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Stabilization of Amorphous State of Indomethacin by Solid Dispersion in Polyvinylpolypyrrolidone[1)]

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Solid dispersion of indomethacin (IMC) in polyvinylpolypyrrolidone (PVPP), in which IMC is in an amorphous state, was prepared from an acetone solution of IMC containing PVPP in suspension, and the stability of the amorphous state of IMC dispersed in PVPP was investigated at various temperature and humidity levels in comparison with that of simple amorphous IMC. The crystallization process of IMC was investigated by powder X-ray diffractometry and differential scanning calorimetry.

Without moisture, IMC dispersed in PVPP remained in the amorphous state for 6, 2 and 1 months at 40, 50, and 60 °C, respectively. Simple amorphous IMC was readily converted to form I at 20, 30, 40, and 50 °C in the absence of moisture. On the other hand, at relative humidity levels of 100 and 89%, IMC dispersed in PVPP was converted to form II in 7 and 28 d, respectively, at 30 °C.

The amorphous state of IMC was thus stabilized against heat and moisture in the solid dispersion in PVPP. This result suggests that fast-dissolving pharmaceutical preparations of IMC providing high bioavailability could be obtained by using solid dispersions in PVPP.

Keywords——indomethacin; polyvinylpolypyrrolidone; solid dispersion; amorphous state; crystalline form; stability against heat and moisture

The amorphous form of indomethacin (IMC) is unstable, being converted to crystalline form I and II.[3)] In a series of studies on the application in the pharmaceutical field of polyvinylpolypyrrolidone (PVPP),[4,5)] the solid dispersion of IMC in PVPP was prepared and the stabilization of the amorphous state of IMC in dispersions was investigated by the X-ray diffraction method and differential scanning calorimetry (DSC) in comparison with simple amorphous IMC.

Experimental

Materials——Crystalline IMC of forms I and II, and amorphous form were the same as reported before.[3)] PVPP marketed as Polyplasdone XL was supplied by GAF Co., Ltd., New York, USA. The solid dispersion of IMC in PVPP was prepared from acetone solution of IMC containing PVPP in suspension by evaporating the acetone in an evaporator at 40 °C. The weight ratio of IMC to PVPP was 1 : 3. The amorphous state of IMC thus dispersed in PVPP was confirmed by the X-ray diffraction method and DSC.[3)]

Powder X-Ray Diffractometry and Differential Scanning Calorimetry——The same procedures as in the previous report were used.[3)]

Measurement of Stability of the Amorphous State of IMC in Solid Dispersions in PVPP and Simple Amorphous IMC——About 2 g samples of IMC dispersed in PVPP or simple amorphous IMC were put on Petri dishes and placed in desiccators containing silica gel at 20, 30, 40, and 50 °C, or in desiccators adjusted to relative humidity (R.H.) values of 100, 89, 79, and 69% at 30 °C. Samples were taken out at appropriate time intervals. The transformation of amorphous IMC to crystalline form I or II was confirmed by the X-ray diffraction method by the appearance of characteristic diffraction peaks of each crystalline form, and also by DSC, as reported before.[3)]

Results and Discussion

The results on the heat stability of amorphous IMC in solid dispersion in PVPP and simple amorphous IMC in the absence of moisture are summarized in Table I. The amorphous state of IMC in the solid dispersion in PVPP was stable even at 60 °C, while simple amorphous IMC was converted to crystalline form I even at 20 °C.

Table II shows the results on heat stability in the presence of moisture in comparison with the data for simple amorphous IMC reported in the previous paper.[3] Amorphous IMC in the solid dispersion in PVPP was converted to crystalline form II at R.H. 100 and 89%, but remained its amorphous state at R.H. 79 and 69% for longer periods.

Although the mechanism of the stabilization of IMC by dispersing it in PVPP is not clear,

Table I. Heat Stability of Amorphous IMC in the Absence of Moisture

Sample	Temperature (°C)	Storage period (d)	Crystalline form and degree of crystallinity
Simple amorphous IMC	20	2	I, 14%
	20	6	I, 42%
	20	14	I, 70%
	30	2	I, 25%
	30	4	I, 64%
	30	6.5	I, 74%
	40	0.125 (3 h)	I, 12%
	40	0.5	I, 50%
	40	1.0	I, 64%
	50	—[a]	I
Amorphous IMC dispersed in PVPP	40	180	Amorphous
	50	60	Amorphous
	60	30	Amorphous

a) Converted very quickly.

Table II. Heat Stability of Amorphous IMC in the Presence of Moisture

Sample	Temperature (°C)	Relative humidity (%)	Storage period (d)	Crystalline form and degree of crystallinity
Simple amorphous IMC[a]	30	100	0.5	II, 50%
	30	89	2	I and II, 50%
	30	79	2	I, 50%
	30	69	2	I, 50%
Amorphous IMC dispersed in PVPP	30	100	7[b]	II, trace
	30	89	28[b]	II, trace
	30	79	180	Amorphous
	30	69	240	Amorphous

a) Data from the previous paper.[3]
b) The time at which the crystallization started.

IMC might exist as a molecular dispersion in PVPP. The present method might also be applicable to other drugs.

These results show that PVPP was effective for stabilizing the amorphous state of IMC. Further, the solid dispersion of IMC in PVPP has good fluidity, that is a low angle of repose, even after being kept under these severe accelerated conditions. Therefore, fast-dissolving pharmaceutical preparations of IMC providing high bioavailability could presumably be obtained by using the solid dispersion in PVPP.

References and Notes

1) This paper forms Part XL of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part XXXIX: Y. Sawayanagi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **31**, 2507 (1983).
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