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Enhancement of Dissolution Properties of Prednisolone from Ground Mixtures with Chitin or Chitosan[1)]

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With a view to an application of chitin and chitosan to pharmaceutical preparations, the dissolution behavior of ground mixtures of prednisolone with chitin and chitosan was investigated. Ground mixtures of prednisolone with chitin and chitosan were prepared by co-grinding in a ball mill. The X-ray diffraction patterns and results of differential scanning calorimetry suggested that the size of crystals of prednisolone was decreased in the ground mixtures. The dissolution rate of prednisolone from the ground mixtures was significantly greater than that from the physical mixture or from intact prednisolone powder. These results indicate that chitin and chitosan can improve the dissolution properties of prednisolone.

Keywords——chitin; chitosan; ground mixture; prednisolone; dissolution rate

The use of ground drug mixtures with crystalline cellulose,[3)] gelatin,[4)] chitin and chitosan[5)] enhances the dissolution properties of poorly soluble drugs. Nakai stated that these phenomena should be confirmed with many drugs.[6)] Therefore, in this study, the dissolution rates of ground mixtures of prednisolone (PDS) with chitin and chitosan were investigated, following our work on ground mixtures of griseofulvin with chitin and chitosan.[5)]

Experimental

Materials——Chitin and chitosan, whose degree of deacetylation was calculated to be 92.7% from the amino group content, for fine chemical use were purchased from Kyowa Oil and Fat Co., Ltd. and were used after passage through a 200-mesh sieve. PDS of J.P. X grade was purchased from Sanwa Kagaku Kenkyusho.

Preparation of Ground Mixtures——Eighteen-gram samples of ground mixtures of PDS with chitin and chitosan in 1 : 2 weight ratio were prepared by grinding in a ceramic ball mill for 24 h.

Preparation of Physical Mixtures——Physical mixtures of PDS with chitin and chitosan in 1 : 2 weight ratio were prepared by simple blending in a ceramic mortar.

Powder X-Ray Diffraction Study——Powder X-ray diffractometry was carried out using a Rigaku Denki Geigerflex Model D-2 diffractometer with Ni-filtered Cu-$K\alpha$ radiation.

Differential Scanning Calorimetry (DSC)——A Perkin–Elmer Model 1B differential scanning calorimeter was used. Each sample, containing 6 mg of PDS, was subjected to DSC in the sample pan for liquid samples at a scanning speed of 8 °C/min.

Dissolution Rate Study——The dissolution rate of PDS from the different preparations was tested in a J.P. X dissolution test apparatus according to Method II (paddle method) in 500 ml of water at an agitation speed of 200 rpm at 37 °C. The amount of PDS used was 100 mg eq. Five ml of sample solution was withdrawn at appropriate intervals through a membrane filter (pore diameter 0.45 μm) and immediately replaced with an equal volume of the test medium. Each sample was analyzed for PDS by the ultraviolet absorption method at 247 nm using a Hitachi 124 spectrophotometer. Experiments were done in triplicate and the mean values were obtained.

Results and Discussion

Powder X-ray diffraction patterns of PDS are shown in Fig. 1. The diffraction intensity of PDS in a ground mixture (GM) was smaller than that of a physical mixture (PM),

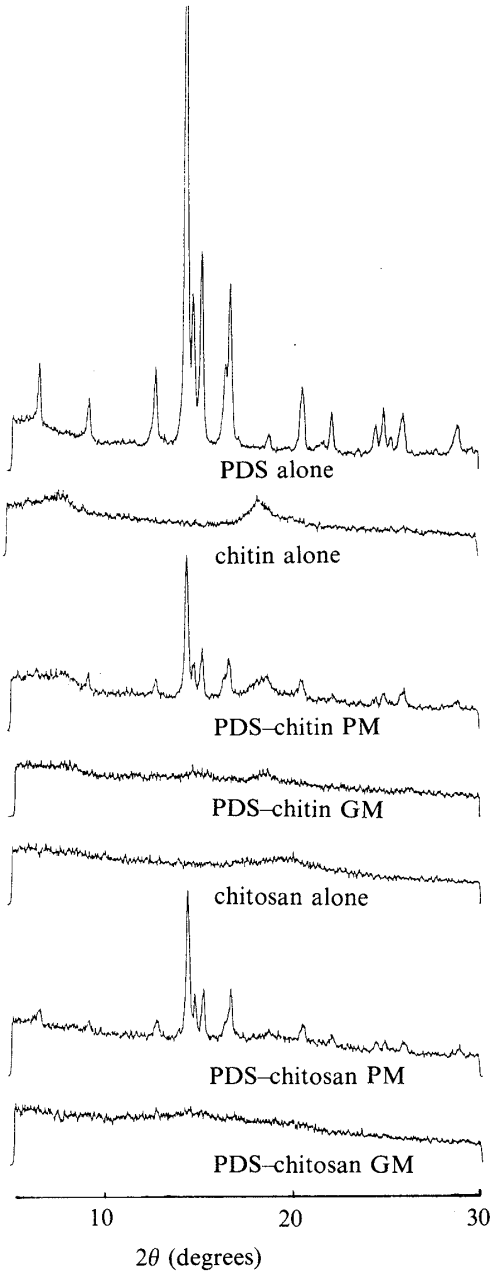

Fig. 1. Powder X-Ray Diffraction Patterns

GM, ground mixture; PM, physical mixture.

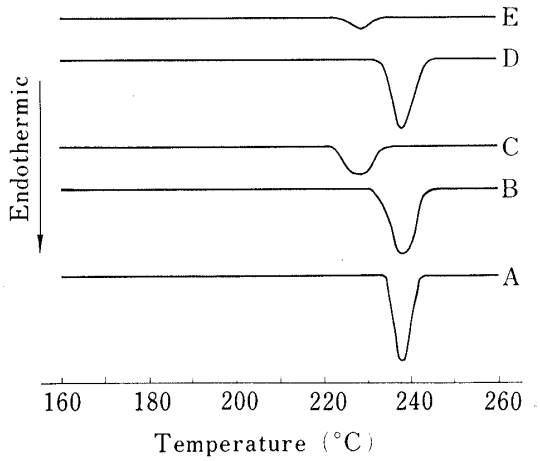

Fig. 2. DSC Thermograms of PDS, Physical Mixtures and Ground Mixtures

A, PDS alone; B, PDS–chitin PM; C, PDS–chitin GM; D, PDS–chitosan PM; E, PDS–chitosan GM.

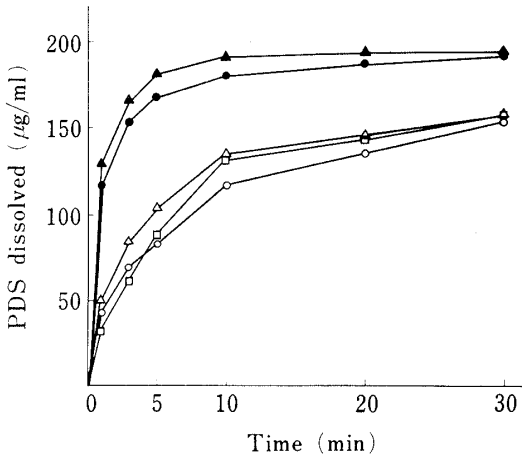

Fig. 3. Dissolution of PDS from Mixtures with Chitin and Chitosan in 500 ml of Water at 37 °C

PDS–chitin GM (●), PDS–chitosan GM (▲), PDS–chitin PM (○), PDS–chitosan PM (△), intact PDS (□).

suggesting that the size of the crystals of PDS was decreased in the ground mixtures.

DSC thermograms of PDS are shown in Fig. 2. Endothermic peaks of melting of PDS in a ground mixture at 228 °C were smaller than those of a physical mixture and of PDS alone at 238 °C. The values of relative enthalpy change of melting[5] of PDS were 0.46 and 0.14 for PDS–chitin GM and PDS–chitosan GM, respectively, suggesting that chitosan had a large reducing effect on the relative enthalpy change of PDS compared with chitin. This reducing effect was considered to be sufficient, because the values of relative enthalpy change of melting of griseofulvin[5] were 0.4 and 0.3 for griseofulvin–chitin (1 : 9) GM and griseofulvin–chitosan (1 : 9) GM, respectively, and a 1 : 2 mixing ratio was used in this study.

Dissolution of PDS from the PDS–excipient (1 : 2) mixtures is shown in Fig. 3 in comparison with that from PDS powder. The dissolution of PDS from the ground mixtures

was significantly greater than that from the physical mixtures, and this difference was attributed to the relative decrease in the size of crystals of PDS in the ground mixtures. The ground mixture with chitosan gave slightly greater dissolution than that with chitin, and this difference reflected the reducing effect of chitosan on the relative enthalpy change of PDS observed in the DSC study.

In conclusion, co-grinding with small amount chitosan reduced the size of the crystals of PDS, and the dissolution rate of PDS was enhanced.

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References and Notes

1) This paper forms Part XXXIX of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part XXXVIII: Y. Sawayanagi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **31**, 2064 (1983).
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