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Influence of sulfobutyl ether β-cyclodextrin (Captisol®) on the dissolution properties of a poorly soluble drug from extrudates prepared by hot-melt extrusion

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Abstract

The aim of this study was to investigate the influence of sulfobutyl ether β-cyclodextrin (SBE_7-β-CD; Captisol®) on the dissolution properties of a poorly water-soluble drug from extrudates prepared by hot-melt extrusion. Ketoprofen was employed as a model drug. Extrudates containing the parent β-cyclodextrin (β-CD) were also produced for comparative evaluation to assess the benefits of SBE_7-β-CD. Hot-melt extrudates were produced at 100 °C, which was close to the melting point of ketoprofen. The physiochemical properties and the *in vitro* drug release properties of ketoprofen from extrudates were investigated and compared with samples prepared by physical mixing, co-grinding, freeze-drying and heat-treatment. The solubilizing effects and the interactions of ketoprofen with SBE_7-β-CD and β-CD were investigated using phase solubility and NMR studies, respectively. The dissolution rate of ketoprofen from samples prepared by hot-melt extrusion with SBE_7-β-CD was significantly faster than both the physical mixture and the hot-melt extrudates prepared with the parent β-CD. Moisture absorption studies revealed that the hygroscopic nature of SBE_7-β-CD led to particle aggregation and a corresponding decrease in drug release rate for all samples. However, the samples prepared by melt extrusion were least affected by exposure to elevated humidity.

Keywords: Hot-melt extrusion; Sulfobutyl ether β-cyclodextrin; Captisol®; Poorly water-soluble drug; Ketoprofen

1. Introduction

The solubility and dissolution rate of a poorly water-soluble drug will substantially influence its bioavailability since an orally administered drug must first dissolve in digestive fluids in order to be absorbed through the biological membranes of the gastrointestinal tract (GI tract). Class II and Class IV drugs in the biopharmaceutics classification system (BCS) are defined as having low aqueous solubility. Particularly for Class II drugs, an increase in the solubility and dissolution rate will result in more efficient drug absorption, since Class II drugs are well absorbed from the GI tract once in solution due to their relatively high lipophilicity.

Many techniques to improve the solubility and dissolution properties of poorly water-soluble drugs have been reported in the scientific literature. Increasing the available surface area for dissolution via particle size reduction is one of the oldest methods for improving the dissolution rates of poorly water-soluble drugs (Thanos et al., 2003). Solid dispersion systems have been widely studied and repeatedly shown to improve the dissolution properties of poorly water-soluble drugs (Serajuddin, 1999; Leuner and Dressman, 2000). In addition, the inclusion complexation of drug with α-, β- and γ-cyclodextrins by kneading (Gil et al., 2004), steam-granulating (Cavallari et al., 2002), coprecipitating (Tommasini et al., 2004), freeze-drying (Guyot et al., 1995) and spray-drying (Villaverde et al., 2004) has also been shown to dramatically increase drug solubility and dissolution rate.

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Although early studies revealed the benefit of cyclodextrins for improving the dissolution properties of poorly water-soluble drugs, toxicity issues limited their pharmaceutical use. However, with the recent identification of various chemically modified cyclodextrins with greatly reduced toxicity, interest has been renewed in cyclodextrins for pharmaceutical use, particularly for improving the dissolution properties and bioavailability of poorly water-soluble drugs (Stella and Rajewski, 1997).

Sulfobutyl ether β-cyclodextrin (SBE_7-β-CD) is a chemically modified β-CD that is a cyclic hydrophilic oligosaccharide which is negatively charged in aqueous media. The solubility in water for SBE_7-β-CD (excess 70 g/100 ml at 25 °C) (Lockwood et al., 2003) is significantly higher than the parent β-CD (1.85 g/100 ml at 25 °C) (Loftsson et al., 2004). Additionally, it does not exhibit the nephrotoxicity associated with β-CD (Rajewski et al., 1995; Frank et al., 1976). Tötterman et al. (1997) demonstrated no cytotoxic effects of SBE_7-β-CD on the integrity of intestinal epithelial Caco-2 cells, while dimethyl-β-CD clearly showed cytotoxic effects. Nagase et al. (2002, 2003) also reported that the drug inclusion complex with SBE_7-β-CD provided a protective effect against drug-induced cytotoxicity. Jain et al. (2002) evaluated the *in vivo* bioavailability of tablets containing inclusion complexes of danazol with SBE_7-β-CD and reported that drug absorption in beagle dogs was significantly increased due to the enhanced solubility of danazol. Based on these advantages, SBE_7-β-CD has been studied as an excipient material to improve the physiochemical properties of poorly water-soluble drugs (Dollo et al., 1999; Lockwood et al., 2003; Jain and Adeyeye, 2001; Nagase et al., 2001).

Hot-melt extrusion is a processing technology that requires neither solvent nor complicated processing steps in order to form matrix composites for controlled drug release or specialized drug delivery systems that are formed by the melting of thermoplastic excipients during processing (McGinity, 2004; Follonier et al., 1995). Polymers having a glass transition temperature (T_g) below drug degradation temperatures such as polyethylene oxide (PEO) (Fukuda et al., 2006a; Zhang and McGinity, 1999), hydroxypropyl cellulose (HPC) (Repka et al., 1999), polyvinyl acetate (Zhang and McGinity, 2000) and polymethacrylates such as Eudragit® RS PO (Fukuda et al., 2006b; Zhu et al., 2002) have been widely utilized as thermal binders and retardants for hot-melt extrusion processing. Rambali et al. (2003) used a hot-melt extrusion process with hydroxypropyl-β-cyclodextrin (HP-β-CD) to improve the poor solubility of itraconazole. The extrusion temperature was set at 250–255 °C as this was near the melting point of HP-β-CD. However, such high temperatures are non-ideal as they could cause the decomposition of many agents during extrusion processing.

The aim of this study was to investigate the influence of SBE_7-β-CD on the dissolution properties of a poorly water-soluble drug from extrudates prepared by hot-melt extrusion at a processing temperature close to the melting point (100 °C) of the model drug, but below the melting point of SBE_7-β-CD (approximately 235 °C). Ketoprofen (Fig. 1) was selected as the model Class II drug and SBE_7-β-CD (Captisol®) having an average degree of sulfobutyl substitution of 6.6 was employed in this study. Extrudates were also produced with the parent β-CD to compare the effects of SBE_7-β-CD on ketoprofen release from the extrudates. The drug release and phase solubility studies were performed in 0.1N HCl simulated gastric pH. Additionally, the properties of ketoprofen-SBE_7-β-CD samples produced by hot-melt extrusion were compared with samples produced by other common methods for drug-cyclodextrin complexation to elucidate differences in the sample characteristics that result from the different processing conditions.

2. Materials and methods

2.1. Materials

Ketoprofen was purchased from Spectrum Chemical (Gardena, CA). SBE_7-β-CD (Captisol®, Batch# CY-04A-04005, average substitution degrees of sulfobutyl group: 6.6, average MW: 2179) was donated by CyDex Inc. (Lenexa, KS). β-CD hydrate (MW: 1135) was purchased from Acros Organics (Morris Plains, NJ). Deuterium oxide (D_2O) was purchased from Aldrich Chemical Co. (Milwaukee, WI). The chemical structures of these β-CDs are shown in Fig. 1.

2.2. Phase solubility studies

2.2.1. Determination of solubility in 0.1N HCl for ketoprofen

Excess ketoprofen (approximately 10 g) was added to 0.1N HCl (50 ml) in a 100 ml Erlenmeyer flask and then stirred with a magnetic stir bar at room temperature for 3 h. The suspension was shaken at 37 °C for 48 h, then cooled to room temperature and centrifuged using a model TJ-6 centrifuge (BECKMAN) at the speed of 3000 rpm for 15 min. The supernatant was then filtered through a 0.45 μm disk-type syringe filter. The first 3 ml was discarded and the remaining 1–2 ml was assayed using a UV spectrophotometer (μQuant, BIO-TEK® Instruments, Inc., Winooski, VT) at 280 nm. The solubility of ketoprofen in 0.1N HCl was calculated using a calibration curve produced from ketoprofen solutions in a concentration range of 1.25–25.0 μg/ml. The solubility was measured six times and the average solubility was reported.

2.2.2. Phase solubility studies

The β-CD solutions in 0.1N HCl with the concentrations of 0.1, 0.3, 0.5, 0.7, and 1% (w/v) and the 0.1–50% (w/v) SBE_7-β-CD in 0.1N HCl were prepared at room temperature. For the concentrations of 3, 5, 10, and 30% (w/v) β-CD in 0.1N HCl, the β-CD suspensions were heated to 45, 55, 65, and 85 °C to dissolve the β-CD, respectively. Once cyclodextrins were dissolved completely, ketoprofen (1.5 g) was added to the 0.1N HCl (10 ml) containing either 0.1–30% (w/v) β-CD or 0.1–50% (w/v) SBE_7-β-CD in a 20 ml vial. The suspensions were shaken at 37 °C for 48 h, and then cooled to room temperature and centrifuged using a model TJ-6 centrifuge at the speed of 3000 rpm for 15 min. After centrifugation, the supernatant was filtered through a 0.45 μm disk-type syringe filter. The first 3 ml was pushed out and the remaining 1–2 ml was assayed. The concentration of ketoprofen in the filtrate was determined using a UV spectrophotometer at 280 nm.

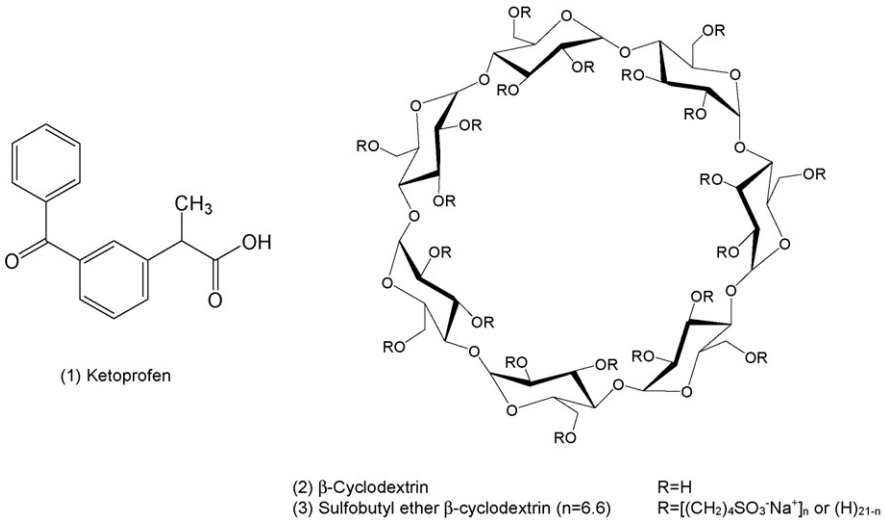

Fig. 1. Chemical structures of (1) ketoprofen, (2) β-cyclodextrin (β-CD) and (3) sulfobutyl ether β-cyclodextrin (SBE_7-β-CD).

2.3. Sample preparations

2.3.1. Hot-melt extrudates

A 200 g sample of powder containing 50% (w/w) ketoprofen and 50% (w/w) of either β-CD or SBE_7-β-CD was first blended in a mortar with a spatula for 2 min, and then blended in a polyethylene (PE) container for 5 min. The blended materials were then fed into the hopper of a single-screw Randcastle Extruder (Model RC 0750, Cedar Grove, NJ). The screw rotation speed was 10 rpm and a 6 mm diameter die was attached to the extruder. Since the melting range of ketoprofen is reported to be 92.0–97.0 °C (USP 29), the processing temperatures were set at 90 °C (zone 1), 95 °C (zone 2), 100 °C (zone 3) and 100 °C (die) in order to only melt ketoprofen in the heated barrel of the extruder. Following extrusion, the dried extrudates were gently ground into a fine powder using a mortar and pestle and then passed through a 250 μm screen for further studies.

2.3.2. Physical mixtures

A 200 g sample of powder containing ketoprofen and SBE_7-β-CD in the weight ratio of 1 to 1 was first blended in a mortar with a spatula for 2 min and then blended in a PE container for 5 min.

2.3.3. Co-ground powders

A 10 g sample of powder containing ketoprofen and SBE_7-β-CD in the weight ratio of 1 to 1 was ground in a mortar and pestle for 10 min.

2.3.4. Freeze-dried powders

A 2 g sample of powder containing ketoprofen and SBE_7-β-CD in the weight ratio of 1 to 1 was placed in a 20 ml scintillation vial. A 10 ml volume of 70% methanol was added to the vial and then shaken to completely dissolve the powders. The solution was fast frozen in liquid nitrogen and freeze-dried using a Labconco freeze dryer (Kansas City, MO) for at least 48 h. The freeze-dried samples were gently ground into a fine powder using a mortar and pestle and then passed through a 250 μm screen for further studies.

2.3.5. Heat-treated powders

A 1 g sample of powder containing ketoprofen and SBE_7-β-CD in the weight ratio of 1 to 1 was blended in a mortar for 3 min and then placed in a 10 ml scintillation vial. The vial was put in an oven at 100 °C for 6 h. The heat-treated samples were first stored at room temperature for 24 h, stirred using a spatula and then stored again at room temperature for 72 h. The dried heat-treated samples were gently ground into a fine powder using a mortar and pestle and then passed through a 250 μm screen for further studies.

2.4. In vitro drug release

2.4.1. Ketoprofen release from samples

The dissolution rate of ketoprofen from a 45 to 50 mg sample (equivalent to 25 mg ketoprofen) was determined using a USP 29 apparatus 2, VARIAN VK 7000 Dissolution Tester equipped with a Van Kel autosampler VK 8000 (Van Kel Industries, Edison, NJ). The dissolution medium was 900 ml of 0.1N HCl. During dissolution testing, the media were maintained at 37 ± 0.5 °C and agitated at 50 rpm. A sample volume of 3 ml was taken at each sampling time point of 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 min. Samples were diluted and analyzed using a UV spectrophotometer at 280 nm. The data were collected using KC4 Version 3.1 software (BIO-TEK® Instruments, Inc., Winooski, VT). The concentration of ketoprofen in media at each sampling point was calculated using an equation generated from a standard calibration curve that was produced from ketoprofen solutions in a concentration range of 1.25–25.0 μg/ml. All dissolution tests were performed in six replicates.

2.4.2. Ketoprofen release in 0.1N HCl containing either β-CD or SBE_7-β-CD

To investigate the effects of hot-melt extrusion processing on ketoprofen release, a 25 mg ketoprofen was accurately weighed

and investigated the release properties in 900 ml of 0.1N HCl containing 25 mg either β-CD or SBE_7-β-CD. The apparatus and conditions, except for the dissolution media, were the same with those described above. All dissolution tests were performed in six replicates.

2.5. Thermal analysis (DSC)

The thermal properties of ketoprofen, SBE_7-β-CD and samples prepared in the present study were investigated using a differential scanning calorimeter (DSC, TA Instruments model 2920, New Castle, DE). Ultra high purity nitrogen was used as the purge gas at a flow rate of 150 ml/min. Samples of approximately 10 mg were accurately weighed into aluminum pans and sealed. The temperature was ramped from 20 to 310 °C at a heating rate of 10 °C/min for all studies.

2.6. Powder X-ray diffraction (XRD)

The crystalline state of ketoprofen in samples prepared in this study was investigated using a PW 1720 X-ray generator and a PW 1710 diffractometer control (Philips Electronic Instrument, Mount Vernon, NY). The X-ray source was Cu Kα radiation under 40 kV and 40 mA. The scanning range (2θ) was from 5° to 35°, and the scan step and scan speed were 0.04° and 0.02°/s, respectively. X-ray patterns were analyzed using Jade 5 XRD pattern processing software (Materials Data Inc., Irvine, CA).

2.7. Nuclear magnetic resonance (NMR) spectroscopy

NMR studies were conducted to investigate the electronic interactions between ketoprofen and CDs. The proton NMR (^{1}H NMR) spectra in D_2O were recorded at 27 °C on a Varian Inova 500 MHz spectrometer (Varian Inc., Palo Alto, CA) operating at 499.352 MHz. Chemical shifts were reported in parts per million (ppm) relative to both the internal standard (sodium 3-(trimethylsilyl)-propionate-2,2,3,3-d_4; TSP-d_4) at 0 ppm and the solvent residual signal of HOD in D_2O at 4.865 ppm.

2.8. Moisture absorption study

In order to investigate the extent of moisture absorption and the resulting affect on the ketoprofen release properties for each of the 1:1 ketoprofen-SBE_7-β-CD binary samples produced by the above described methods, each of the samples was placed in a 40 °C and 75% relative humidity (40 °C/75%RH) environment in opened high-density polyethylene (HDPE) bottles for 7 days.

The weight gain of samples at 40 °C/75%RH was calculated by the following procedure. A sample of approximately 250 mg was weighed on a glass dish and put in a room equilibrated at 40 °C/75%RH. The weight gain (G) of samples was calculated using the following Eq. (1):

$$G(\%) = \frac{W_s - W_i}{S} \times 100 \quad (1)$$

where S is the weight of sample before moisture absorption, W_i is the weight of a glass dish with sample before moisture absorption and W_s is the weight of a glass dish with sample after moisture absorption. All measurements were performed in triplicate. The ketoprofen release from the moisture-absorbed samples was also investigated by the above described methods and compared with the initial data.

3. Results and discussion

3.1. Phase solubility studies

As seen in Fig. 2, when the concentration of SBE_7-β-CD in 0.1N HCl was elevated to 50% (w/v), the average solubility of ketoprofen increased 230 times from 0.13 to 48.51 mg/ml. While the increase in solubility for ketoprofen depended on the SBE_7-β-CD concentration in 0.1N HCl, the solubility for ketoprofen in 0.1N HCl containing β-CD increased only up to a β-CD concentration of 3% (w/v). When the concentration of β-CD in 0.1N HCl exceeded 3% (w/v), no further increase in the solubility of ketoprofen was observed. These results suggested that β-CD functioned as a solubilizer only at low concentrations, whereas SBE_7-β-CD exhibited strong solubilizing effects over a wide concentration range. This effect could be due to the high solubility of SBE_7-β-CD compared to the parent β-CD. Similar observations have been reported by previous researchers and it has also been demonstrated that the strong solubilizing effect of SBE_7-β-CD is independent of drug properties, including the molecular charge of drug in solution (Dollo et al., 1999; Zheng et al., 2005; Zia et al., 1997).

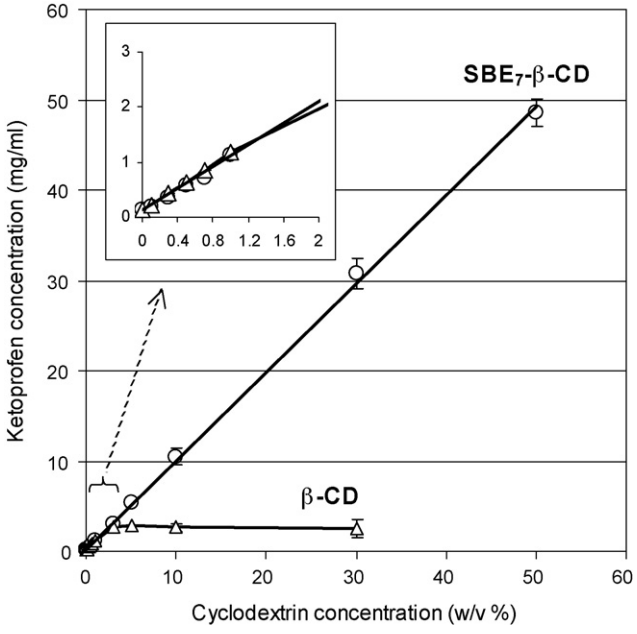

Fig. 2. Phase solubility diagrams of ketoprofen in 0.1N HCl in the presence of either (◯) SBE_7-β-CD or (△)β-CD.

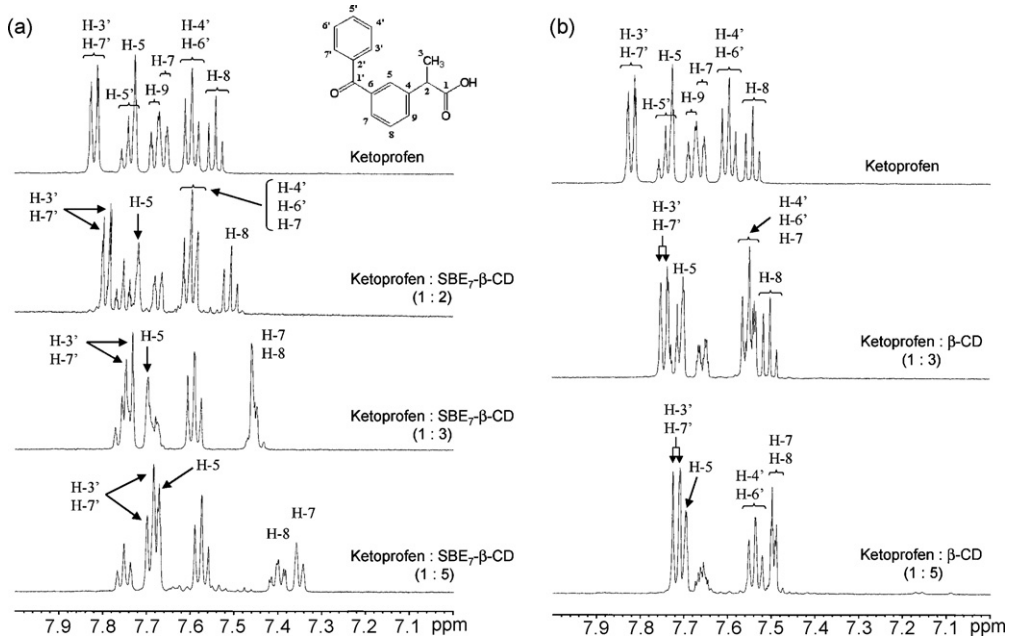

Fig. 3. ^{1}H NMR (500 MHz) spectra in D_2O of binary systems containing ketoprofen and either (a) SBE_7-β-CD or (b) β-CD.

3.2. ^{1}H NMR spectra for binary systems containing ketoprofen and cyclodextrins

The electronic interaction between ketoprofen and cyclodextrins (SBE_7-β-CD and β-CD) was investigated by NMR studies. The ^{1}H NMR spectra of ketoprofen in D_2O in the absence and presence of either SBE_7-β-CD or β-CD at the molar ratio of up to 1:5 are shown in Fig. 3. The aromatic proton signals for ketoprofen were assigned from an article published by Zovko et al. (2003). When β-CDs were present with ketoprofen in D_2O, the aromatic protons (δ 7.53–7.83) of ketoprofen were shifted upfield due to electronic interactions resulting from the formation of inclusion complexes of ketoprofen in the β-CDs cavities. Aromatic protons of H-5, H-7, H-8, H-3′ and H-7′ of ketoprofen in the presence of SBE_7-β-CD were shifted upfield with an increase in the molar ratio of SBE_7-β-CD. This signal shift in the aromatic protons of ketoprofen was more significant when SBE_7-β-CD was present in the ketoprofen D_2O solution as compared to β-CD. These results suggested that the electronic interaction such as hydrogen bonding of ketoprofen with SBE_7-β-CD was stronger than the parent β-CD, further supporting the enhanced solubilizing effect of SBE_7-β-CD over β-CD.

3.3. Dissolution profiles of pure ketoprofen in 0.1N HCl containing either SBE_7-β-CD or β-CD

The dissolution of ketoprofen (25 mg) in 900 ml of 0.1N HCl containing 25 mg of either SBE_7-β-CD or β-CD was conducted as a comparison for evaluating the effects of hot-melt extrusion processing on ketoprofen release. As shown in Fig. 4, no differences in the ketoprofen release profiles were observed between dissolution testing conducted in 0.1N HCl containing SBE_7-β-CD or β-CD. This result was supported by the phase solubility studies shown in Fig. 2. Since the concentration of SBE_7-β-CD and β-CD in dissolution media was so low (27.8 μg/ml = 0.00278% (w/v)), the increase in the solubility of ketoprofen was not dependant on the chemical modifications on β-CD as the solubility increase of ketoprofen in this range is controlled by only the concentration of the cyclodextrins (SBE_7-β-CD and β-CD) in the media. Therefore, there was no difference in the ketoprofen release profiles in 0.1N HCl containing either SBE_7-β-CD or β-CD.

3.4. Effect of hot-melt extrusion processing on ketoprofen release

The ketoprofen release in 0.1N HCl from the sample containing SBE_7-β-CD prepared by hot-melt extrusion exhibited a rapid rate of drug release with 91.6 and 99.9% of ketoprofen contained in the extrudates dissolved within 30 and 120 min, respectively,

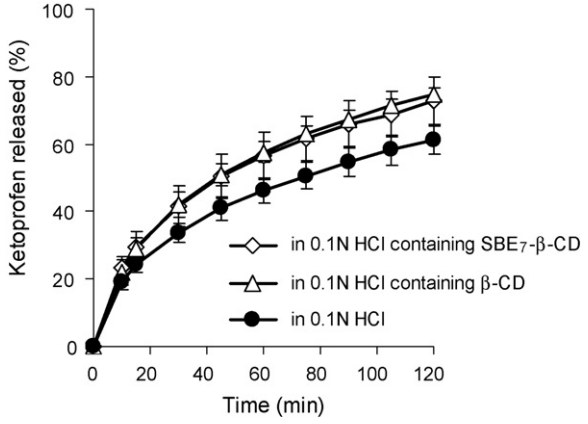

Fig. 4. Release profiles of pure ketoprofen in 900 ml of (●) 0.1N HCl and 0.1N HCl containing either (◊) 25 mg SBE_7-β-CD or (△) 25 mg β-CD at 37 ± 0.5 °C (USP 29 Apparatus 2, 50 rpm). Each point represents the mean ± standard deviation, $n = 6$.

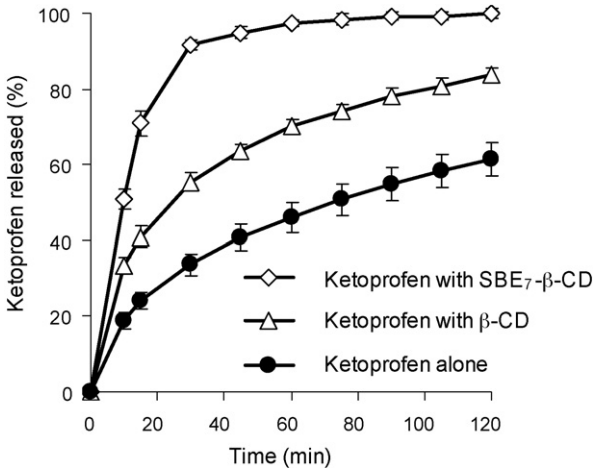

Fig. 5. Effect of hot-melt extrusion processing with either SBE_7-β-CD or β-CD on ketoprofen release in 900 ml of 0.1N HCl at 37 ± 0.5 °C (USP 29 Apparatus 2, 50 rpm). Each point represents the mean ± standard deviation, $n = 6$.

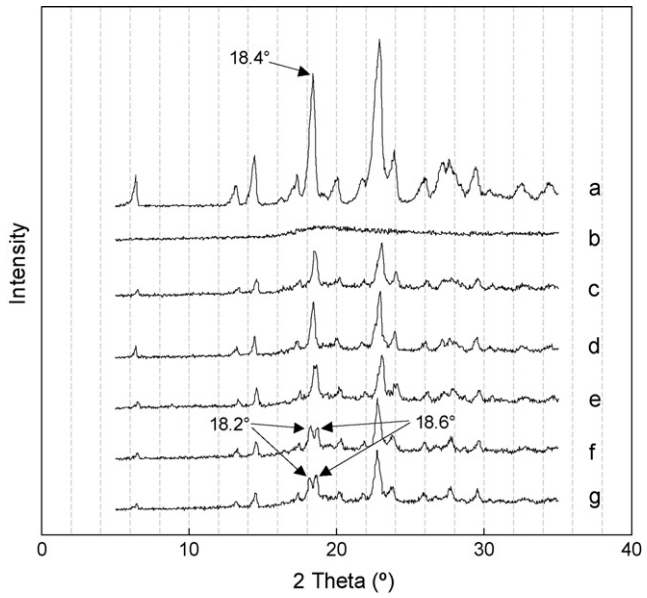

Fig. 6. Powder X-ray diffraction patterns of (a) ketoprofen, (b) SBE_7-β-CD and 1:1 ketoprofen-SBE_7-β-CD binary systems: (c) physical mixtures, (d) co-ground, (e) freeze-dried, (f) heat-treated at 100 °C for 6 h and (g) hot-melt extruded samples.

whereas the amount of ketoprofen released after 30 min from pure drug and the hot-melt extrudates prepared with the parent β-CD was 33.7 and 55.4%, respectively (Fig. 5). Furthermore, as shown in Fig. 4, the ketoprofen released after 30 and 120 min in 0.1N HCl containing SBE_7-β-CD was approximately 41.6 and 73.0%, respectively. These results suggested that the complexation and/or solid dispersion formation of ketoprofen with SBE_7-β-CD allowed the cyclodextrin to function as a solubilizing and wetting agent for ketoprofen in 0.1N HCl. In addition, due to the high solubility of SBE_7-β-CD in aqueous media as compared to the parent β-CD, the extrudates produced with SBE_7-β-CD showed a substantial improvement in dissolution rate over extrudates produced with β-CD.

3.5. Solid characteristics and dissolution profiles of binary systems containing ketoprofen and SBE_7-β-CD

3.5.1. Thermal characteristics

DSC studies for ketoprofen, SBE_7-β-CD and 1:1 ketoprofen-SBE_7-β-CD binary samples were conducted to investigate the influence of sample preparation methods on the thermograms for ketoprofen and SBE_7-β-CD (data not shown). The DSC thermograms for ketoprofen and SBE_7-β-CD exhibited endothermic peaks at 96.1 °C and approximately 265 °C, which correspond to their respective melting points. For the binary systems prepared by hot-melt extrusion, co-grinding, freeze-drying and heat-treatment, the endothermic melting peak of ketoprofen occurred at a slightly lower temperature due to the incorporation of SBE_7-β-CD. The melting peak for SBE_7-β-CD of approximately 265 °C disappeared from the profile and two new endothermic peaks at approximately 240 and 275 °C appeared. These thermal changes could simply be due to the presence of ketoprofen since the DSC thermograph for the physical mixture also revealed a pattern similar to the other binary systems. At temperatures above 200 °C, ketoprofen is molten and decomposed which could alter the melting profiles for SBE_7-β-CD.

3.5.2. Evaluation of drug crystalline states in samples with XRD

The crystalline states of ketoprofen in samples were investigated with XRD studies. As shown in Fig. 6, physical mixtures, co-ground and freeze-dried samples exhibited patterns indicative of crystalline ketoprofen. The samples prepared by hot-melt extrusion and heat-treatment exhibited altered XRD patterns. These results demonstrated that the crystal form of ketoprofen was not affected by the processes of co-grinding and freeze-drying, whereas thermal processing by hot-melt extrusion and heat-treatment influenced the crystal form of ketoprofen. In the XRD patterns of both the hot-melt extruded and the heat-treated samples, two new crystalline peaks were observed at 18.2° (2θ) and 18.6° (2θ) while the peak at 18.4° (2θ) corresponding to the native ketoprofen crystal was absent. This was due to the crystalline transformation of ketoprofen by thermal processing at a temperature above the melting point of ketoprofen since pure ketoprofen stored at 100 °C for 6 h also showed the same XRD pattern (data not shown).

This XRD experiment revealed that no significant loss of crystalline ketoprofen occurred from processing for all samples. This was attributed to the sample composition of ketoprofen and SBE_7-β-CD in a 1 to 1 weight ratio which corresponds to approximately a 9:1 molar ratio. Therefore, only 12% of ketoprofen in the sample can theoretically form an inclusion complex with SBE_7-β-CD during processing. Since the formation of inclusion complexes corresponds to a maximum of 6% of the total sample weight, no significant difference on XRD patterns would be observed.

3.5.3. Ketoprofen release from samples

Fig. 7 shows the release properties of ketoprofen from 1:1 ketoprofen-SBE_7-β-CD binary samples prepared by physical

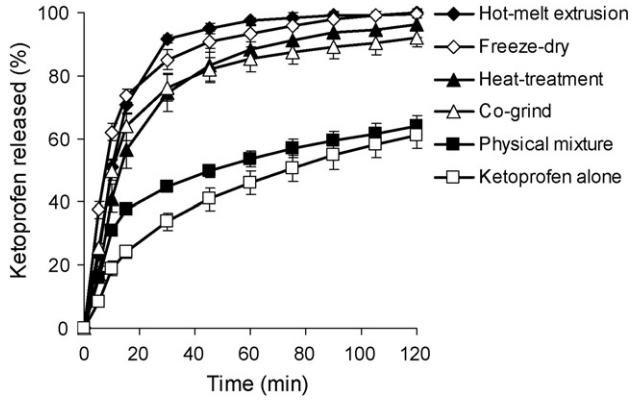

Fig. 7. Release profiles of pure ketoprofen and 1:1 ketoprofen-SBE_7-β-CD binary systems prepared by physical mixing, co-grinding, freeze-drying, heat-treatment at 100 °C for 6 h and hot-melt extrusion in 900 ml of 0.1N HCl at 37 ± 0.5 °C (USP 29 Apparatus 2, 50 rpm). Each point represents the mean ± standard deviation, $n = 6$.

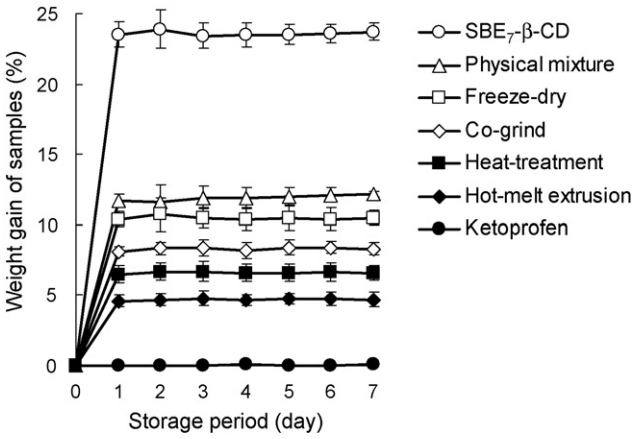

Fig. 8. Weight gain of ketoprofen, SBE_7-β-CD and 1:1 ketoprofen-SBE_7-β-CD binary samples prepared by physical mixing, freeze-drying, co-grinding, heat-treatment at 100 °C for 6 h and hot-melt extrusion on storage at 40 °C/75%RH in opened HDPE bottles for 7 days. Each point represents the mean ± standard deviation, $n = 3$.

mixing, co-grinding, freeze-drying, heat-treatment and hot-melt extrusion as well as pure ketoprofen. In addition to the hot-melt extruded sample, the samples prepared by co-grinding, freeze-drying and heat-treatment also exhibited an increase in the ketoprofen release rate in 0.1N HCl as compared to the physical mixture and pure drug. The ketoprofen release rates in 0.1N HCl from the physical mixture and pure drug were both very slow with less than 65% dissolved within 120 min, while each of the processed samples exhibited between 92 and 100% release in 120 min.

These results demonstrated that SBE_7-β-CD would improve both the solubility and the dissolution rate for poorly soluble drugs by thermal processing, freeze-drying and co-grinding, but not with simple physical mixing; thus, indicating that the intimacy of mixing and extent of complexation substantially affects the ability of SBE_7-β-CD to improve the dissolution properties of a poorly water-soluble drug.

3.6. Moisture absorption study

Since SBE_7-β-CD is quite hygroscopic, it was hypothesized that differences in the intimacy of mixing and the extent of complexation between ketoprofen and SBE_7-β-CD could be elucidated for the different sample preparation methods by investigating the extent of moisture absorption and the resulting change in drug release for each sample. It was hypothesized that the extent of moisture absorption was directly proportional to the amount of hygroscopic surface area on the ketoprofen-SBE_7-β-CD particles. Thus, moisture absorption would be indicative of the intimacy of mixing of ketoprofen with SBE_7-β-CD in each sample, namely the extent of complexation and ketoprofen coverage on the SBE_7-β-CD particle surface.

In order to investigate the extent of moisture absorption and the resulting affect on drug release properties, each of the 1:1 ketoprofen–SBE_7-β-CD binary samples prepared by physical mixing, co-grinding, freeze-drying, heat-treatment and hot-melt extrusion was placed in a 40 °C/75%RH environment in opened HDPE bottles for 7 days and subsequently evaluated for absorbed moisture and change in drug release profile. As shown in Fig. 8, SBE_7-β-CD absorbed substantial moisture (23.4–23.9%) following the first 24 h of storage which was maintained for the remainder of the study, whereas ketoprofen powder alone showed no weight gain over 7 days. Interestingly, for the processed binary samples, the hot-melt extruded sample showed the least extent of moisture absorption (4.6–4.8%) followed by the heat-treated sample (6.5–6.7%), the co-ground sample (8.1–8.4%), the freeze-dried sample (10.4–10.7%), and the physical mixture (11.6–12.2%).

This result suggested that the most intimate mixture between ketoprofen and SBE_7-β-CD was achieved with hot-melt extrusion followed by heat-treatment, co-grinding, freeze-drying, and physically mixing. It is clear that the act of melting ketoprofen in the presence of SBE_7-β-CD allows for a greater extent of inclusion complexation and formation of a solid dispersion of ketoprofen on SBE_7-β-CD particles than with the other investigated non-melt methods as there appears to be less available hygroscopic surface area in these samples. Additionally, it appears that improved intimacy of mixing is achieved with hot-melt extrusion processing over heat-treatment. This is likely due to more extensive dispersion of molten ketoprofen onto the SBE_7-β-CD particles by the mechanical agitation of the rotating screw in the barrel of extruder during processing. Conversely, the dispersed state of ketoprofen in the heat-treated samples could be incomplete since no mechanical agitation was utilized during processing.

The change in ketoprofen release profile following the moisture absorption study for the co-ground, freeze-dried, hot-melt extruded, and heat-treated samples is shown in Fig. 9. In this figure, it can be seen that the ketoprofen release rates from the co-ground and freeze-dried samples were found to substantially decrease following storage. The thermally processed samples exhibited less decrease in the drug release rate than the non-melt processing methods with the hot-melt extruded sample showing slightly less reduction in release rate than the heat-treated sample.

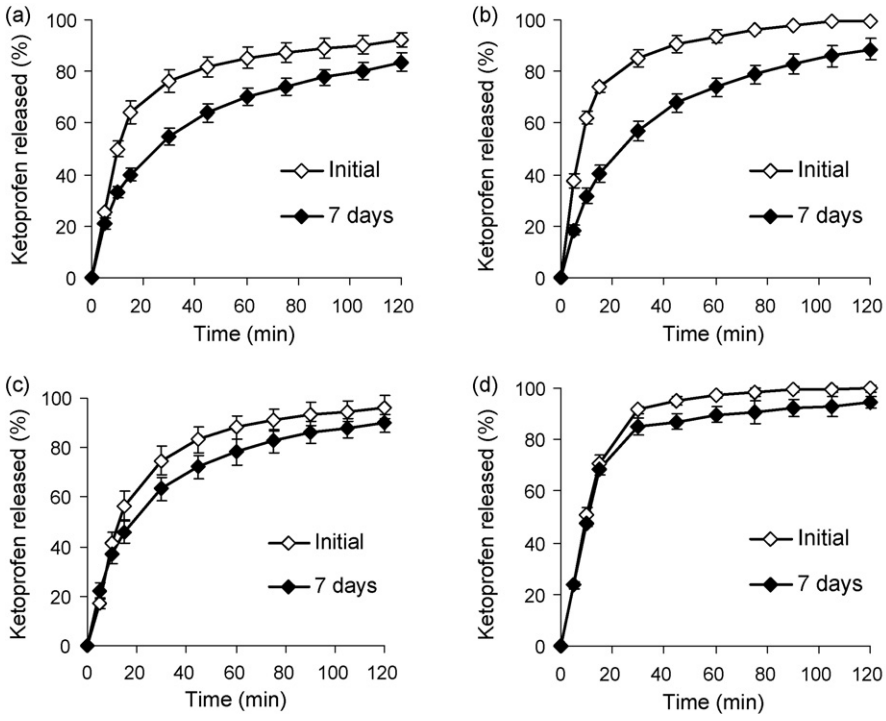

Fig. 9. Ketoprofen release from 1:1 ketoprofen-SBE_7-β-CD binary samples stored at 40 °C/75%RH in opened HDPE bottles for 7 days in 900 ml of 0.1N HCl at 37 ± 0.5 °C (USP 29 Apparatus 2, 50 rpm): (a) co-ground, (b) freeze-dried, (c) heat-treated and (d) hot-melt extruded samples. Each point represents the mean ± standard deviation, $n = 6$.

From visual observation of the samples following exposure to the 40 °C/75%RH environment, it was seen that particle aggregation occurred in accordance with moisture absorption. Hence, the samples that absorbed the most moisture tended to aggregate to a greater extent. Since particle aggregation causes a reduction in surface area available for dissolution, the ultimate result was reduction in the release rate of ketoprofen from each sample in proportion to the amount of absorbed moisture. In this study, the extrudates of ketoprofen with SBE_7-β-CD exhibited no significant particle aggregation and the least moisture absorption when exposed to elevated humidity, resulting in the lowest change in drug release under a high humidity condition among the samples prepared in this study. Evaluation of each sample by XRD revealed that no morphological changes occurred on exposure to the 40 °C/75%RH environment that could have contributed to the observed reduction in dissolution rate (data not shown). This suggests that changes in the drug release properties with moisture absorption are attributable entirely to particle aggregation resulting from moisture absorption, and not according to alteration of the crystalline state of ketoprofen during storage.

Considering the results of this moisture absorption study along with the physiochemical characterization of the samples, it is apparent that hot-melt extrusion processing of ketoprofen with SBE_7-β-CD increases the dissolution properties of ketoprofen due to the synergistic effects of the formation of an intimate solid dispersion of ketoprofen on SBE_7-β-CD particles, and partial complexation of ketoprofen with SBE_7-β-CD during extrusion processing. The unique qualities of the hot-melt extruded ketoprofen-SBE_7-β-CD sample in combination with the efficiency of processing and lack of solvent required indicate substantial benefits for the utilization of hot-melt extrusion for combining poorly water-soluble drugs with cyclodextrins.

4. Conclusions

SBE_7-β-CD was found to be a more effective solubilizing agent for ketoprofen than β-CD due to greater electronic interactions between ketoprofen and SBE_7-β-CD than with the parent β-CD. Complexation of ketoprofen with SBE_7-β-CD and/or the formation of an intimate dispersion of ketoprofen with SBE_7-β-CD particles were found to be essential to achieving the solubilization effect of the cyclodextrin. Hot-melt extrusion processing of ketoprofen with SBE_7-β-CD at an extrusion temperature close to the melting point of ketoprofen (100 °C) and considerably lower than the melting point of SBE_7-β-CD (approximately 235 °C) resulted in an intimate dispersion of ketoprofen on SBE_7-β-CD particles, partial complexation of ketoprofen with SBE_7-β-CD, as well as a crystalline polymorph of the drug. Especially, the extent of intimacy of mixing achieved with hot-melt extrusion was seen to be superior to that of co-grinding, freeze-drying, and heat-treatment. The hot-melt extrudates exhibited no particle aggregation and the least change in the drug release rate when exposed to elevated humidity, while both co-ground and freeze-dried samples showed significant particle aggregation and a decrease in the drug release rate due to a reduction in surface area available for dissolution. As a result of this improved mixing, the enhancement of the dissolution properties of ketoprofen by hot-melt extrusion with SBE_7-β-CD was found to be more substantial than with the binary samples prepared by co-grinding and freeze-drying. The present study

therefore demonstrated that hot-melt extrusion with SBE_7-β-CD at a temperature close to the melting point of the model drug would be useful to increase the solubility and enhance the drug release properties of poorly water-soluble drugs without the use of solvents or complicated processing steps.

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