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Enhancement of Dissolution Properties of Ketoprofen from Ground Mixtures with Chitin or Chitosan

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The ground mixtures of ketoprofen with chitin or chitosan were prepared by grinding in a ball mill to increase the dissolution rate. The ground mixture showed a faster and more enhanced dissolution rate than the physical mixture or intact ketoprofen.

The X-ray diffraction peaks indicated the production of the amorphous form of ketoprofen in the ground mixture. An interaction, in the ground mixture, such as association between the functional groups of ketoprofen and chitin or chitosan might occur in the molecular level. The endothermic peak due to the fusion of ketoprofen disappeared in the ground mixture indicating the different thermal property.

The co-grinding technique with chitin or chitosan provided a promising way enhancing the dissolution rate of practically insoluble drug.

When a relatively insoluble drug is administered orally, the dissolution step often plays an important role in the rate of absorption. Therefore, great efforts[1-12] have been made to increase the dissoltion rates.

In earlier studies, it was shown that polyvinylpyrrolidone and polyethylene glycol, in the form of coprecipitates with furosemide,[8-12] allobarbital,[12] and phenobarbital,[11] enhanced markedly the rate of dissolution of these water-insoluble drugs.

In preparing the powdered products, grinding is generally used for reducing the particle size, since the dissolution rate is strongly affected by the particle size. It has been reported that a strong grinding force gives to a solid an increase in the activation energy[13,14] on the surface and in the distortion of the crystal lattice[15,16] together with reducing the size.

Recently, it was reported that co-grinding of drug with crystalline cellulose,[17,18] gelatin,[19] chitin and chitosan[20] enhanced the dissolution properties of practically insoluble drugs.

In this paper, co-grinding technique of ketoprofen with chitin or chitosan which is innocuous and biodegradable natural material is reported. The dissolution properties and physicochemical modification of ground mixtures of ketoprofen were investigated by infrared spectroscopy (IR), X-ray diffractometry, differential thermal analysis (DTA) and thermogravimetric analysis (TGA) studies.

EXPERIMENTAL

Materials

Ketoprofen between 100 and 200 mesh was pharmaceutical grade from Il-yang Pharm. Co., Ltd. (Korea). Chitin and chitosan from Sigma Chemical Co., (U.S.A.) was ground in a ball mill and used after passing a 100 mesh sieve. All other chemicals used were reagent grade.

Apparatus

Dissolution tester (Prolabo dissolution tester), UV spectrophotometer (Perkin-Elmer Lamda 5), X-ray diffractometer (Rigaku Geigerflex), in-

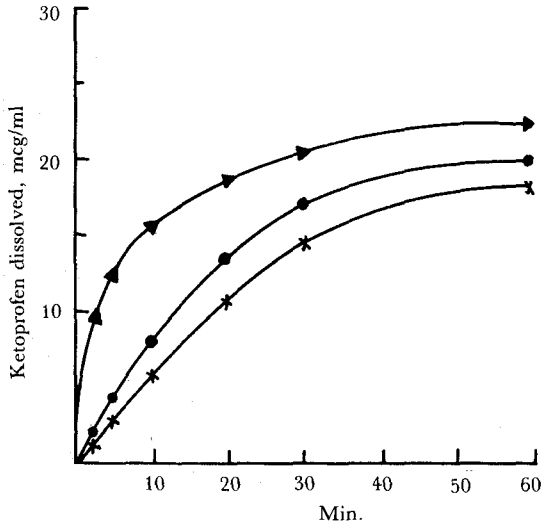

Figure 1—Dissolution rates of ketoprofen at 37°C and 150 rpm.
Key: ×, intact ketoprofen; ●, 1:2 ketoprofen-chitin physical mixture; ▲, 1:2 ketoprofen-chitin ground mixture

frared spectrophotometer (Perkin-Elmer 783) and TG-DTA apparatus (Rigaku Thermoflex) were used.

Preparation of Ketoprofen Test Systems

The 1:2 ground mixtures were prepared by adding 50g of ketoprofen to 100g of chitin or chitosan and grinding in a ceramic ball mill for 24 hours. The same ratio physical mixtures were also prepared respectively by tumbling in a bottle and simple blending in a ceramic mortar.

Dissolution Test

Dissolution rates of ketoprofen from the different test preparations were measured in 300 ml of pharmacopeial disintegration medium of pH 1.2 at 37°C and 150 rpm. Each test preparation equivalent to 40 mg of ketoprofen was transferred directly into the dissolution medium and stirred at 150 rpm. At appropriate time intervals, a suitable aliquot of test solution was withdrawn and filtered through Millipore filter (0.45 μm) and determined at 255 nm. An equal volume of fresh medium was replaced immediately.

X-Ray Diffractometry

Rigaku Geigerflex X-ray diffractometer was used for X-ray diffraction. The target was Cu-tube (Ni-filter), 35 KV, 15 A and the detector

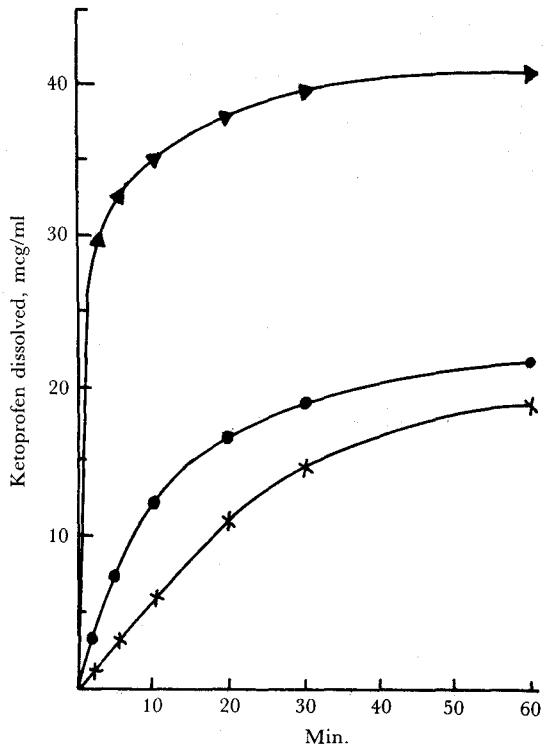

Figure 2—Dissolution rates of ketoprofen at 37°C and 150 rpm.
Key: ×, intact ketoprofen; ●, 1:2 ketoprofen-chitosan physical mixture; ▲, 1:2 ketoprofen-chitosan ground mixture

was proportional counter, 1.7 KV for detector voltage.

IR Absorption Spectroscopy

Infrared spectra for ketoprofen test systems were recorded by potassium bromide disk method, using a double beam infrared spec-

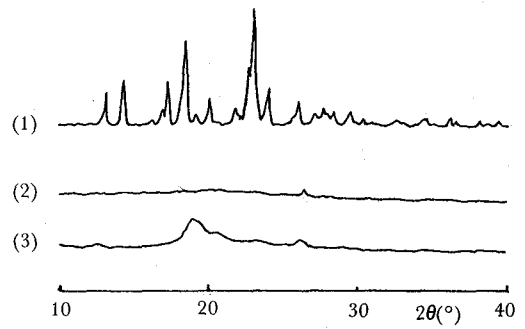

Figure 3—Comparison of X-ray diffraction patterns.
Key: (1), pure ketoprofen (before or after grinding); (2), pure chitosan; (3), pure chitin

trophotometer.

Thermometric Measurements

Thermogravimetric and differential thermal analysis were carried out using TG-DTA apparatus, fitted with platinum dish.

RESULTS AND DISCUSSION

Dissolution Rate Studies

The dissolution patterns of ketoprofen from the 1:2 ketoprofen-chitin ground mixture and the same ratio physical mixture are shown in Fig. 1 and those from the ketoprofen-chitosan test systems are shown in Fig. 2. The dissolution rate of ketoprofen from the physical mixture with chitin or chitosan was observed to be a little faster than that from the intact ketoprofen, while the dissolution rate from the ground mixture with chitin or chitosan was more rapidly, markedly enhanced than that from the same ratio physical mixture, respectively.

This result indicates that the mere presence of chitin or chitosan in the ground mixture as compared with the physical mixture is not responsible for the enhanced dissolution rate of ketoprofen. The slight increase noted in the dissolution rate of ketoprofen from the physical mixture as compared with the pure ketoprofen is almost likely due to the ability of chitin or chitosan to enhance the wettability of the hydrophobic ketoprofen particles. A comparison of dissolution characteristics of the 1:2 ground mixtures with chitin or chitosan with those of the same ratio physical mixtures indicates that ground mixtures go into solution at faster rates than the physical mixtures.

In addition, the role of chitin or chitosan in the different enhancement of the ketoprofen dissolution rate between the ground mixture and the corresponding physical mixture is quite interesting.

In other words, ketoprofen and chitin or chitosan act independently in the physical mixture, while chitin or chitosan in the ground mixture alters the physical properties and solubility of ketoprofen.

In comparison with the dissolution characteristics of ground mixtures with chitin and with chitosan, the ground mixture with chitosan showed faster dissolution rate than that with chitin.

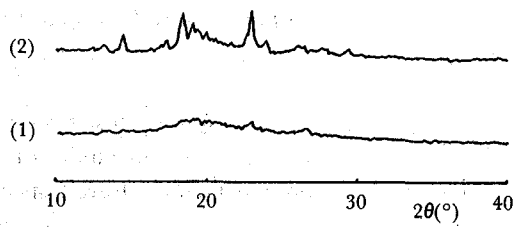

Figure 4—Comparison of X-ray diffraction patterns. Key: (1), 1:2 ketoprofen-chitin physical mixture; (2), 1:2 ketoprofen-chitin ground mixture

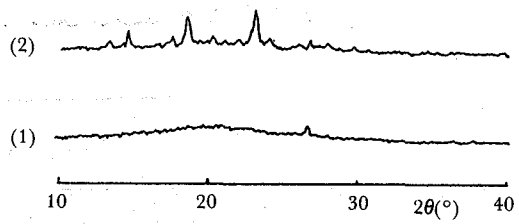

Figure 5—Comparison of X-ray diffraction patterns. Key: (1), 1:2 ketoprofen-chitosan physical mixture; (2), 1:2 ketoprofen-chitosan ground mixture

X-Ray Diffraction Studies

Even though the ratio of drug to chitin or chitosan was same, the dissolution rates between the physical mixture and the ground mixture were different. So, one can postulate that different phases are present in the ground mixtures. In an attempt to elucidate this physicochemical modification, X-ray diffraction studies were undertaken.

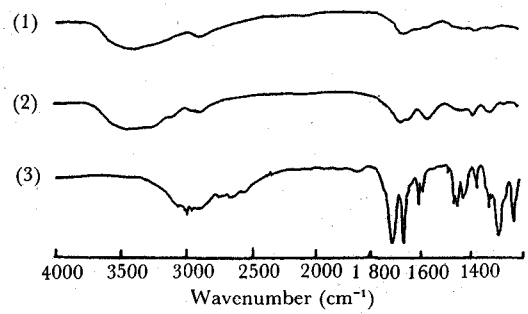

Figure 6—Comparison of infrared spectra. Key: (1), pure chitosan; (2), pure chitin; (3), pure ketoprofen

Fig. 3 shows the X-ray diffraction patterns for pure ketoprofen, pure chitin, and pure chitosan, Fig. 4 shows those for the 1:2 ketoprofen-chitin physical mixture and the same ratio ground mixture, and Fig. 5 shows those for the chitosan systems.

Pure ketoprofen showed diffraction peaks at 2θ degree of 14.4, 18.4, 22.9 etc., indicating the presence of crystalline ketoprofen (Fig. 3). The physical mixture also showed sharp diffraction peaks derived from the remaining crystalline ketoprofen, however, all the ground mixtures did not show any crystallinity of ketoprofen.

Apparently, X-ray diffraction patterns of the 1:2 physical mixture and ground mixture were quite different (Fig. 4 and 5). Thus, the mere presence of chitin or chitosan in the physical mixture should not interfere with the characterization of ketoprofen present.

The changes of the X-ray diffraction patterns in the ground mixtures indicate the transition of ketoprofen from the crystalline state to the amorphous form.

The amorphous property of ketoprofen in the ground mixture was considered to be mainly responsible for the enhanced dissolution.

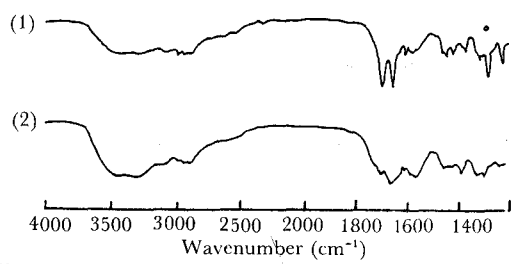

Figure 7—Comparison of infrared spectra.
Key: (1), 1:2 ketoprofen-chitin physical mixture; (2), 1:2 ketoprofen-chitin ground mixture

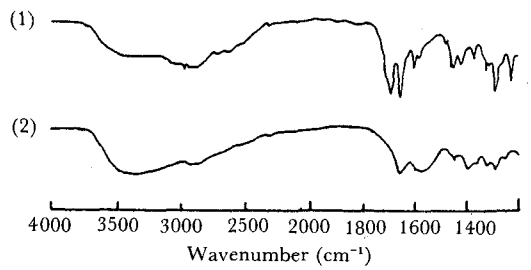

Figure 8—Comparison of infrared spectra.
Key: (1), 1:2 ketoprofen-chitosan physical mixture; (2), 1:2 ketoprofen-chitosan ground mixture

IR Spectra

Infrared absorption spectra were undertaken in an attempt to elucidate further physicochemical property.

Fig. 6 shows the infrared spectra for the pure ketoprofen, chitin, chitosan, and Fig. 7 shows those for the ketoprofen-chitin physical mixture and the same ratio ground mixture, and Fig. 8 shows those for the chitosan systems. The physical mixture showed the absorption bands illustrating the mere presence of ketoprofen and chitin or chitosan. However, the two sharp bands observed at 1700 and 1650 cm^{-1} became broad and weak in the ground mixture. Comparing the spectra of the physical mixture and the ground

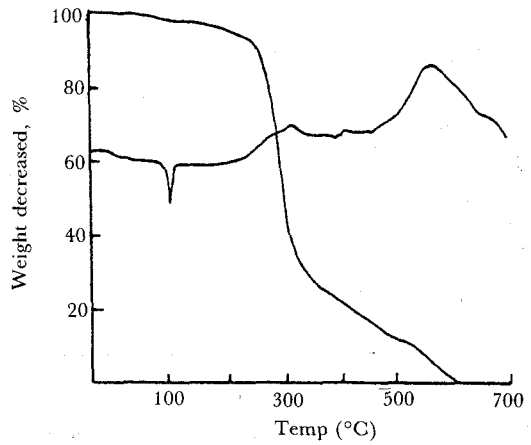

Figure 9—DTA and TGA thermogram of ketoprofen.

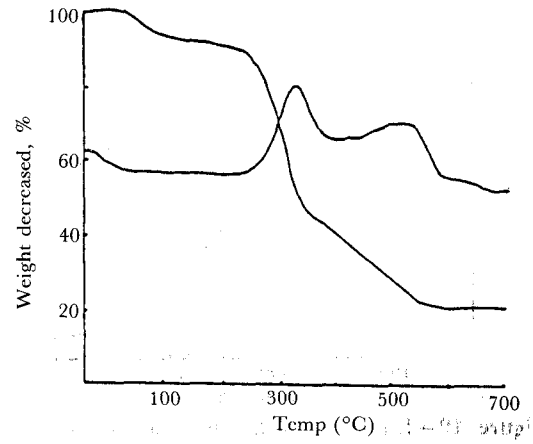

Figure 10—DTA and TGA thermogram of chitin.

mixture, the stretching bands assigned to the carbonyl group of ketoprofen became broad and weak in the ground mixture, whereas, the physical mixture showed the stretching vibrations.

From these results, it was expected that the interaction such as association between the functional groups of ketoprofen and chitin or chitosan might occur in the molecular level.

DTA and TGA Studies

Fig. 9-15 show the DTA and TGA thermograms for the ketoprofen test systems.

Endothermic peak of melting of ketoprofen was shown at 94°C (Fig. 9). The weight loss of about 2 % until 100°C in TGA curves of ketoprofen, and 12 % in chitin or chitosan shows

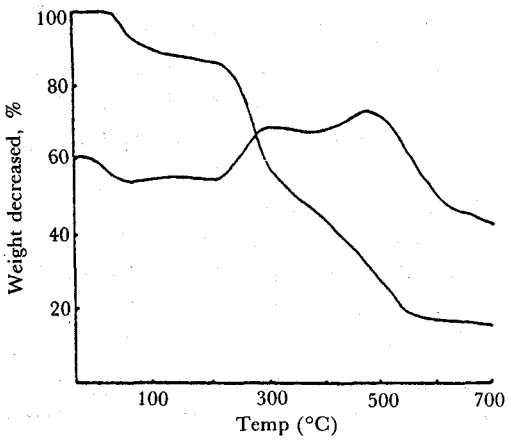

Figure 11—DTA and TGA thermogram of chitosan.

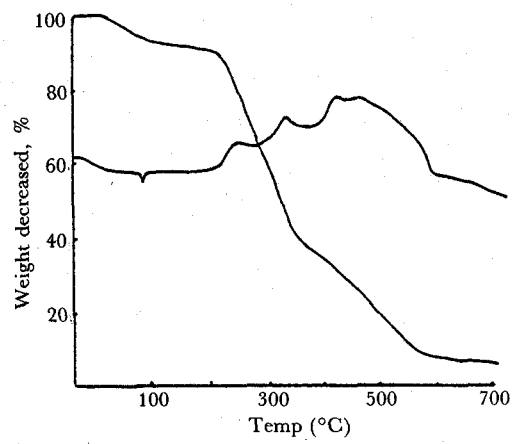

Figure 12—DTA and TGA thermogram of 1:2 ketoprofen-chitin physical mixture.

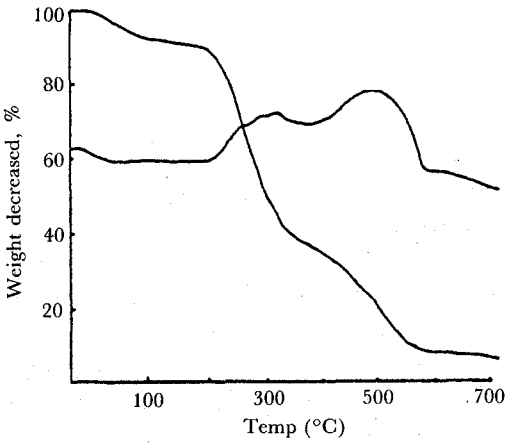

Figure 13—DTA and TGA thermogram of 1:2 ketoprofen-chitin ground mixture.

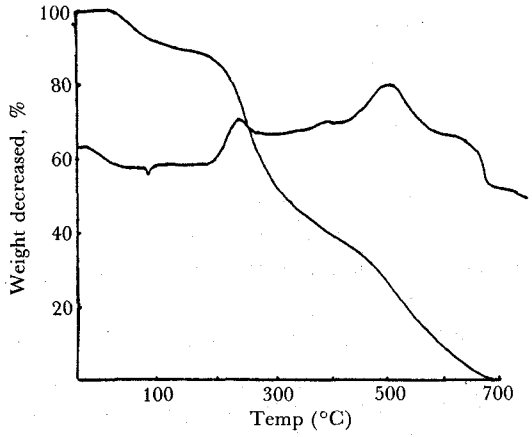

Figure 14—DTA and TGA thermogram of 1:2 ketoprofen-chitosan physical mixture.

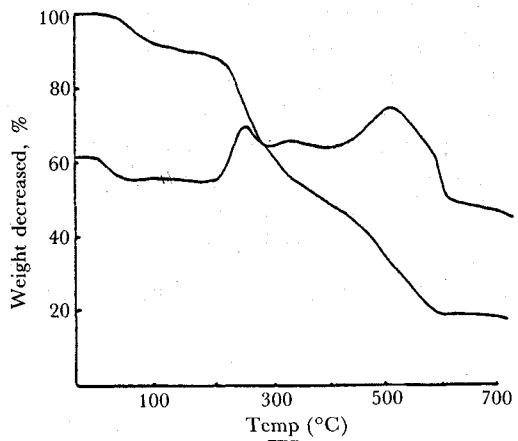

Figure 15—DTA and TGA thermogram of 1:2 ketoprofen-chitosan ground mixture.

dehydration (Fig. 10 and 11). The physical mixture and the ground mixture showed all the same patterns in TGA curves (Fig. 12 and 13). A peak due to the fusion of ketoprofen in the physical mixture appeared near 94°C on the DTA thermogram, whereas that in the ground mixture disappeared. It was unusual that the heat of fusion of ketoprofen was not recorded on the thermograms of the ground mixture with chitin or chitosan.

It was supposed that the thermal property was changed by co-grinding of ketoprofen with chitin or chistosan.

CONCLUSIONS

From the present investigations, following facts could be summarized;

1. The dissolution rate of ketoprofen was significantly enhanced by co-grinding with chitin or chitosan.
2. The extent of enhancing the dissolution of ketoprofen from ground mixtures was in the order of chitosan and then chitin.
3. The co-grinding technique with chitin or chitosan provided a promising way of enhancing the dissolution rate of practically insoluble drug.
4. X-ray diffraction peak indicated the production of the amorphous from of ketoprofen in the ground mixture.
5. An interaction, in the ground mixture, such as association between the functional groups of ketoprofen and chitin or chitosan might occur in the molecular level.
6. The endothermic peak due to the fusion of ketoprofen disappeared in the ground mixture indicating the different thermal property.

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