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Comparative studies of different modifications of calcium valproate

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Abstract

The crystalline state of calcium valproate (CaV) in different modifications, prepared by us, was investigated using infrared (IR) spectroscopy, X-ray powder diffraction patterns, simultaneous thermal analysis (STA combined thermogravimetry TG and differential thermal analysis DTA), and scanning electron microscopy (SEM). The influence of the simple recrystallized solvent on the crystal state of the drug is evident.

Keywords: Calcium valproate; Antiepileptic drug; Crystalline modification; Infrared spectroscopy; Thermogravimetry; Differential thermal analysis; Scanning electron microscopy; Recrystallization

The antiepileptic drug calcium valproate (Convulex, Depakine, Epilini, etc.) is not included in the list of drugs with proven polymorphism/pseudopolymorphism (Thoma and Serno, 1984; Borka and Haleblian, 1990). We were not able to find any data concerning this problem in the literature and in the most recent pharmacopoeial publications (British Pharmacopoeia, 1988; Martindale, 1989; US Pharmacopoeia, 1990; European Pharmacopoeia, 1992).

The necessity of studying the crystalline modifications of drugs has been substantiated in a great number of reviews (Haleblian and McCrone, 1969; Haleblian, 1975; Borka, 1976; Luukko and Laine, 1981; Burger, 1982; Bettinetti, 1988; Borka and Haleblian, 1990). The use of valproic acid in combination therapy with other antiepileptic drugs results in teratogenicity and hepatotoxicity (Kondo et al., 1990). Many authors have investigated the crystal polymorphism of carbamazepine (Laine et al., 1984; Krahn and Mielck, 1987, 1989; Lowes et al., 1987; Lefebvre et al., 1987).

We investigated the crystal polymorphism/pseudopolymorphism of CaV. Following the published data, we tried to prepare modifications by recrystallization from a series of 14 simple solvents. To characterize the crystalline modifications, we used IR spectroscopy, X-ray powder diffraction patterns (XRD), combined thermogravimetry (TG) differential thermal analysis (DTA), and scanning electron microscopy (SEM). The purpose of this communication is to report

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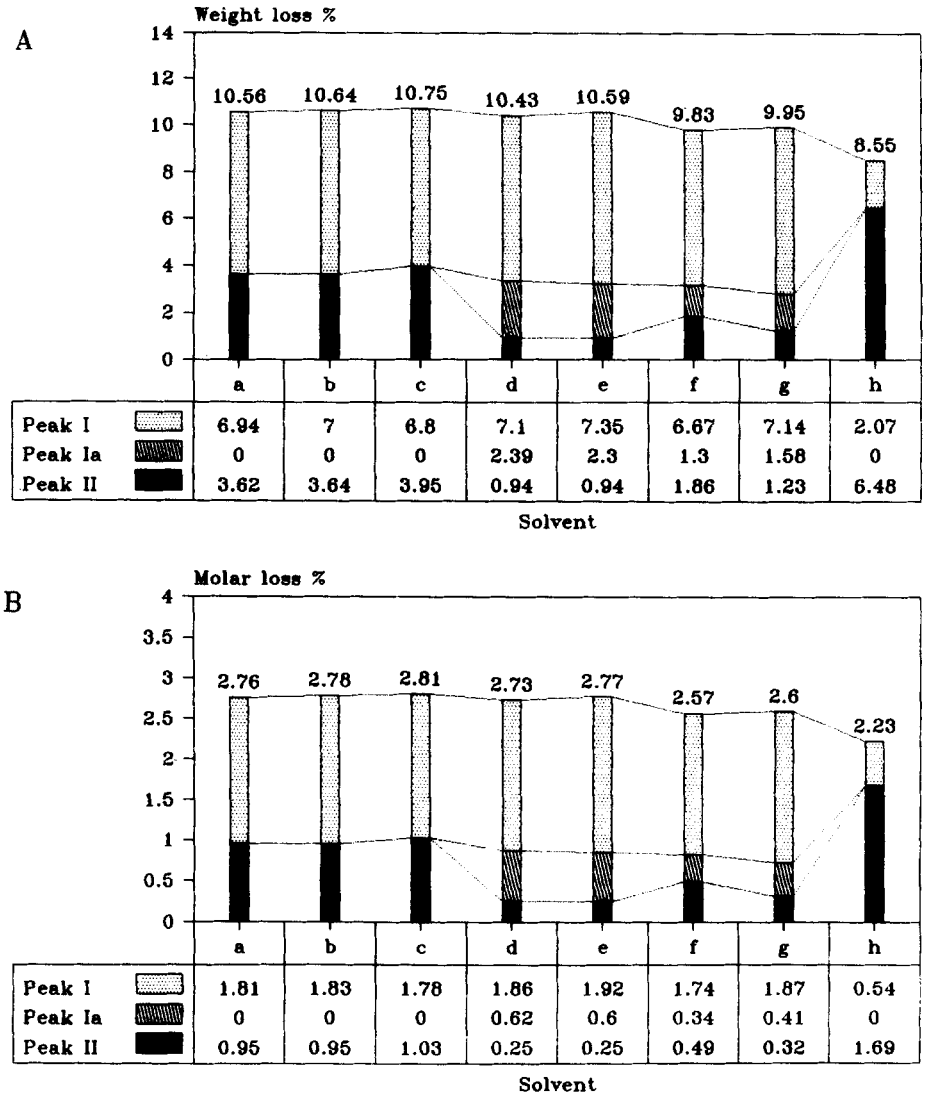


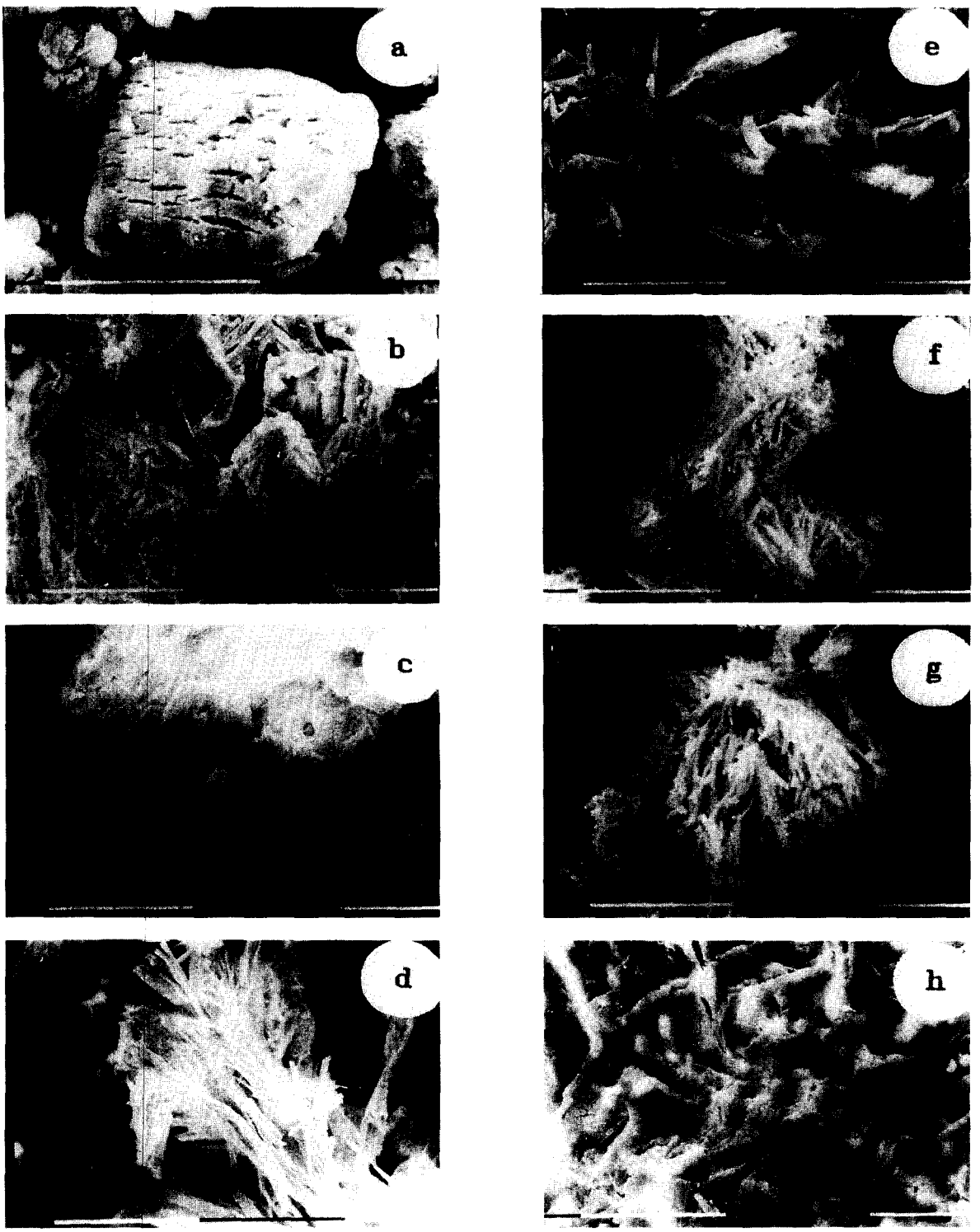
Fig. 1. Histograms of calcium valproate (a) and calcium valproate recrystallized from water (b), chloroform (c), acetonitrile (d), methanol (e), 1,4-dioxane (f), acetone (g), and 1-butanol (h).

some results of the studies of these crystalline modifications. Calcium valproate (Pharmaceuticals Dresden, Germany) was used as received. All solvents were of spectroscopic grade (Merck, Germany). An appropriate amount (w/v) of calcium valproate was dissolved/suspended in a solvent. The different crystalline modifications were obtained via slow evaporation of the solvent at room temperature.

The IR spectra of the various crystal modifications of CaV, and of the original CaV preparation in nujol suspension, were recorded and interpreted in detail in the region 3800–400 cm^{-1}.

The crystallization water plays a significant

Fig. 2. Scanning electron microphotographs of calcium valproate (a) (×600, marker 100 μm), and calcium valproate recrystallized (×400, marker 100 μm) from: water (b), chloroform (c), acetonitrile (d), methanol (e), 1,4-dioxane (f), acetone (g), 1-butanol (h).


a
b
c
d
e
f
g
h

role in the formation of the IR spectral characteristics; according to the manufacturer's certificate the preparation is a dihydrate. As is known, crystallization water has absorption bands in the following ranges: 3550–3200 cm^{-1} (asymmetric and symmetric OH vibrations), and at 1630–1600 cm^{-1} for δ H-O-H. The libration vibrations appear in the low-frequency region (600–300 cm^{-1}).

Comparing the IR spectra of the different modifications with that of the standard substance (a), one can see a significant decrease of the crystallization water band at 1630 cm^{-1}.

We compared the X-ray diffractograms of CaV (a), dehydrated (a'), and recrystallized from 1-butanol (h). The differences between the three patterns are obvious. The amorphous type 'halo' peak has a maximum at 13.5°(θ°) for (a') and (h), and at 12.75°(θ°) for (a).

The results of the DTA and TG analysis are presented in Fig. 1 as histograms showing the quantity (in weight and mole percent) of water released by the respective substances studied. The weight percentage loss is calculated with respect to a 'dry' substance at 135°C, with the exception of the (h) substance, where the loss is calculated with respect to a dry substance at 160°C.

Fig. 2 illustrates the differences in the crystal habits of the various CaV modifications observed by scanning electron microscopy.

The crystalline state of CaV has not been described and discussed in the literature. The results of the present studies enabled us to draw the following conclusions:

CaV can exist in different crystalline modifications, as proven by IR spectroscopy, STA and SEM analysis, and X-ray diffraction patterns.

The nature of the solvents (mainly polarity, solvents power, etc.) strongly influences the crystalline state of the recrystallized drug samples.

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