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Enhanced Dissolution Rates of Piroxicam from the Ground Mixtures with Chitin or Chitosan

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Abstract□To increase the dissolution rate of piroxicam, chitin and chitosan which are widely occurring biodegradable natural materials were used as drug carriers. The ground mixtures of piroxicam with chitin or chitosan were prepared by grinding in a ball mill.

The dissolution rates of piroxicam from the ground mixtures were enhanced markedly than that from the physical mixtures or from intact piroxicam.

The X-ray diffraction peaks disappeared in the ground mixture indicating the production of the amorphous form.

The comparison of infrared spectra of the physical mixture and the ground minture showed an interaction such as association between the functional groups of piroxicam and chitin or chitosan in the molecular level.

The weight losses in TGA curves showed all the same patterns. However, in the ground mixture by DTA curve, the endothermic peak due to the fusion of piroxicam was disappeared indicating the different thermal property.

Keywords□Piroxicam, Chitin, Chitosan, Ground Mixture, Dissolution Rate, IR, X-ray diffraction, DTA, TGA.

The dissolution step often plays an important role in the drug absorption process when water insolube drugs are orally administered. To increase the dissolution rate of relatively insoluble drugs, great efforts have been made.

A number of investigators[1-17] demonstrated that the formation of coprecipitates or solid dispersions can increase their in vitro dissolution rates and/or in vivo absorption.

In the previous studies, the dissolution rates of allobarbital[13], phenobarbital[14] and furosemide[15-17] were enhanced markedly by formation of coprecipitates with pharmacologically inert, polymeric materials such as polyvinylpyrrolidone, polyethylene glycol.

Recently, the ground mixtures of some drugs with crystalline cellulose[18, 19], gelatin[20], chitin and chitosan[21] were reported to enhance the dissolution proberties of practically insoluble drugs.

Chitin and chitosan have structural formula analogous to that of cellulose and have been reported to be useful for pharmaceutical preparations[22-29]. chitin (poly-N-acetylglucosamine), [(1—4)-2-acetamide-2-deoxy-ß-D-glucan], a widely occurring natural structural material, and chitosan prepared by alkaline deacetylation of chitin, are biodegradable by lysozyme and do not present any biological hazard.

The purpose of the present study was to ascertain the general applicability of chitin and chitosan to be used for more enhanced dissolution of piroxicam.

In an attempt to elucidate physicochemical modification of ground mixture of piroxicam with chitin or chitosan, the extensive investigations such as IR, X-ray diffraction, thermometric studies were carride out.

EXPERIMENTAL METHODS

Materials

Chitin and chitosan from Sigma chemical co., (U.S.A) was ground in a ball mill and used after passing through a 100 mesh sieve. Piroxicam in 100 mesh sieve sized was pharmaceutical grade from Yuhan corporation (Korea). All other chemicals used were reagent grade and used as received.

Apparatus

Dissolution tester (Prolabo dissolution tester), UV-spectrophotometer (Perkin-Elmer Lamda 5), X-ray diffractometer (Rigaku Geigerflex), infrared spectrophotometer (Perkin-Elmer, 783), TG-DTA appratus (Rigaku Thermoflex).

Preparation of Piroxicam Test Systems.

The 1:2 ground mixtures of piroxicam with chitin or

chitosan were prepared by grinding in a ceramic ball mill for 24 hours and the same ratio physical mixtures were prepared by simple mixing in a ceramic mortar with care to avoid any grinding action.

Dissolution Rate Studies

The dissolution rate tests of piroxicam from the different test preparations were carried out at 37°C, 150 rpm. Each test preparation equivalent to 40 mg of piroxicam, an excess amount of drug beyond its equilibrium solubility were transferred into 300 ml of KP-4 disintegration medium No. 1 (pH 1.2). A 3.0 ml sample solution was withdrawn at the specified time and filtered through Millipore filter (0.45 μm) and immediately replaced with an equal volume of fresh dissolution medium. Each filtrate was determined at 334 nm with UV spectrophotometer.

X-ray Diffraction

X-ray diffraction was carried out using Rigaku Geigerflex X-ray diffractometer. The target was Cu-tube (Ni-filter), 35 KV, 15 mA and the detector was proportional counter 1.7 KV for detector voltage.

IR.

Infrared spectra for piroxicam test systems were observed by potassium bromide disk method, with a double beam, infrared spectrophotometer.

Thermometric Measurements

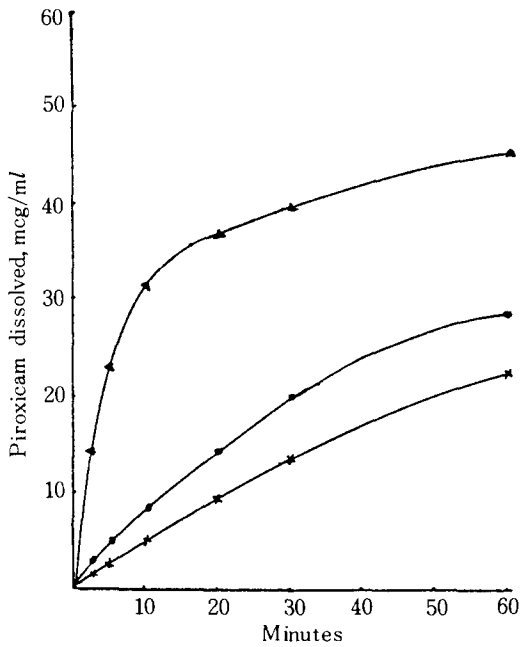

Fig. 1. Dissolution rates of piroxicam at 37°C, 150 rpm.

x=Intact piroxicam;
●=1:2 piroxicam-chitin physical mixture;
▲=1:2 piroxicam-chitin ground mixture.

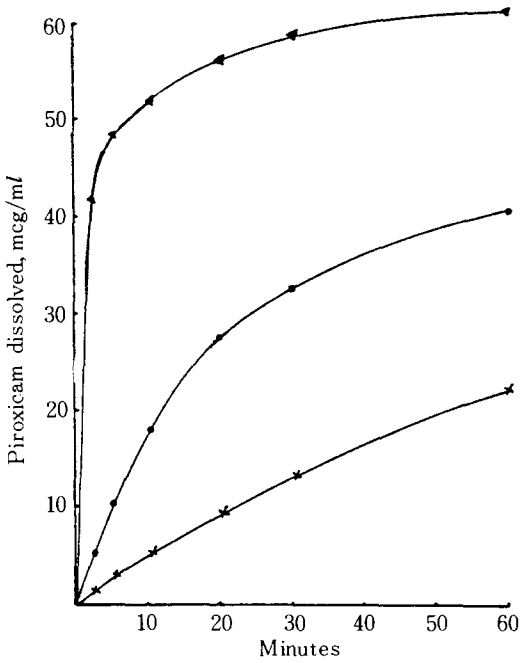

Fig. 2. Dissolution rates of piroxicam at 37°C, 150 rpm.

x=Intact piroxicam;
●=1:2 piroxicam-chitosan physical mixture;
▲=1:2 piroxicam-chitosan ground mixture.

Thermogravimetric and differential analyses were carried out using TG-DTA apparatus, fitted with Pt dish. The reference material was 5 mg of alpha-alumina, the heating rate, 10°C/min, and the upper temperature limit, 600°C.

RESULTS AND DISCUSSION

Stability of Piroxicam in Dissolution Medium

The change of piroxicam concentration in dissolution medium was tested to verify its chemical stability during the dissolution rate experiment. The piroxicam in dissolution medium was stable during experiment.

Dissolution Rate Studies

The effect of chitin or chitosan on the dissolution of piroxicam was investigated for the piroxicam test preparations. The dissolved amount of piroxicam for the 1:2 piroxicam-chitin ground mixture and the same ratio physical mixture are shown in Fig. 1 as mcg/ml against time in comparison with piroxicam powder and those for the piroxicam-chitosan test systems are shown in Fig. 2.

The dissolution rate of piroxicam from the physical mixture was slightly increased comparing with intact piroxicam. This difference in dissolution of piroxicam between the physical mixture and intact piroxicam is

considered to be simply attributable to the difference in wettability of hydrophobic piroxicam particles. This was supported by the observation that intact piroxicam floats on the surface of the dissolution medium longer than the physical mixture.

A comparison of dissolution characteristics of the 1:2 piroxicam-chitin ground mixture with those of the same ratio physical mixture indicates that ground mixture preparation goes into solution at faster rate than the physical mixture.

A marked influence of dispersion methods such as simple blending, solvent deposition, ball milling, and muller milling on the dissolution rate and bioavailability of digoxin has recently been reported[30, 31]. 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.

This result indicates that the mere presence of chitin in the ground mixture as compared to the physical mixture is not responsible for the enhanced dissolution rate of piroxicam. The dissolution of piroxicam from the ground mixtures with chitosan was significantly greater than intact piroxicam, and the ground mixture with chitosan gave the greatest dissolution followed by that with chitin.

No difference of dissolution of piroxicam, same mesh sieve sized, from intact piroxicam and piroxicam ground in a ball mill was observed. In conclusion, co-grinding with chitin and chitosan gave the fast dissolution of piroxicam.

The role of chitin or chitosan in the different enhancement of the piroxicam dissolution rate among the ground mixture and the physical mixture is quite interesting. Apparently, piroxicam and chitin or chitosan act independently in the physical mixture, while the

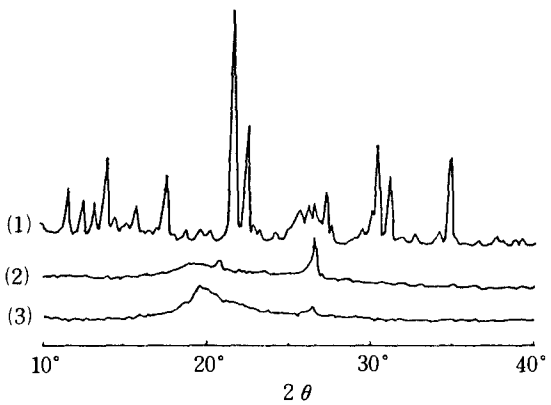

Fig. 3. Comparison of X-ray diffraction spectra.
(1) =pure piroxicam (before or after grinding);
(2) =pure chitin;
(3) =pure chitosan.

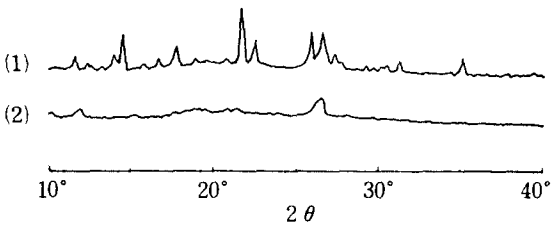

Fig. 4. Comparison of X-ray diffraction spectra.
(1) =1:2 piroxicam-chitin physical mixture;
(2) =1:2 piroxicam-chitin ground mixture.

role of chitin or chitosan in the ground mixture alters the physical characteristics of piroxicam. Therefore, one can postulate that there might be interaction between piroxicam and chitin or chitosan.

X-ray diffraction Studies

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.

Even though the same particle size and same combination ratio of drug to chitin or chitosan, the dissolution rates between the physical mixture and the ground mixture were differentiated and there might be a possibilty that different phases are present.

At this point, X-ray diffraction studies were undertaken to unravel this phenomena. X-ray diffraction spectra for pure piroxicam, pure chitin, and pure chitosan are shown in Fig. 3. X-ray diffraction spectra for the 1:2 piroxicam-chitin physical mixture and same ratio ground mixture are shown in Fig. 4 and for the chitosan systems are in Fig. 5.

The pure piroxicam showed the same diffraction peaks at 2θ degree of 21.6, 22.4, 30.4, 31.2 and 35.0 etc, indicating the presence of crystalline piroxicam (Fig. 3). The physical mixture also showed crystallinity supposed due to the presence of crystalline piroxicam and the extent of diffraction peaks was dependent on the combination ratio of piroxicam and chitin or chitosan.

When pure piroxicam was ground in a similar man-

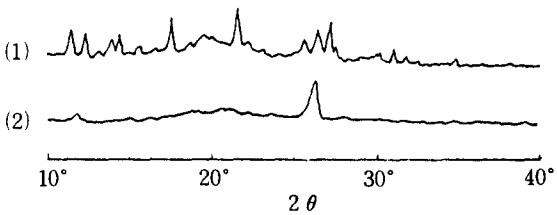

Fig. 5. Comparison of X-ray diffraction spectra
(1) =piroxicam-chitosan physical mixture;
(2) =piroxicam-chitosan ground mixture.

ner, but in the absence of chitin or chitosan, the crystalline structure of piroxicam was retained as judged by X-ray diffraction peaks. Thus, the mere presence of chitin or chitosan in the physical mixture or grinding process of piroxicam should not interfere with the characterization of piroxicam present.

On the other hand, X-ray diffraction peaks disappeared in the ground mixture indicating the production of the amorphous state. It is also reported that amorphous states of drugs can be obtained by grinding the drugs with microcrystalline cellulose[32].

This result implies that piroxicam is present as an amorphous form in the 1:2 ground mixture. The amorphous property of piroxicam in the ground mixture is considered to be mainly responsible for the enhanced dissolution.

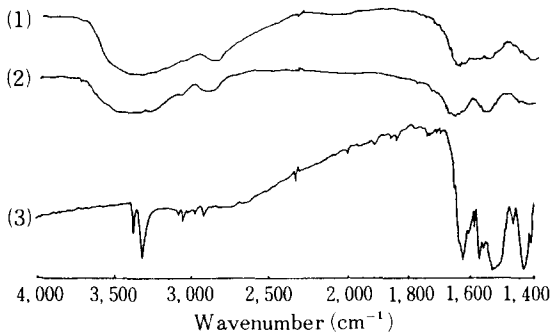

Fig. 6 Comparison of Infrared spectra.

(1) =pure chitosan;
(2) =pure chitin;
(3) =pure piroxicam.

IR Spectra

When the drug was ground with chitin or chitosan, rapid disappearance of X-ray diffraction peaks was occurred. In an attempt to elucidate further physicochemical property, the conditions of the drug molecules in the ground mixtures were investigated using IR spectropscopy. The infrared spectra for the 1:2 piroxicam-chitin physical mixture and the same ratio ground mixtue are shown in Fig. 7 and those for the chitosan systems are in Fig. 8 with pure piroxicam, chitin and chitosan as reference (Fig. 6).

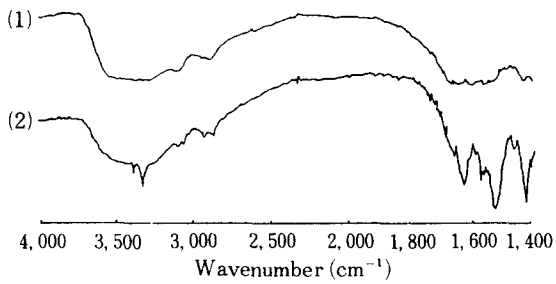

Fig. 7. Compariosn of Infrared sperxtra.

(1) =1:2 piroxicam-chitin ground mixture;
(2) =1:2 piroxicam-chitin physical mixture.

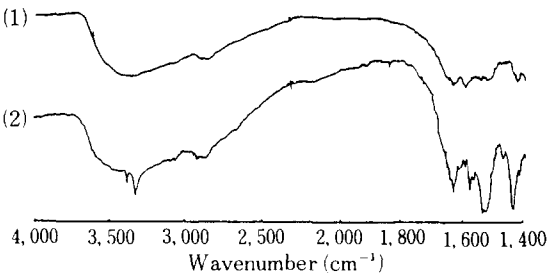

Fig. 8. comparison of Infrared spectra.

(1) =1:2 piroxicam-chitosan ground mixture;
(2) =1:2 piroxicam-chitosan physical mixture.

The infrared spectrum of the physical mixture showed the absorption bands illustrating the presence of piroxicam and chitin or chitosan. However, in the spectrum of the ground mixture, the two sharp bands observed at 3340, 3950 m^{-1} became broad and weak. From the comparison of the spectra of the physical mixture and the ground mixture, the stretching bands assigned to the NH-group in the piroxicam molecule became weak and broad in the ground mixture whereas the physical mixture showed the stretching vibrations.

From these results, it would be reasonable to consider that in the ground mixtures of chitin or chitosan, the drug molecules were present monomolecularly presumably interacting with chitin or chitosan molecules. The interaction forces between drug molecules and chitin or chitosan may take place in the ground mixture and would be destroyed by the water molecule, so the release of drug from the matrixes may be enhanced.

It is presumed that the ground mixture shows an interaction such as association between the functional

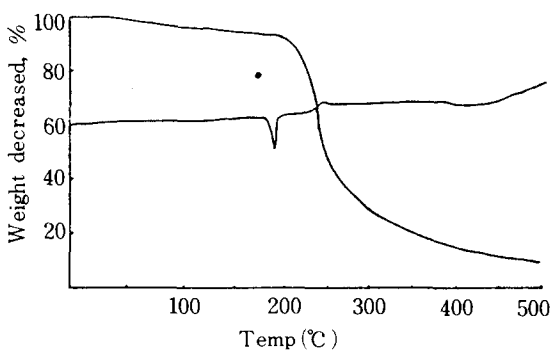

Fig. 9. DTA and TGA thermograms of piroxicam.

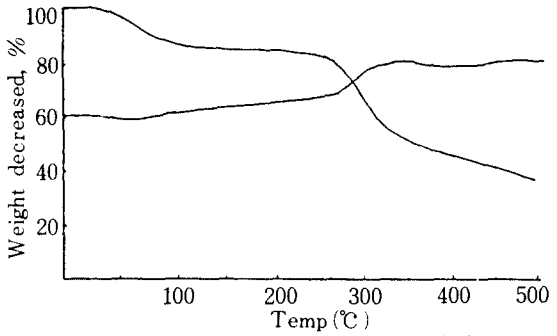

Fig. 10. DTA and TGA thermograms of chitin.

groups of piroxicam and chitin or chitosan in the molecular level. The association between piroxicam and chitin or chitosan is expected to be most probable between the imino group of piroxicam and hydroxyl guoup of chitin or chitosan.

DTA AND TGA STUDIES

The thermal characteristics of the ground mixtures by DTA and TGA are shown in Fig. 9-15.

The piroxicam showed a single sharp endothermic peak at 199° which was within the reported melting point range of 198-200° and a weight loss of about 6%

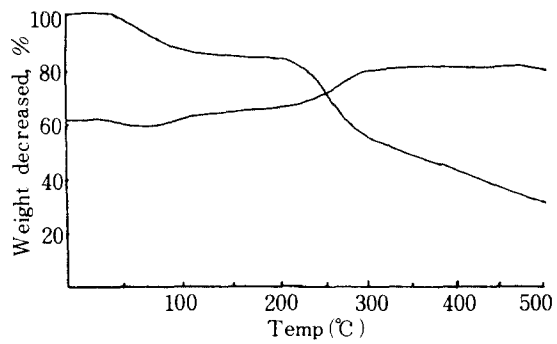

Fig. 11. DTA and TGA thermograms of chitosan.

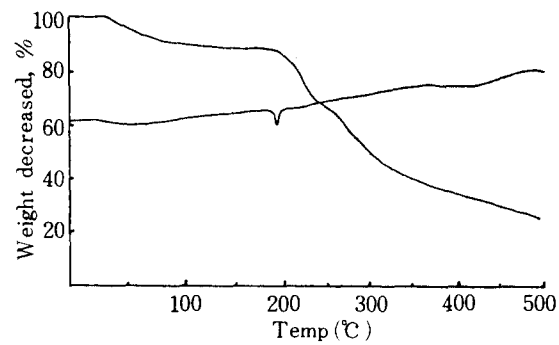

Fig. 1 , DTA and TGA thermograms of 1:2 piroxicam-chitin physical mixture.

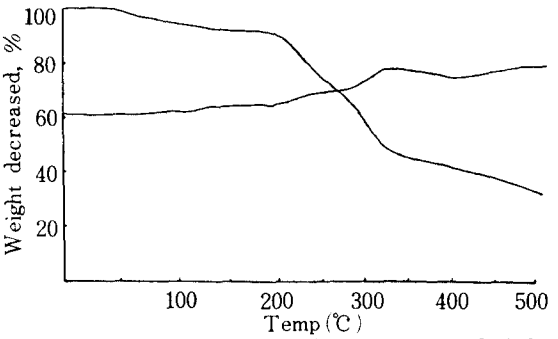

Fig. 13. DTA and TGA thermograms of 1:2 piroxicam-chitin ground mixture.

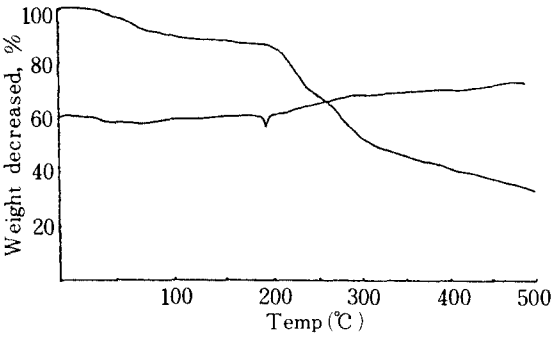

Fig.14 DTA and TGA thermograms of 1:2 piroxicam-chitosan physical mixture.

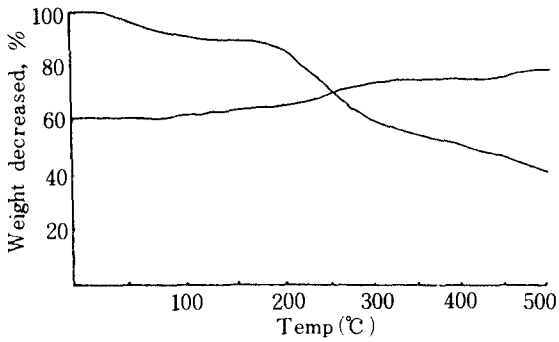

Fig.15 DTA and TGA thermograms of 1:2 piroxicam-chitosan ground mixture.

with decomposition (Fig. 9). The weight loss of about 12% until 100°C in TGA curves of chitin (Fig. 10) and chitosan (Fig. 11) shows dehydration. TGA curves of the physical mixture and the ground mixture (Fig. 12 and 13) showed all the same patterns. The single endothermic peak due to the fusion of piroxicam was observed in the physical mixture of piroxicam with chitin or chitosan, but the endothermic peak, heat of fusion due to the crystalline piroxicam, was disappeared in the ground mixture (Fig. 12-15).

This phenomena can be explained by the concept that the ground mixture may be regarded as an "en-

tropy frozen solution"[32] that a drug dissolved into chitin or chitosan without the ability of molecules to move throughout the whole system.

It was reported that an apparent amorphous state of benzoic acid on vibrational ball milling with microcrystalline cellulose has been demonstrated by its lack of melting point from differential thermal calorimetric measurements[33]. Some of the possible transformation 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 piroxicam powder and its interaction with chitin or chitosan or by production of lattice defect due to the shear stress and impact stress[19].

The effect of grinding on the heat of fusion and that on the crystalline peaks of 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 chitin or chitosan matrix of the ground mixture and the thermal property was changed.

CONCLUSIONS

From the present investigations, these results could be obtained as following;

1. The dissolution rate of piroxicam was rapid and markedly enhanced by co-grinding with chitin or chitosan.
2. The ground mixture with chitosan gave the faster dissolution rate than that with chitin.
3. X-ray diffraction study revealed that pure piroxicam and piroxicam contained within the physical mixture were crystalline in nature and there was no crystallinity in the ground mixture system.
4. A comparison of the IR spectra showed that an association between the functional groups of piroxicam and chitin or chitosan might occur in the molecular level.
5. The weight loss in TGA curves showed all the same patterns, however, the endothermic peak due to the fusion of piroxicam was disappeared indicating the different thermal property by DTA curves.

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