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Enhancement of Dissolution Properties of Griseofulvin from Ground Mixtures with Chitin or Chitosan[1,2]

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The dissolution step of practically insoluble drugs plays an important role in the drug absorption. In this study, with a view to an application of chitin and chitosan to pharmaceutical preparations, the dissolution behavior of ground mixtures of griseofulvin with chitin and chitosan was investigated.

Ground mixtures of griseofulvin with chitin, chitosan and crystalline cellulose were prepared by grinding in a ball mill. The X-ray diffraction patterns and results of differential scanning calorimetry suggested a relative decrease in the size of the crystals of griseofulvin in the ground mixtures. The dissolution rate of griseofulvin from the ground mixtures was significantly greater than that from the physical mixture or from intact griseofulvin powder. The ground mixture with chitosan showed fastest dissolution. These results indicate that chitin and chitosan can improve the dissolution properties of griseofulvin.

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

When a poorly soluble drug is administered orally, the bioavailability, *i.e.*, the rate and extent of the absorption, depends mainly on the dissolution rate in the gastrointestinal fluids. If the bioavailability of such a drug is enhanced, the dose required, and consequently the side effects, may be reduced. Therefore, great efforts have been made to increase the dissolution rate of such drugs.[3] For example, the dissolution and bioavailability of griseofulvin (GRF) were enhanced by dispersion of the drug in polyvinylpyrolidone[4] and polyethylene glycol 6000,[5] and by using the ground mixture with crystalline cellulose (MCC).[6] Chitin and chitosan have structural formulae analogous to that of cellulose,[7] and have been reported to be useful for pharmaceutical preparations.[7,8]

In this study, with a view to further application of chitin and chitodsan to pharmaceutical preparations following studies on directly compressed tablets containing chitin and chitosan,[8b] the effect of grinding them with GRF on the dissolution behavior of the drug was investigated. In addition to chitin and chitosan, MCC was also used as a vehicle. The physicochemical and dissolution properties of the ground mixtures of GRF with excipients were investigated.

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. MCC of JP X grade, marketed as "Avicel PH-101," was used after passage through a 200-mesh sieve. GRF of JP X grade was used after passage through a 200-mesh sieve.

Preparation of Ground Mixtures——Eighteen-gram samples of ground mixtures of GRF with chitin, chitosan and MCC in 1: 2, 1: 4 and 1: 9 weight ratios were prepared by grinding in a ceramic ball mill for 24 h.

Preparations of Physical Mixtures——Physical mixtures of GRF with chitin, chitosan and MCC in 1: 2, 1: 4 and 1: 9 weight ratios 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 2 mg of GRF, was subjected to DSC in the sample pan for liquid samples at a scanning speed of 8°C/min.

Dissolution Rate Study——Dissolution rates of GRF from the different preparations into 500 ml of JP X

disintegration medium No. 1 (pH 1.2) were measured at 37°C in a constant-temperature water bath. The amount of GRF used was 26 mg-equivalent, because the saturated concentration of GRF in JP X disintegration medium No. 1 at 37°C was measured to be 52 mg/l. Each preparation was transferred directly into the dissolution medium and stirred with a four-bladed stainless steel paddle at 300 rpm. 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 GRF with a ultraviolet (UV) spectrophotometer at 295 nm. Since the adsorption of GRF on a membrane filter is known to occur,[9] the absorbance of the standard solution was measured after filtration through a membrane filter to obtain a calibration curve for GRF. Experiments were done in triplicate, and the mean values were obtained.

Results and Discussion

Powder X-ray diffraction patterns of GRF is shown in Fig. 1. The diffraction intensity of GRF in a ground mixture (GM) was smaller than that of a physical mixture (PM), suggesting a relative decrease in the size of the crystals of GRF in the ground mixtures. The relative enthalpy change of melting of GRF obtained by differential scanning calorimetry is shown in Table I. This relative enthalpy change may be considered to correspond to the apparent degree of crystallinity. Table I indicates clearly that the greater the ratio of excipient, the smaller the relative enthalpy change, and that the reducing effect of chitosan on the relative enthalpy change of GRF was the largest, followed by chitin and MCC in that order.

Dissolution of GRF from the GRF-excipients (1 : 2) mixtures is shown in Fig. 2 in comparison with that from GRF powder. The dissolution of GRF from mixtures was significantly greater than that from GRF alone, and the ground mixture with chitosan gave the greatest

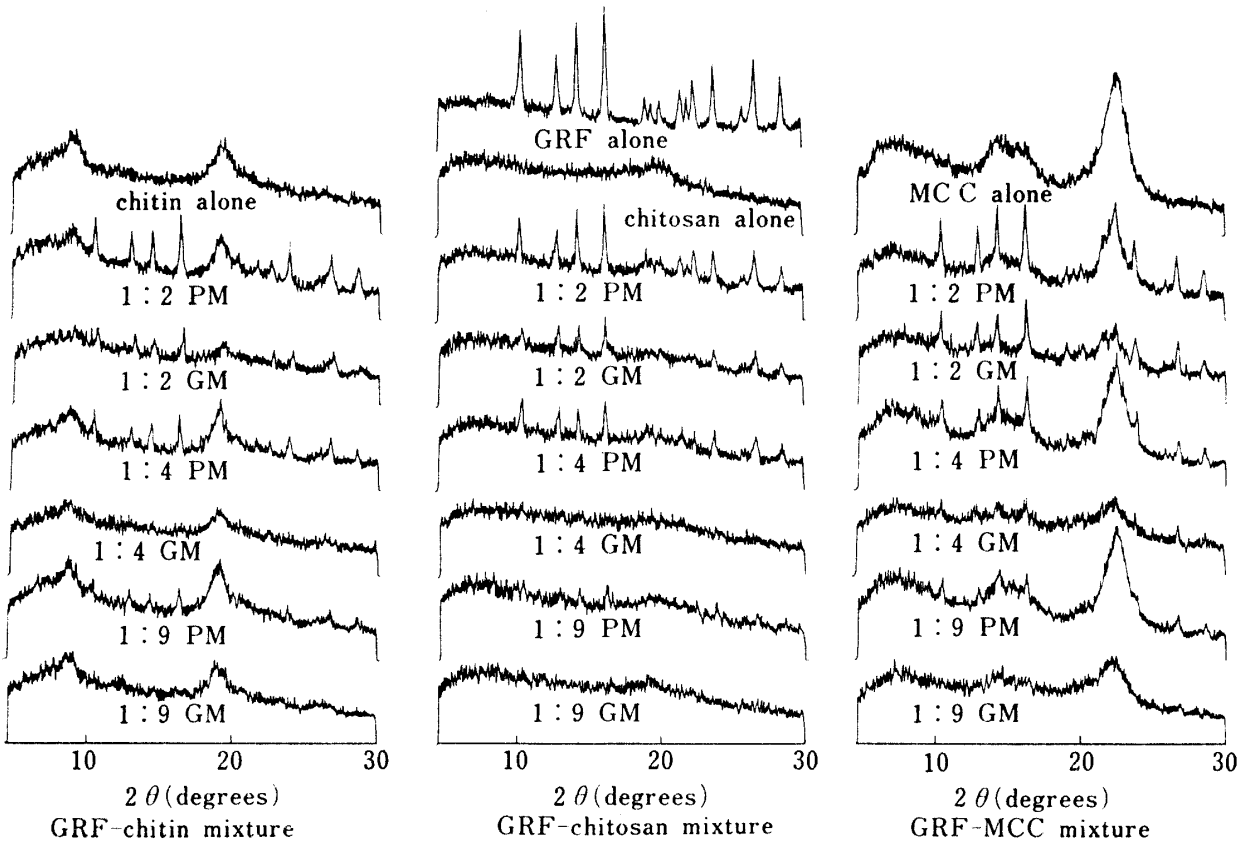

Fig. 1. Powder X-Ray Diffraction Patterns

GM: ground mixture; PM: physical mixture.

Table I. Relative Enthalpy Change of Melting of GRF[a] at Various Mixing Ratios

	1 : 2	1 : 4	1 : 9
GRF–Chitin	0.6	0.6	0.4
GRF–Chitosan	0.6	0.4	0.3
GRF–MCC	0.8	0.6	0.6

a) $\frac{\Delta H \text{ of GM}}{\Delta H \text{ of PM}}$ (ΔH: enthalpy change of melting obtained by DSC).

dissolution, followed by that with chitin, whereas the ground mixture with MCC gave almost the same extent of dissolution as the physical mixture with chitosan.

Dissolution of GRF from the GRF–excipient (1 : 9) mixtures is shown in Fig. 3 in comparison with that from GRF alone. Every ground mixture gave greater dissolution than every physical mixture. The ground mixture with chitosan gave the greatest dissolution followed by that with chitin and with MCC, *i.e.*, the same order at the mixing ratio of 1 : 2. In comparison with the mixing ratio of 1 : 2, the 1 : 9 ground mixtures with chitin and with chitosan showed greatly enhanced initial dissolution rate and concentration of GRF dissolved after 30 min, while the mixture with MCC showed only slightly enhancement. These results were in accord with the relative enthalpy changes of GRF shown in Table I. In this study, the dissolution rate at the initial stage, that is, up to 30 min, was considered. The amount dissolved at 30 min was smaller than the saturated concentration.

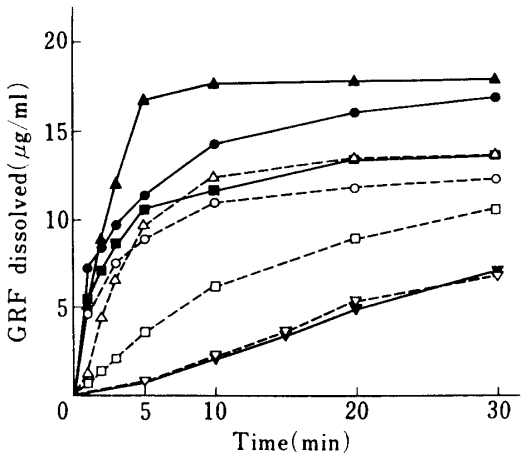

Fig. 2. Dissolution of GRF from Mixtures (1 : 2) with Chitin, Chitosan and MCC in 500 ml of JP X Disintegration Medium No. 1 (pH 1.2) at 37°C

—●—: 78 mg of GRF–chitin GM;
—▲—: 78 mg of GRF–chitosan GM;
—■—: 78 mg of GRF–MCC GM;
—▼—: 26 mg of GRF ground alone;
--○--: 78 mg of GRF–chitin PM;
--△--: 78 mg of GRF–chitosan PM;
--□--: 78 mg of GRF–MCC PM
--▽--: 26 mg of intact GRF.

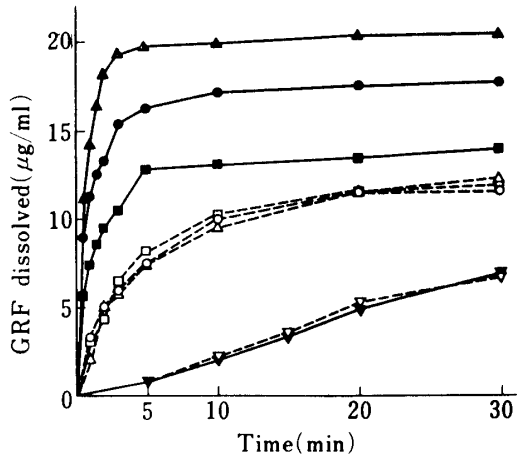

Fig. 3. Dissolution of GRF from Mixtures (1 : 9) with Chitin, Chitosan and MCC in 500 ml of JP X Disintegration Medium No. 1 (pH 1.2) at 37°C

—●—: 260 mg of GRF–chitin GM;
—▲—: 260 mg of GRF–chitosan GM;
—■—: 260 mg of GRF–MCC GM;
—▼—: 26 mg of GRF ground alone;
--○--: 260 mg of GRF–chitin PM;
--△--: 260 mg of GRF–chitosan PM;
--□--: 260 mg of GRF–MCC PM;
--▽--: 26 mg of intact GRF.

The difference of dissolution of GRF from ground mixture and physical mixture was attributed to the relative decrease in the size of the crystals of GRF in the ground mixtures. The difference of dissolution of GRF from physical mixtures and GRF alone was considered to be simply attributable to the difference in wettability of GRF between them; this was supported by the finding that GRF alone floats on the surface of the dissolution medium longer

than the physical mixtures. No difference of dissolution of GRF from intact GRF and GRF ground alone in a ball mill for 24 h was observed, presumably because intact GRF was itself very fine.

Considering the usual clinical dose of GRF used in practice, the amonut of excipient should be small for formulation. Therefore, the 1 : 2 mixing ratio of GRF–excipient might be suitable, and the results obtained at this ratio could be practically useful.

In conclusion, co-grinding with chitin and chitosan reduced the size of the crystals of GRF, and the dissolution rate of GRF was greatly enhanced.

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References and Notes

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