[Chem. Pharm. Bull. 33(9)4050—4053(1985)]

Photo-Stability of Several Crystal Forms of Cianidanol

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(Received November 30, 1984)

The photo-stabilities of five crystal forms of cianidanol, monohydrate·I, tetrahydrate·I, monohydrate·II, anhydrate·II and anhydrate·IV, on exposure to ultraviolet (UV) irradiation were investigated. Monohydrate·II was quite stable to UV irradiation at 20 °C and 0—96% relative humidity, while the photo-stabilities of the other four crystal forms were influenced by humidity. Lower permeability of oxygen into the crystals as compared to the other crystal forms was assumed to be one of the reasons for the high photo-stability of monohydrate·II.

Keywords——cianidanol; photo-stability; crystal form; transformation; hepatoprotector; photo-oxidation; relative humidity

There are many pharmaceutical medicaments which undergo light-induced degradation when exposed to natural or artificial light. However, little work has been done on the photo-stability of medicaments in the solid state because of the complexity of photo-reaction in the solid state. On the other hand, many reports relating to polymorphism of medicaments have appeared. However, there have been few reports on differences of photo-stability between polymorphs except for some work on dihydrophenylalanine,[1] hydrocortisone 21-*tert*-butylacetate[2] and so on, for which some qualitative data were presented.

The therapeutic effect of orally administered cianidanol on hepatitis has been recently noted.[3] To determine optimum formulations and package forms, we have investigated its stability in aqueous solution[4] and its photo-stability in aqueous solution and in the solid state.[5] A difference of photo-stability between monohydrate·I and tetrahydrate·I was found. Furthermore, we have recently found that seven crystal forms of cianidanol (anhydrate·I, II, III, IV, monohydrate·I, II and tetrahydrate·I) exist, and monohydrate·II was most stable to humidity.[6]

In this study, we quantitatively compared the photo-stabilities of five crystal forms; anhydrate·I and anhydrate·III were excluded because they undergo rapid transformation to monohydrate·I under the conditions of the photo-stability study.

Experimental

Materials——Cianidanol was obtained from Zyma S.A. and recerystallized from water, then dried over P_2O_5. Other chemicals were of reagent-grade quality.

Preparation of Five Crystal Forms of Cianidanol——Twenty-five microliters of 2% (w/v) aqueous solution of cianidanol prepared at 60 °C and 25 μl of water were mixed in a hole of a slide glass (diameter of hole; 15 mm), then allowed to stand to give white crystals, which were converted to four crystal forms according to the procedure reported previously[6] as follows. The precipitated crystals of cianidanol were air-dried on a slide glass and then stored for 2 d at 20 °C and 75% relative humidity (R.H.) to afford tetrahydrate·I. On the other hand, the monohydrate·I was stored on a slide glass at 60 °C and 75% R.H. for 14 d to yeild monohydrate·II, which was converted to anhydrate·II by drying at 130 °C under reduced pressure (approximately 5 mmHg) for 4 h. The sample of anhydrate·IV was prepared as follows. The monohydrate·I obtained above was stored at 20 °C for 2 h in a desiccator over ethanol, then it was dried under reduced pressure (approximately 10 mmHg) at 20 °C for 24 h to afford anhydrate·IV.[7]

Ultraviolet (UV) Irradiation——A high-pressure mercury lamp (300 W) was used as a light source.

When the effects of relative humidity on the photo-stabilities of the five crystal forms were examined, irradiation of the sample on a slide glass was carried out as follows. The sample (on a slide glass) was mounted in a Pyrex glass tube (220 mm × 22.5 mm i.d.) over a saturated salt solution (KNO_3, NaCl and NaBr) or P_2O_5. The tube was irradiated with the high-pressure mercury lamp at 20 °C. The residual cianidanol was assayed by the gas-liquid chromatography (GLC) method reported previously.[5)]

Results and Discussion

Photo-Stability of Five Crystal Forms of Cianidanol

Crystals of tetrahydrate·I, monohydrate·I, II and anhydrate·II, IV laid on slide glasses were exposed to the same amount of UV light under ambient conditions (20 °C and 51%—58% R.H.). It was found that the crystals of monohydrate·II were most stable, followed by anhydrate·IV (or anhydrate·II), monohydrate·I and tetrahydrate·I in that order, as shown in Fig. 1. Each crystal form remained unchanged during the photo-stability test, as confirmed by differential thermal analysis (DTA) and thermogravimetry (TG). Next, the photo-stability of each form at various levels of humidity was investigated.

Influence of Humidity on the Photo-Stability of Five Crystal Forms

Crystals of tetrahydrate·I, monohydrate·I, anhydrate·II, monohydrate·II and anhydrate·IV laid on slide glasses were irradiated with a high-pressure mercury lamp at 20 °C and 0%—98% R.H. Tetrahydrate·I was most unstable (Fig. 2(d)). As shown in Fig. 2(a) and (b), residual intact cianidanol (percent) decreased significantly with increasing relative humidity in the case of anhydrate·IV and anhydrate·II. Further, the DTA curves showed that anhydrate·II and anhydrate·IV were partly converted to tetrahydrate·I during storage for 16 h in the dark at over 60% R.H.

In the case of monohydrate·I, as shown in Fig. 2(c), an additional decrease of the remaining cianidanol was found on irradiation for longer than 16 h at over 60% R.H. Since a sample stored in the dark for 24 h at over 60% R.H. was confirmed by DTA to be transformed to tetrahydrate·I, the decrease after 16 h reflected the photo-decomposition of the unstable tetrahydrate·I. Tetrahydrate·I, as shown in Fig. 2(d), was quite stable at 0% R.H. from 8 to 24 h, but was unstable at over 60% R.H. This phenomenon was assumed to be due to the ready elimination of water of crystallization of tetrahydrate·I at 0% R.H., resulting in transformation to monohydrate·I, as reported in a previous study.[6)] Consequently, the decreases in the photo-stability of monohydrate·I, anhydrate·II and anhydrate·IV at high humidity were assumed to be due to partial transformation to tetrahydrate·I by absorption of moisture during the photo-stability test.

On the other hand, monohydrate·II was quite stable. Further, humidity had little influence on the photo-stability in the range of 0%—95% R.H., as shown in Fig. 2(e). In contrast to the other four crystal forms, monohydrate·II was nonhygroscopic at 20 °C and

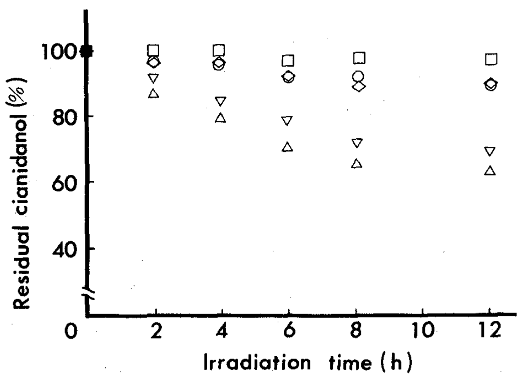

Fig. 1. Photo-Stability of Various Crystal Forms of Cianidanol under Irradiation with a High-Pressure Mercury Lamp under Ambient Conditions

△, tetrahydrate·I; ▽, monohydrate·I; □, monohydrate·II; ◇, anhydrate·II; ○, anhydrate·IV.

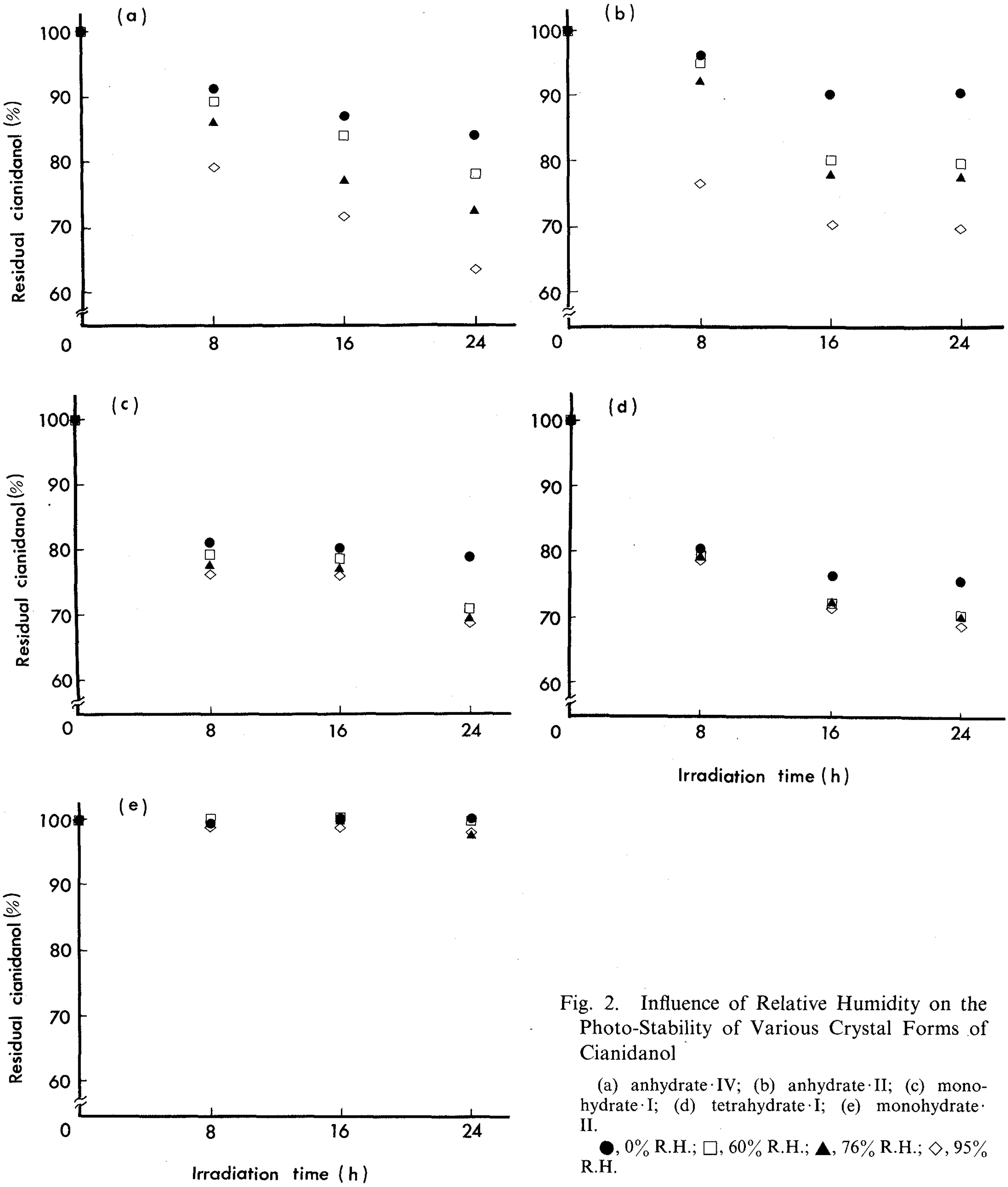

Fig. 2. Influence of Relative Humidity on the Photo-Stability of Various Crystal Forms of Cianidanol

(a) anhydrate·IV; (b) anhydrate·II; (c) monohydrate·I; (d) tetrahydrate·I; (e) monohydrate·II.

●, 0% R.H.; □, 60% R.H.; ▲, 76% R.H.; ◇, 95% R.H.

0%—95% R.H., as shown in a previous report.[6] Thus, the difference in the influence of humidity between monohydrate·II and the other crystal forms was assumed to be attributable to the difference in hygroscopic character. Recently, Lin *et al.*[2] reported qualitative differences in photo-stability between five crystal forms of hydrocortisone 21-*tert*-butylacetate and suggested that a difference in the permeability of oxygen into the polymorphs might be the reason. In the case of cianidanol, the photo-decomposition is a light-induced autoxidation, like that of hydrocortisone 21-*tert*-butylacetate, as shown in a previous report.[5] Taking into account the differences in photo-stability and TG curve[6] between monohydrate·I and monohydrate·II, the weakly bound water of crystallization of monohydrate·I may aid oxygen penetration into crystals. However, further crystallographic investigations are required to determine the actual reason for the difference in photo-stability between monohydrate·I and monohydrate·II.

Conclusion

Monohydrate·II was the most stable form to UV light of five crystal forms of cianidanol at 20 °C and 0%—95% R.H. Lower permeability of oxygen into the crystals compared to other crystal forms may be one reason for this. The decreases in the photo-stabilities of anhydrate·II, anhydrate·IV, and monohydrate·I at high relative humidity are considered to be attributable to their transformation to the most photo-labile form, tetrahydrate·I.

References and Notes

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