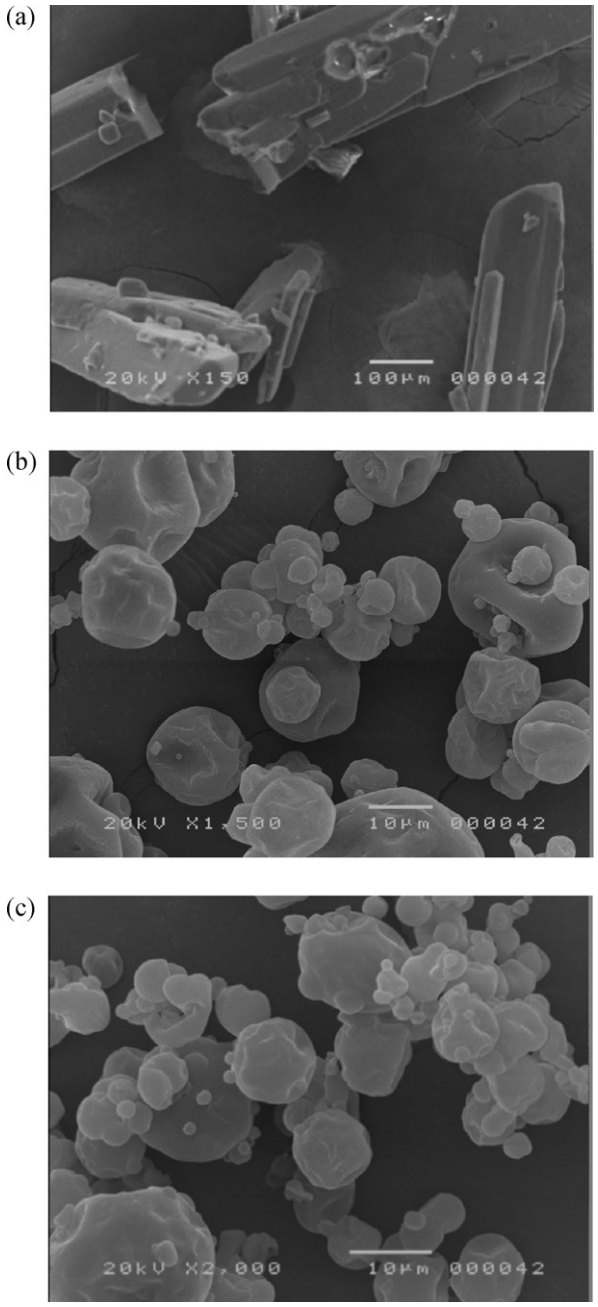

Fig. 1. Scanning electron micrograph of dexibuprofen powder (a), DDE-3 (b) and CDDE-2 (c).

result from the thickness of Eudragit® RS, coating wall membrane. From the SEM images and particle size analysis, the large particle size of dexibuprofen crystal was reduced in spray dried DDE and CDDE. Therefore, it is possible that an increased surface area and close contact between hydrophilic carrier and dexibuprofen may be responsible for the enhanced drug solubility and dissolution rate of the DDE and CDDE.

Table 3
Particle size and SPAN value of DDE-3 and CDDE-2 ($n = 3$).

Formulation	Size (μm)[a]	SPAN value[b]
DDE-3	12.43	2.42
CDDE-2	19.94	2.93

[a] Volume weighted mean diameter.
[b] SPAN value $= \frac{d(v,0.9)-d(v,0.1)}{d(v,0.5)}$.

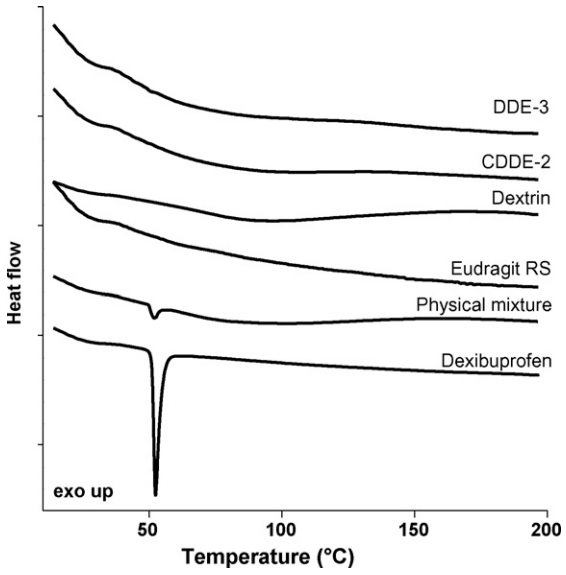

Fig. 2. DSC thermograms of DDE-3, CDDE-2, dextrin, Eudragit® RS, physical mixture and dexibuprofen powder.

3.1.2. DSC thermodiagram of dexibuprofen dry elixir formulations

The DSC thermograms of dexibuprofen powder, dextrin, Eudragit® RS, physical mixture, DDE-3 and CDDE-2 are demonstrated in Fig. 2. Under the experimental condition, an endothermic peak of melting of dexibuprofen at 52.44 °C was shortened for the physical mixture. There was no detectable melting endothermic peak although enough amount of drug presents in the DDE-3 and CDDE-2. These results correspond to general spray dried formulations (Corrigan, 1995). Thus, it is concluded that dexibuprofen exists as an amorphous state in the DDE and CDDE. It is known that the nature of drug inside polymer matrix can be assessed using the DSC analysis of drug, polymer materials and produced microspheres (Johansen et al., 2000). Since the spray drying is able to form an amorphous drug due to rapid drying of the solution droplets (Corrigan, 1995), the faster solvent removal may result in amorphous drug by not giving the adequate time for crystallization to the drug and polymer molecules. A higher thermodynamic activity of amorphous drug has particular pharmaceutical significance compared to a common crystalline form, because its increased solubility corresponds to improved biological activity.

3.1.3. Contents of drug and ethanol in dexibuprofen microcapsules

To determine the optimal content of dextrin, the concentrations of dextrin were varied in preparing the dexibuprofen dry elixir (DDE-1, DDE-2 and DDE-3) (Table 1). The drug and ethanol contents in the dry elixir were dependent on the dextrin content in composition (Table 4). Drug content in DDE was decreased at high dextrin content due to increase in total mass. On the contrary, ethanol content in DDE was increased at high dextrin content since

Table 4
Drug and ethanol contents in DDE and CDDE and the production yields ($n = 3$).

Formulation	Content (%)		Production yield (%)
	Dexibuprofen	Ethanol	
DDE-1	57.0 ± 8.7	5.9 ± 0.2	51.4 ± 3.8
DDE-2	27.7 ± 1.9	10.0 ± 0.1	56.0 ± 3.0
DDE-3	11.1 ± 0.4	22.4 ± 0.3	62.7 ± 13.2
CDDE-1	8.8 ± 1.9	10.9 ± 0.8	49.3 ± 7.1
CDDE-2	8.2 ± 1.2	5.6 ± 0.3	47.0 ± 5.2
CDDE-3	8.0 ± 1.1	6.4 ± 0.6	38.5 ± 6.9

semipermeable dextrin membrane was rapidly formed at the surface of the droplets. It is desirable to maximize the ethanol content in dry elixir in order to improve the solubility and dissolution rate in aqueous media as result of the cosolvent effects of ethanol. It is known that the ethanol content in the dry elixir can be affected by various formulation and manufacturing conditions. Most of all, the type and concentration of the wall forming material, concentration of the surfactant and inlet air temperature were primarily important to maximize the ethanol content in the dry elixir. In previous study, dextrin was selected as wall forming material, because of superior properties such as low cost, favorable chemical and physical properties and leading to greater ethanol content in the dry elixir compared to other wall forming materials (Kim et al., 1994). Thus, finding an optimal dextrin concentration may be critical because the excess amount of dextrin at high concentrations does not provide any effective wall forming capability.

For determination of Eudragit® RS content, the selected dry elixir DDE-3 was coated with various amount of Eudragit® RS to obtain the coated dexibuprofen dry elixir (CDDE-1, CDDE-2 and CDDE-3) (Table 2). Drug content in each formulation was similar regardless of the content of coating material. However, the ethanol content in the coated dry elixir was more dependent on the Eudragit® RS amount in the composition than drug content (Table 4). Moreover, the drug and ethanol contents in the all CDDE formulations were decreased compared with the uncoated DDE-3. The decrease in drug and ethanol contents of CDDE might be due to the mass increase by coating with resin, as supported by the size increase of particle.

In addition to the contents of drug and ethanol, the production yields of preparation were slightly affected by composition (Table 4). Large amount of dextrin showed an increasing tendency in the production yield, whereas high amount of Eudragit® RS might tend to decrease the production yield. When an excess of coating material was used, most product adhered to the inside wall of drying chamber. Whereas, too small amount of coating material was used, coating effect was negligible. Therefore, it is important to determine a proper amount of coating material. From the results, the DDE-3 and CDDE-2 were selected for *in vitro* dissolution and bioavailability study.

3.1.4. Long-term stability of dexibuprofen dry elixir formulations

Stability of dexibuprofen dry elixir was evaluated by the loss of encapsulated drug and ethanol contents for 90 days at room temperature. The dexibuprofen dry elixir formulations did not show any significant change in appearance, color and flow ability after 90 days storage at room temperature. No significant decrease in content of dexibuprofen in DDE-3 and CDDE-2 was observed until 90 days at room temperature (Fig. 3). However, the contents of ethanol in DDE-3 and CDDE-2 were slightly decreased after 90 days storage. Therefore, it is indicated that the DDE-3 and CDDE-2 were relatively stable for 90 days.

3.2. In vitro dissolution

The dissolution profiles of dexibuprofen from DDE, CDDE and dexibuprofen powder alone are illustrated in Fig. 4. The initial dissolution rate (IDR) and the release percentage of dexibuprofen in various formulations are shown in Table 5. The IDR of dexibuprofen in the DDE-3 was dramatically increased compared to dexibuprofen powder alone in distilled water and SGF (Fig. 4a and b). The dissolution of dexibuprofen from DDE-3 in distilled water and SGF for 60 min was higher than that from dexibuprofen powder alone (94.65% vs. 66.64% and 87.93% vs. 43.62%, respectively). However, the IDR of dexibuprofen from the CDDE-2 was significantly reduced compared to the DDE-3 in distilled water and SGF. The dissolution of dexibuprofen from the CDDE-2 for 60 min was much lower than that from DDE-3 (34.05% vs. 94.65% and 29.44% vs. 87.93%, respectively). Fast dissolution of drug from the DDE could be explained by microenvironmental solubilization due to either cosolvent effect of ethanol or rapid dissolution of an amorphous dexibuprofen. In addition, the results indicated that the coating of DDE markedly retarded the release rate of dexibuprofen in distilled water and SGF. It is thought that this remarkable retardation of

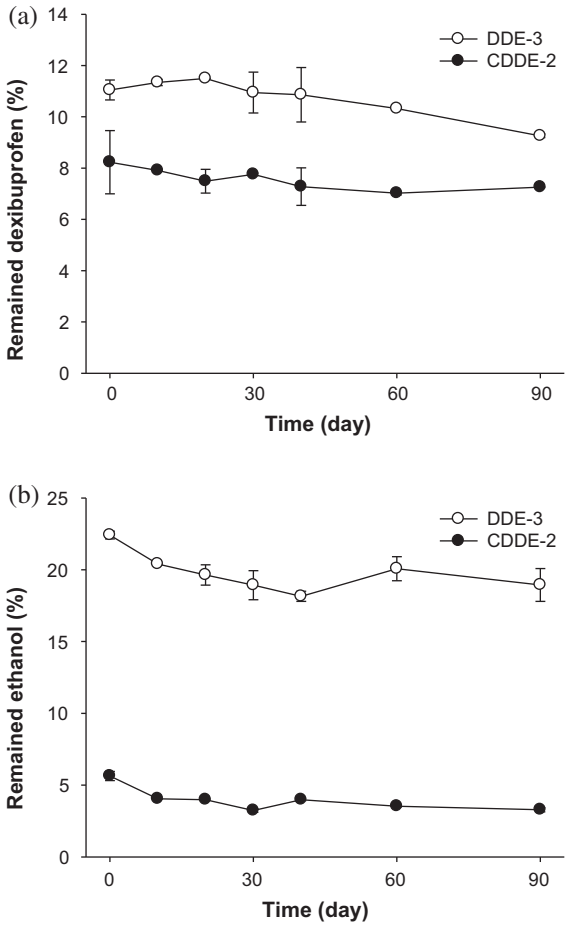

Fig. 3. Stability of DDE-3 and CDDE-2 for 90 days storage at room temperature: the amount of dexibuprofen (a) and ethanol (b) in DDE and CDDE ($n = 3$).

Table 5
Release and initial dissolution rate of dexibuprofen in distilled water and SGF at 37 °C ($n = 3$).

Formulation	Released (%)		IDR[a] (μg/ml/min)
	15 min	60 min	
Distilled water			
DDE-1	69.8 ± 7.0	71.9 ± 4.4	4.14
DDE-2	79.2 ± 4.0	79.7 ± 3.9	4.69
DDE-3	95.3 ± 5.6	94.7 ± 5.6	5.65
CDDE-1	67.8 ± 7.0	78.7 ± 2.9	4.02
CDDE-2	24.7 ± 0.6	34.1 ± 1.0	1.46
CDDE-3	18.1 ± 8.8	27.0 ± 8.9	1.07
Powder	21.3 ± 2.9	66.6 ± 11.3	1.26
SGF			
DDE-1	46.0 ± 3.4	58.9 ± 5.3	3.06
DDE-2	70.8 ± 0.8	70.6 ± 1.4	4.20
DDE-3	86.3 ± 4.0	88.0 ± 4.1	5.11
CDDE-1	62.8 ± 4.1	71.7 ± 4.0	3.72
CDDE-2	18.1 ± 0.2	29.4 ± 0.8	1.07
CDDE-3	7.4 ± 1.0	15.1 ± 2.7	0.44
Powder	9.9 ± 2.0	44.6 ± 0.8	0.58

[a] Initial dissolution rate of drug within first 15 min (μg/ml/min).

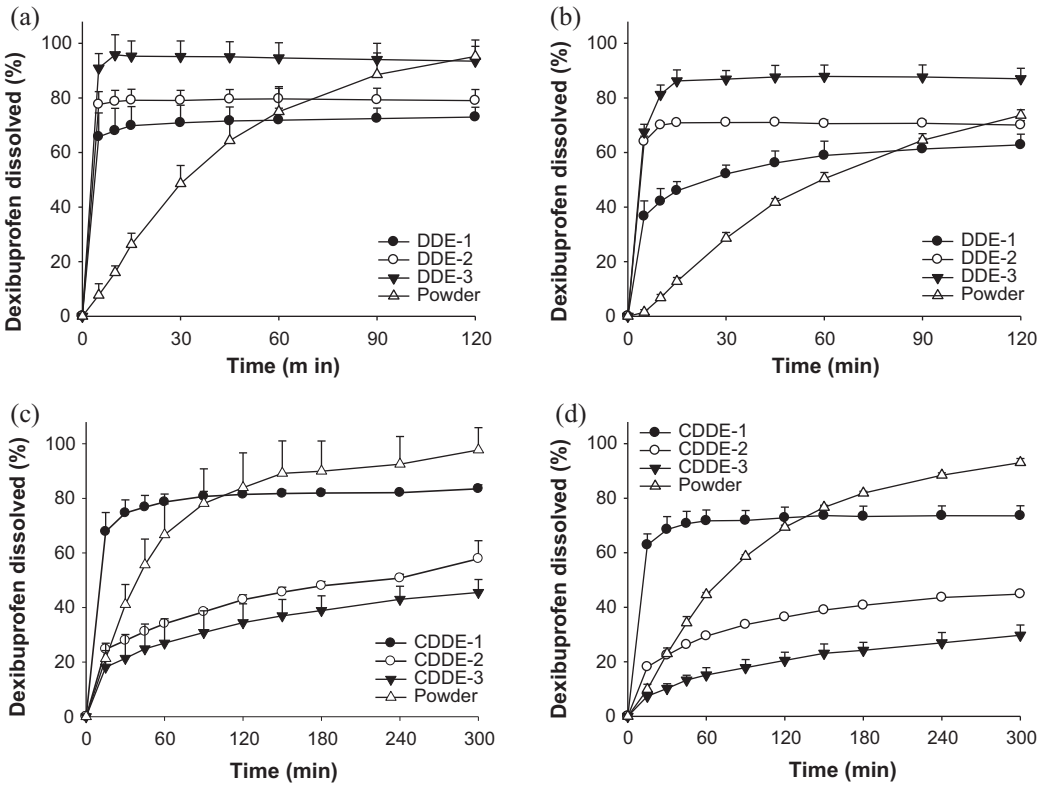

Fig. 4. Dissolution profiles of DDE in distilled water (a) and SGF (b), and CDDE in distilled water (c) and SGF (d) at 37 °C ($n = 3$).

release would be due to the insolubility of Eudragit® RS in aqueous medium.

Moreover, the dissolution rates of dexibuprofen from the DDE, CDDE and dexibuprofen powder alone were affected by the pH of the dissolution media (e.g., faster in distilled water than in pH 1.2 SGF). In earlier work, it was shown that the solubility of dexibuprofen was highly dependent on the pH of the medium used (Cox et al., 1999). Since dexibuprofen are poorly water soluble at low pH (0.1 mg/ml at pH 2.0), the solubility of drug was dramatically improved by increasing pH.

These findings suggest that dry elixir simultaneously containing ethanol and drug is useful for improving the dissolution rate of poorly water soluble drug as well as dexibuprofen. However, too fast IDR of drug with narrow therapeutic range might induce an adverse effect. Therefore, it is expected that the coated dry elixir would retard the dissolution rate of drug from dry elixir by reducing initial burst.

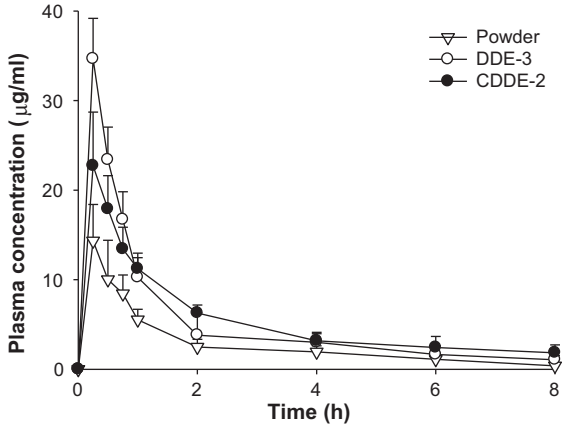

Fig. 5. Plasma concentration profiles of dexibuprofen in the male Sprague–Dawley rats after oral administration of dexibuprofen powder, DDE-3 and CDDE-2 ($n = 5$).

3.3. *In vivo pharmacokinetic study*

Plasma concentration–time profiles of dexibuprofen from microparticles after oral administration to rats are illustrated in Fig. 5. The pharmacokinetic parameters in Table 6 are calculated based on the observed plasma data. The $AUC_{0-8\,h}$ and C_{max} of dexibuprofen in the DDE-3 were increased 2- and 2.5-fold compared to dexibuprofen powder alone, respectively (39.96 μg h/ml vs. 21.24 μg h/ml and 34.66 μg/ml vs. 14.34 μg/ml). The t_{max} and $t_{1/2}$ of dexibuprofen in the DDE-3 were similar to those of powder. From the results, it was suggested that the increased dissolution rate would be responsible for the improvement of bioavailability of dexibuprofen in the DDE over powder alone. In other words, the enhanced bioavailability and C_{max} of dexibuprofen in the DDE seem to result from the marked increase in the absorption rate of dexibuprofen due to the increase in dissolution rate of dexibuprofen from the DDE in the GI tract. However, these phenomena may induce adverse effect of dexibuprofen because of too high initial burst out plasma peak. For this reason, the DDE should be coated with polymer such as Eudragit® RS to control the release rate of dexibuprofen.

Table 6
Pharmacokinetic parameters after oral administration of dexibuprofen powder, DDE-3 and CDDE-2 to the male Sprague–Dawley rats ($n = 5$).

Formulation	Pharmacokinetic parameters			
	$AUC_{0-8\,h}$ (μg h/ml)	C_{max} (μg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Powder	21.2 ± 3.8	14.3 ± 4.1	0.25 ± 0.13	1.78 ± 0.28
DDE-3	40.0 ± 6.4*	34.7 ± 4.5*	0.25 ± 0.11	2.06 ± 0.59
CDDE-2	42.1 ± 5.5*	23.4 ± 5.7*	0.30 ± 0.11	3.10 ± 1.95

* Significantly different from dexibuprofen powder ($p < 0.05$).

Meanwhile, the C_{max} of dexibuprofen in CDDE-2 was reduced compared to that in the DDE-3 (23.41 μg/ml vs. 34.66 μg/ml). However, the $AUC_{0-8\,h}$, t_{max} and $t_{1/2}$ of dexibuprofen in CDDE-2 were slightly increased, but comparable to the DDE-3. Therefore, it is supposed that the CDDE can lower the initial high plasma concentration of dexibuprofen in the DDE without reducing AUC, t_{max} and $t_{1/2}$. From these results, it was obvious that the CDDE, coated with Eudragit® RS, could maintain the effective plasma level of dexibuprofen a longer period compared with DDE and thereby the bioavailability of dexibuprofen was enhanced.

4. Conclusions

The dry elixir and coated dry elixir containing dexibuprofen were prepared in one step using a spray drying technique. The dissolution rate and bioavailability of dexibuprofen in the DDE were improved compared with that of the dexibuprofen powder. Moreover, the coated DDE was designed in order to control the release rate of dexibuprofen from dry elixir and to reduce the initial burst of dexibuprofen. Therefore, it is concluded that the CDDE of dexibuprofen could be an effective drug delivery system to increase the therapeutic benefits and to minimize the adverse effects.

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