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The polymorphism of triamcinolone diacetate

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Summary

Triamcinolone diacetate was examined for the existence of polymorphism both in pure form and in commercially available preparations. Two polymorphic modifications and one solvate could be prepared.

Examination of the material in triamcinolone diacetate suspensions for injection showed it to be Form II. However, in one batch a significant amount of Form I (approximately 10%) was found in addition to Form II. IR spectroscopy and melting point determination proved to be the simplest analytical methods for identification of the crystal forms.

Introduction

The terms 'post-injection flare' and 'crystal-induced synovitis' are often mentioned in medical literature in connection with corticosteroid derivatives. These derivatives, being insoluble in water, are used as crystal suspensions for injection in the treatment of synovial inflammations. However, 2–4% of the patients react adversely, with enhanced inflammation symptoms after injection into the joint (McCarty and Hogan, 1964).

Since crystal polymorphism is a well-known phenomenon, the question may be raised whether crystal changes in the suspensions cause the adverse reactions or are they genuine body reactions for a narrow range of patients. We examined some of the widely used triamcinolone derivatives, e.g. triamcinolone acetonide, hexacetonide and diacetate for the existence of crystal polymorphism or habit changes. Only triamcinolone diacetate could be prepared in polymorphic modifications.

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Materials and Methods

Triamcinolone diacetate and two lots of Aristocort 40 mg/ml suspension for injection (Lederle) were studied. Solvents were of analytical grade: dichloromethane, chloroform, ether, ethyl acetate, dioxane, and N,N-dimethylacetamide (DMA) were used for the recrystallization experiments.

The experiments were carried out by dissolving approximately 0.5 g, accurately weighed, of the pure drug substance at room temperature, filtering and evaporating the filtrate in an open crystallization dish at room temperature. Solvation effects were controlled by weighing the recrystallized mass. The evidence of polymorphism was checked by melting points and infra red (IR) spectroscopy, then confirmed by differential thermal analysis (DTA).

Melting points, or rather melting behaviours, of recrystallization products were observed by thermomicroscopy, using a Mettler FP 52 microscope hot-stage coupled to the FP 5 control unit. The IR spectra were recorded with a Beckman IR 10 spectrophotometer with nujol mulling or KBr pelleting. The DTA data were collected on a Mettler TA 2000 System equipment.

The substances were controlled for chromatographic purity by TLC using fluorescing silica gel plates, developed in ethyl acetate and the spots were visualized in UV 254 light.

Results and Discussion

Recrystallization experiments — polymorphism and solvatization

Triamcinolone diacetate could be prepared in 3 crystal forms. Slow evaporation of a dichloromethane solution leaves long plates, up to 1 mm. The melting point was the same as that of the originally received substance, 147°C. The IR spectra were identical before and after recrystallization. This form was found to be a metastable modification, Form II (see Fig. 1).

Chloroform yields Form II as a microcrystalline powder with particles 1–2 μm in diameter. These would be ideal for suspension formulation of the material.

N,N-Dimethylacetamide (DMA) yields rod-shaped 1 : 1 solvate upon air-drying. On heating, from 90°C at a heating rate of 10°C/min, the crystals release the solvent and sluggishly melt at 103°C, with simultaneous growth from the melt of new crystals (plates), which in turn, melt at 147°C. Then, some new crystals grow slowly (Form I), contaminated with thermal decomposition products. In this way all 3 forms can be observed by thermomicroscopy in one single preparation.

Pure Form I can be produced by removing the DMA at 105°C. The solvent evaporates, the crystals collapse and slowly transform into Form I (m.p. 186–188°C). Solvent release, melting and the formation of new crystals are performed in one operation. TLC showed practically no decomposition during this process. Keeping Form II at 155°C (slightly above its melting point), produced much slower growth of Form I. The prolonged heating caused colouration of the substance and TLC revealed some decomposition.

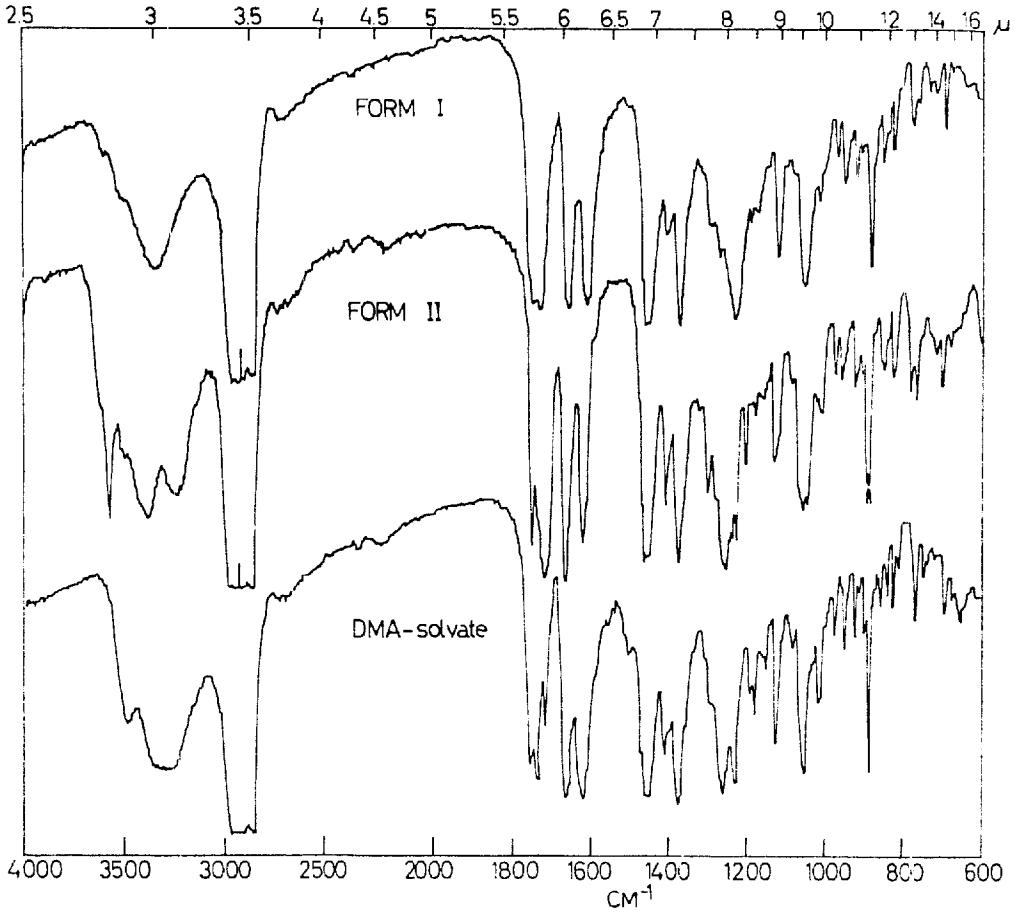

Fig. 1. IR spectra of the polymorphic modifications and DMA solvate of triamcinolone diacetate (nujol mull).

None of the solvents in these experiments yielded Form I directly. This may explain why the commercial preparations are in Form II.

The melting point of the solvent-free Form I was 186–188°C. This finding contradicts The Merck Index IX statement that triamcinolone diacetate exists as 'solvated crystals, m.p. 186–188°C (with effervescence, m.p. 235°C after drying)'. From this statement the information about the solvent is lacking and in none of our experiments could this high melting point be observed. We find the form melting at 186–188° to be solvent-free.

Crystal form in commercial injections of triamcinolone diacetate

Having established the existence of polymorphism, commercial preparations were examined for crystal forms. The crystals were collected by filtration, rinsed with water and air-dried. Of two different lot numbers, one contained pure Form II crystals, the other approximately 10% of Form I in addition to Form II as determined by melting point and IR spectra.

Crystal lattice changes during IR spectroscopy

When recording the IR spectra of Form II by the KBr pellet technique, sometimes mixtures of the spectra of Form I and II appeared. Depending on the duration and intensity of the pressure applied, the crystal lattice of Form II more or less transformed into Form I. Such sensitivity to mechanical stress of a lower melting modification has been described by Borka and Valdimarsdottir (1975). Further IR spectra were recorded using the more gentle nujol mull technique.

Conclusions

Three distinctly melting forms of triamcinolone diacetate were prepared and they proved to be Form I (188°C), Form II (151°C) and DMA solvate (103°C), respectively. They all have distinct IR spectra making differentiation easy.

The DMA solvate was found to be a useful starting material to produce Form I by prolonged heating at 105°C and letting the Form I crystals grow. A series of commonly used solvents produced Form II.

Infra red spectra of triamcinolone diacetate polymorphs should be recorded by using the nujol mull technique. The mechanical stress involved in the preparation of KBr discs (milling, pressure) leads to crystal lattice changes of Form II into Form I resulting in false IR spectra.

Acknowledgement

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