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Enhanced dissolution of furosemide by coprecipitating or cogrinding with crospovidone

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Abstract

To increase the dissolution rate of furosemide, cogrinding or coprecipitating of furosemide with crospovidone was carried out. The 1:2 (w/w) ground mixture of furosemide with crospovidone was prepared by cogrinding in a ceramic ball mill and the coprecipitate was prepared by the solvent method using methanol. The dissolution test was carried at 37 ± 0.5°C and 150 rpm in simulated gastric fluids (pH 1.2). The dissolution rate of furosemide was rapid and markedly enhanced by cogrinding or coprecipitating with crospovidone. The X-ray diffraction, IR, DTA and TGA studies showed the physicochemical modifications of the furosemide from the ground mixture or the coprecipitate. Furosemide alone or furosemide contained within a physical mixture was crystalline in nature, whereas furosemide in the ground mixture or the coprecipitate was not crystalline even when preserved at room temperature for 1 year. An interaction, in the ground mixture or in the coprecipitate, such as an association between the functional groups of furosemide and crospovidone may have occurred at the molecular level, changed the thermal property and increased the dissolution of furosemide. The cogrinding or coprecipitating techniques with crospovidone provide a promising way to increase the dissolution rate of poorly soluble drugs.

Keywords: Furosemide; Ground mixture; Coprecipitate; Crospovidone; Dissolution; Physicochemical characterization

1. Introduction

When a relatively water insoluble drug is administered orally, the dissolution may be the rate-determining step for the appearance of the medicinal effect. Therefore, great efforts have been made to increase the dissolution rate.

One of the techniques that can potentially enhance the dissolution rate of hydrophobic drugs is the formation of coprecipitates with pharmacologically inert, polymeric materials. A number of investigations (Shin, 1979a,b; Shah et al., 1995;

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Iwata and Ueda, 1996; Kai et al., 1996; Shin and Cho, 1997; Okimoto et al., 1997; Nagarsenker and Garad, 1998) demonstrates that the formation of molecular solid dispersions or coprecipitates of relatively water insoluble drugs with various water-soluble polymers can significantly increase their in vitro dissolution rates and/or in vivo absorption.

In preparing the powdered products, grinding is generally used for reducing particle size, since the dissolution rate is strongly affected by particle size. It has been reported that a strong force (such as grinding) may increase the surface energy and cause distortion of the crystal lattice as well as reducing particle size (Yamaguchi and Sakamoto, 1959) together with reducing the size. It was reported that cogrinding of drug with hydroxypropylmethylcellulose (Sugimoto et al., 1998), β-cyclodextrin (Mitrevej et al., 1996; Arias et al., 1997), chitin and chitosan (Koh et al., 1986a,b), crystalline cellulose (Yamamoto et al., 1974, 1976; Nakai et al., 1978), and gelatine (Kigasawa et al., 1981), enhanced the dissolution properties of relatively water insoluble drugs.

In this study, the dissolution enhancement of furosemide, a weak acid having pK_a 3.8, was attempted by a cogrinding or coprecipitating technique with crospovidone, a physically crosslinked insoluble polyvinylpyrrolidone (BASF Corporation, 1996). The dissolution properties and physicochemical properties of the ground mixtures and the coprecipitates of furosemide with crospovidone were investigated by dissolution test, infrared spectroscopy (IR), X-ray diffractometry, differential thermal analysis (DTA) and thermogravimetric analysis (TGA).

2. Materials and methods

2.1. Materials

Furosemide (Teva Middle East Pharm. and Chemical Works), crospovidone (BASF Corporation, Germany) in 100 mesh sieve sized were of pharmaceutical grade. All other chemicals were reagent grade and used as received.

2.2. Preparation of furosemide test preparations

The 1:2 (w/w) ratio physical mixture of furosemide and crospovidone were mixed uniformly through a 100 mesh sieve screen with care to avoid any grinding action. The 1:2 (w/w) ground mixture of furosemide and crospovidone was prepared by cogrinding in a ceramic ball mill for 24 h. The mill consisted of a porcelain jar filled with spherical grinding media of different size in order to obtain intimate contact between the powder and media themselves. The 1:2 ratio furosemide–crospovidone coprecipitate were prepared by the solvent method (Shin, 1979a) using methanol.

2.3. Dissolution test

The dissolution test of furosemide from the different test preparations was carried out in triplicate at 37 ± 0.5°C and 150 rpm in simulated gastric fluids (pH 1.2, USP-23) using a Prolabo dissolution tester. Each test preparation equivalent to 40 mg of furosemide, which is an excess amount of drug beyond its equilibrium solubility, was transferred into 500 ml dissolution medium. A 2.0 ml sample solution was withdrawn at appropriate time intervals and filtered through a 0.45 μm millipore filter and immediately replaced with an equal volume of fresh dissolution medium. The amount dissolved was calculated by determining the absorbance of an appropriately diluted solution at 274 nm.

2.4. Spectroscopic characterization of furosemide–crospovidone test preparation

Powder X-ray diffraction patterns of furosemide test preparations, even preserved for 1 year, were measured using a Rigaku Geigerflex X-ray diffractometer. The target was a Cu-tube (Ni-filter), 35 kV, 15 mA and the detector was a proportional counter with a voltage of 1.7 kV. Infrared spectra for the furosemide test systems were observed by the potassium bromide disk method, with a double beam, Perkin-Elmer infrared spectrophotometer. Thermogravimetric and differential thermal analyses were carried out

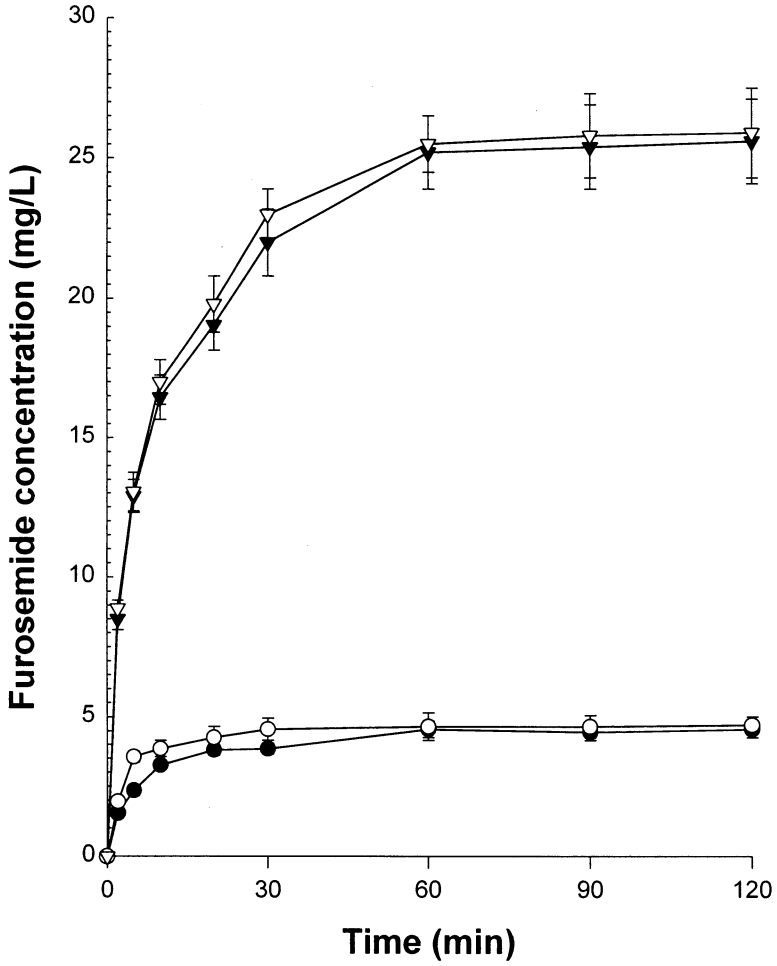

Fig. 1. Dissolution profiles of furosemide at 37°C and 150 rpm. ●, Pure furosemide; ○, the 1:2 furosemide–crospovidone physical mixture; ▼, the 1:2 furosemide–crospovidone coprecipitate; and ▽, the 1:2 furosemide–crospovidone ground mixture.

using a Seiko TG-DTA apparatus, fitted with a Pt dish. The reference material was 5 mg of α-alumina, the heating rate, 10°C/min, and the upper temperature limit, 600°C.

3. Results and discussion

3.1. Dissolution rate studies

The effect of crospovidone on the dissolution of furosemide was investigated for the furosemide test preparations. The dissolved amounts of furosemide from the 1:2 furosemide–crospovidone ground mixture and the coprecipitate were increased about 5.8-fold compared with that of pure furosemide at 120 min. The amount of furosemide in solution from the 1:2 furosemide–crospovidone ground mixture or the coprecipitate rapidly and markedly exceeded that from the same ratio physical mixture (Fig. 1).

Of considerable interest was the fact that even though the size of the drug available for dissolution was same, the dissolution phenomena of furosemide from the pure furosemide and the physical mixture were quite different. The pure furosemide was observed to float on the surface of the dissolution medium for longer than the physi-

cal mixture. The slight increase noted in the rate of solution of furosemide from the physical mixture as compared with the pure drug is almost likely due to the ability of the polymer to enhance the wettability of the hydrophobic furosemide particles and could also be a 'microenvironment effect'. This suggests that simple particle size reduction is not responsible for the enhanced dissolution of furosemide experienced with the ground mixture or the coprecipitate system. This result indicates the mere presence of crospovidone in the ground mixture, as compared to the physical mixture, is not responsible for the enhanced dissolution rate of furosemide.

A marked influence of the dispersion methods such as simple blending, solvent deposition, ball milling, and Muller milling on the dissolution rate and bioavailability of digoxin has been reported (Ampolsuk et al., 1974; Shah et al., 1974). Triturations prepared by ball milling and Muller milling have been shown to dissolve much faster than a simple blend, which in turn dissolved slightly faster than digoxin. A comparison of dissolution characteristics of the 1:2 furosemide–crospovidone ground mixture and the coprecipitate with those of the same ratio physical mixture indicates that both the ground mixture and the coprecipitate preparations go into solution at a much faster rate than the physical mixture. The role of crospovidone in the different enhancement of dissolution rate of furosemide from the ground mixture, coprecipitate, and the physical mixture is quite interesting. In conclusion, cogrinding of furosemide with crospovidone gave the fastest dissolution of furosemide. Apparently, furosemide and crospovidone act independently in the physical mixture, while the role of crospovidone in the ground mixture alters the physical characteristics of furosemide. Therefore, one can postulate that there might be an interaction between furosemide and crospovidone.

3.2. X-ray diffraction

In preparing the powdered products, grinding is generally used for reducing the particle size, and the dissolution rate is often strongly affected by the particle size. In spite of the same combination ratio of drug to crospovidone and same particle size, the dissolution rate of furosemide from the ground mixture or the coprecipitate were markedly enhanced compared with that of the physical mixture. At this point, X-ray diffraction studies were undertaken in an attempt to unravel these phenomena.

The pure furosemide showed the same diffraction peaks at 2θ degree of 18.0, 18.9, 24.7 and 28.6 etc., indicating the presence of crystalline furosemide. Interestingly, the physical mixture also showed crystallinity supposedly due to the presence of crystalline furosemide. Thus, the mere presence of crospovidone in the physical mixture does not interfere with the characterization of the coexisting furosemide. On the other hand, the 1:2 ratio furosemide–crospovidone ground mixture or the coprecipitate (Fig. 2) did not show any crystallinity (even when preserved at room temperature for 1 year). This result implies that furosemide is present in an amorphous form both in the ground mixture and the coprecipitate.

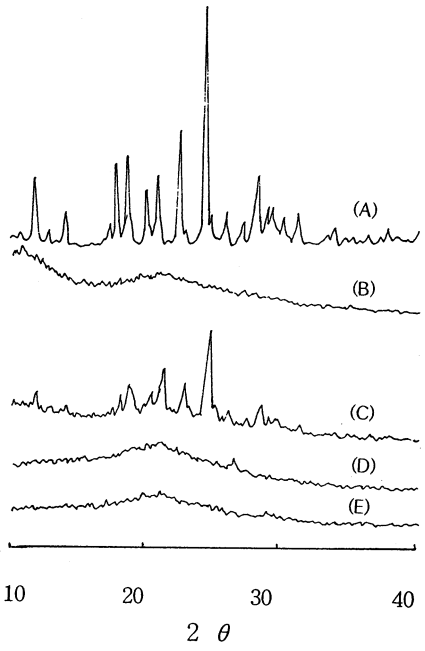

Fig. 2. X-ray diffraction data of 1:2 furosemide–crospovidone test preparations: A, pure furosemide; B, pure crospovidone; C, the physical mixture; D, the ground mixture (the same as that preserved for 1 year); and E, the coprecipitate (the same as that preserved for 1 year).

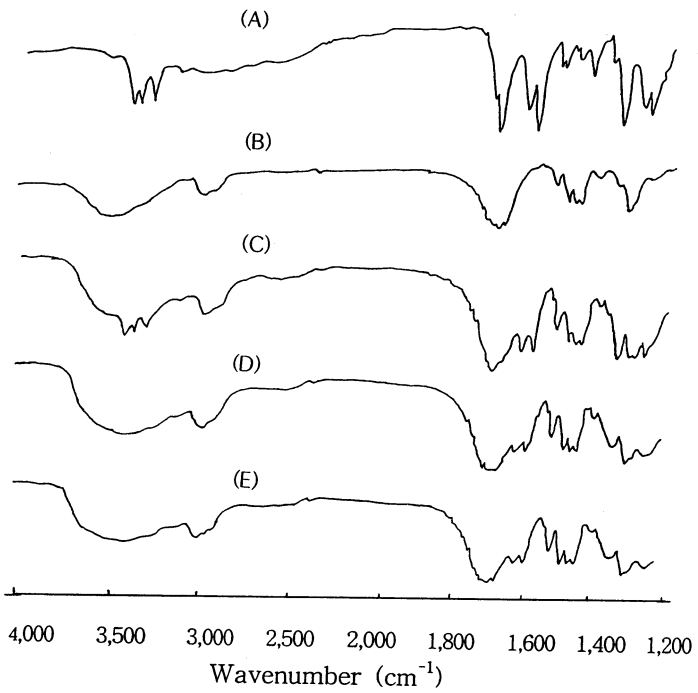

Fig. 3. Infrared spectrograms of 1:2 furosemide–crospovidone test preparations: A, pure furosemide; B, pure crospovidone; C, the physical mixture; D, the ground mixture; and E, the coprecipitate.

When pure furosemide without crospovidone was ground in a similar manner, the crystalline structure of furosemide was not changed. According to these results, the amorphous property of furosemide in the ground mixture is considered to be mainly responsible for the enhanced dissolution. In general, crospovidone forms molecular adducts with many organic substances (BASF Corporation, 1996). Since crospovidone is a macromolecular polymer, one can postulate that furosemide might be interwoven among the crospovidone frame structure, with the functional groups of furosemide and crospovidone interacting relatively and, hence, the crystallinity of the furosemide was not shown by X-ray diffraction.

3.3. IR spectroscopy

As an interaction between furosemide and crospovidone in the solid state was suggested, IR absorption spectroscopy was carried out to further elucidate the physicochemical properties.

From the infrared spectrum of pure furosemide, an absorption band was observed at 3340 cm^{-1} and 3260 cm^{-1} in the region of 3500–3200 cm^{-1}, and a sharp band was observed at 1665 cm^{-1} and 1560 cm^{-1} in the region of 1700–1500 cm^{-1} (Fig. 3). The 3340 cm^{-1} band is assigned to the NH stretching vibration of $Ar–NHCH_2$ and the 3260 cm^{-1} band to the stretching vibration of SO_2NH_2, the 1665 cm^{-1} band, which appears at such a high frequency region, is assigned to the bending vibration of the amino group, the 1560 cm^{-1} band is assigned to the asymmetric stretching vibration of the carboxyl group and the 1318 cm^{-1} band is to that of sulfonyl group in the furosemide structure. Crospovidone shows the same infrared spectrum as povidone (BASF Corporation, 1996) with absorption bands at 1680 cm^{-1} due to the carboxyl group, and at 2940 cm^{-1} due to the CH-stretching vibration. However, the absorption band at 3500 cm^{-1} is probably due to the adsorbed water, which was identified by the Karl–Fischer water determina-

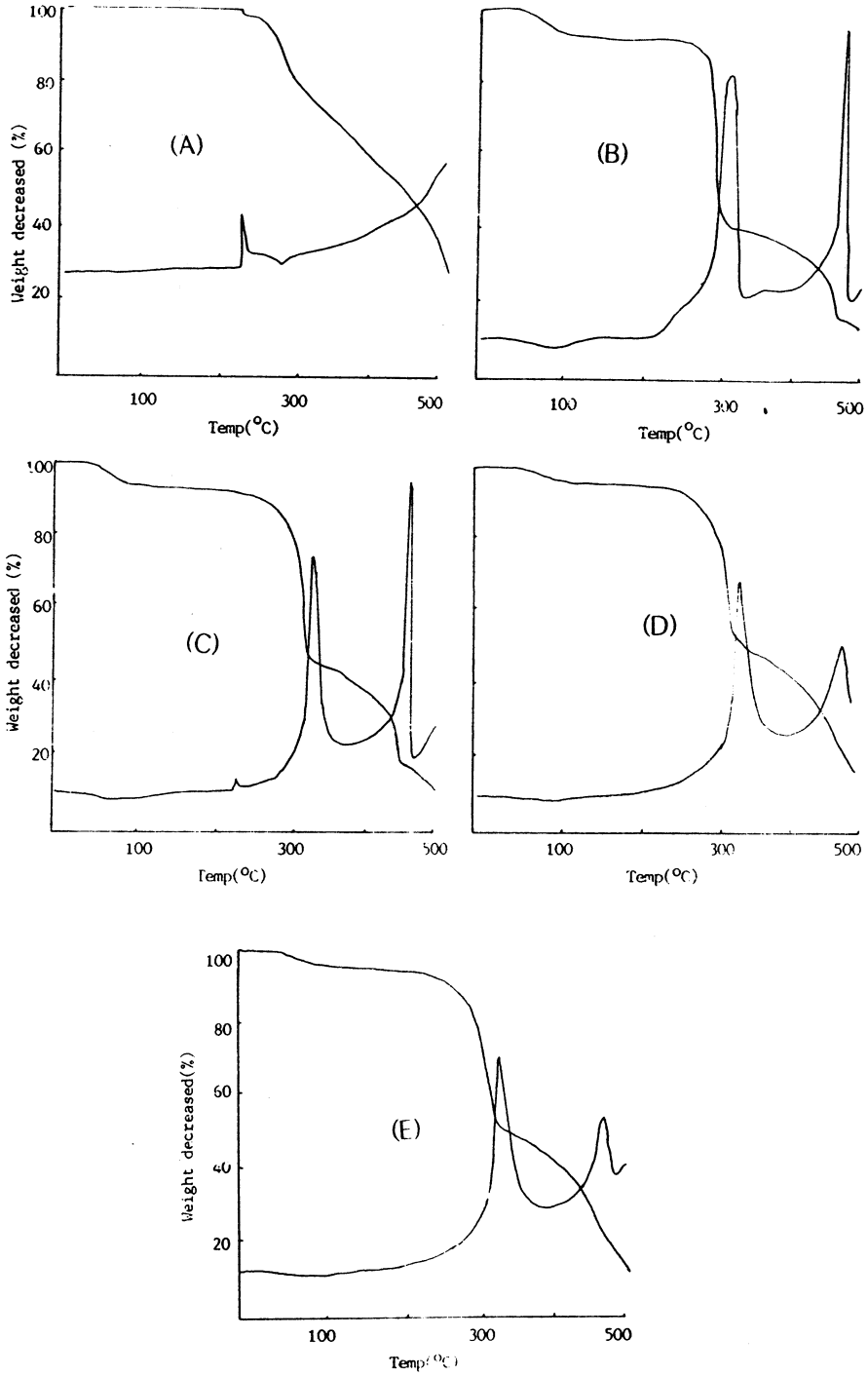

Fig. 4. DTA and TGA thermograms of 1:2 furosemide–crospovidone test preparations: A, pure furosemide; B, pure crospovidone; C, the physical mixture; D, the ground mixture; and E, the coprecipitate.

tion method and DT/TGA results, according to assignment by Oster (Oster and Immergut, 1954).

The stretching bands in the region of 3500–3200 cm^{-1}, assigned to the non-bonded aromatic imino group and sulfonylamide group in the furosemide molecule, was seen in the infrared spectrum of the physical mixture, but was not seen (Fig. 3) in the spectra of the ground mixture and the coprecipitate. Therefore, it is presumed that the ground mixture and the coprecipitate show an interaction such as an association between the functional groups of furosemide and crospovidone at the molecular level. The association between furosemide and crospovidone is expected to be most probable between the imino group and the sulfonylamide group of furosemide and the carboxyl group of crospovidone.

3.4. Thermal analyses

The DTA and the TGA thermograms for the furosemide test systems are shown in Fig. 4. The TGA thermograms of furosemide showed a weight loss of about 3.3% at 205°C which was within the reported melting point range of 203–206°C with decomposition, and the weight loss up to 300°C was about 22%, and the DTA curves of furosemide exhibited a single, sharp exothermic peak at a temperature of 220°C and an endothermic peak at about 280°C. The weight loss of about 3.3% at 205°C in the TGA thermograms seems most probably to be due to ammonia decomposition in the furosemide molecule. The weight loss of about 5% up to 100°C in the TGA curves of crospovidone (Fig. 4) and the water content of 5% determined by the Karl–Fisher method was in good agreement, indicating that the water was adsorbed into the crospovidone polymer frame structure. TGA thermograms of crospovidone showed very slow weight loss in the range 100–250°C. In the temperature range 400–450°C it is supposed that crospovidone was decomposed, and this decomposition was also supported by the DTA results. In the literature (BASF Corporation, 1996), several conflicting values of a glass transition temperature for poly(*N*-vinylpyrrolidone) were found ranging from 54 to 175°C. These may be attributed to the influence of sorbed moisture due to the hygroscopic nature of crospovidone. TGA curves of the physical mixture, the ground mixture and the coprecipitate (Fig. 4) showed the same patterns. All these showed the same weight loss of about 5% up to 100°C meaning dehydration, and high weight loss of about 40% between 250–400°C showing the degradation.

A comparison of DTA thermograms of the physical mixture and the ground mixture showed a transition peak, whereas furosemide only showed the sharp exothermic peak at 205°C resulting from the decomposition of furosemide. Their temperature range of transition appeared to be somewhat different from that of furosemide. It was reported that an apparent amorphous state of benzoic acid produced by vibrational ball milling with microcrystalline cellulose has been demonstrated (Yamamoto et al., 1976) by its lack of melting point from differential thermal calorimetric measurements. Some of the possible transformations that may take place during the ball milling process seems to be the formation of an amorphous structure either by partial melting of the crystalline furosemide powder and its interaction with furosemide or by the production of lattice defects due to the shear stress and impact stress. The effect of grinding on the heat of fusion and on the crystalline peaks of the X-ray diffraction are closely correlated to each other. The relative enthalpy change may be considered to correspond to the disappearance of crystallinity. It may be said that the drug molecules are dispersed in the crospovidone matrix of the ground mixture or the coprecipitate and the thermal property was changed.

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