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Crystallisation of carbamazepine in tablets stored at elevated temperatures

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Summary

Carbamazepine crystals were shown to grow on the surfaces of tablets containing stearic acid if the tablets were stored at 50 ° C or 80 ° C. This effect was not observed at 35 ° C or in tablets not containing stearic acid. The phenomenon was due to recrystallisation of carbamazepine probably from solution in molten stearic acid and illustrates an alternative crystal growth mechanism to the more common water-mediated phenomenon.

Introduction

Crystals were observed to form on the surfaces of certain experimental carbamazepine tablet formulations on storage at 50 ° C. Such crystal growth may be a cause for concern because of the potential for adversely affecting the appearance and properties of tablets (Hess, 1987; Stahl, 1980). In particular, recrystallisation of carbamazepine is undesirable because of its poor solubility and associated particle size effects on dissolution and because of the existence of several polymorphs with possibly different solubility characteristics (Kahela et al., 1983; Kaneniwa et al., 1984; Krahn and Mielck, 1987; Laine et al., 1984; Pöhlmann et al., 1975; Umeda et al., 1984).

Crystal growth in tablets is a phenomenon usually associated with the presence of water (Ando et al., 1985; Ando et al., 1986; Laine et al., 1984; Stahl, 1980); however, extensive preliminary tests showed that in this case moisture content of the tablets was not implicated. The same investigations eliminated most of the excipients, with the exception of stearic acid, as causative agents. Accordingly, experiments were performed to investigate the effect of stearic acid on recrystallisation of carbamazepine in tablets.

Although stearic acid is a commonly used tabletting lubricant, it was necessary to use an additional lubricant (magnesium stearate) to assist in tabletting samples.

Materials and Methods

The materials used in this study were carbamazepine B.P. from Ciba-Geigy, Basle, Switzerland, stearic acid B.P.C. 1973 from Durham

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TABLE 1

Composition of stearic acid B.P.C. 1973 by GCMS

Tetradecanoic acid (myristic acid)	3% w/w
Hexadecanoic acid (palmitic acid)	67% w/w
Octadecanoic acid (stearic acid)	30% w/w

Chemicals Ltd., Birtley, U.K., and magnesium stearate B.P. from Unichema Chemicals Ltd., Bebington, U.K.

The composition of the stearic acid B.P.C. 1973 was determined by gas chromatography/mass spectroscopy (Finnigan 1020 GC/MS). Results are given in Table 1.

Methods

Tablets were prepared to the formulae given in Table 2. The method of preparation of the tablets was as follows.

Formulation 1. Carbamazepine B.P. was mixed with magnesium stearate B.P. in a Turbula mixer (W.A. Bachofen, Basle, Switzerland) for 2 min. The resulting mixture was compressed into round flat tablets with bevelled edges and of 11.5 mm diameter using a D3A (Manesty Machines, Liverpool, U.K.) rotary tablet machine.

Formulation 2. Carbamazepine B.P. and stearic acid B.P.C. 1973 were mixed in a Turbula mixer for 15 min and then lubricated with magnesium stearate B.P. and compressed in the same manner as Formulation 1.

Sample storage and inspection. Samples of the tablets were stored in closed plastic containers (Securitainers, Johnson & Jorgensen) at various temperatures and examined at 0, 5 days and 6 weeks using light microscopy.

At 6 weeks the tablets were also inspected by scanning electron microscopy (Cambridge S200 scanning electron microscope). The samples were sputter-coated with gold before examination.

TABLE 2

Tablet formulae used in the study

Ingredient	Formulation 1	Formulation 2
Carbamazepine B.P.	441 mg/tab	435 mg/tab
Stearic acid B.P.C. 1973	–	6 mg/tab
Magnesium stearate B.P.	9 mg/tab	9 mg/tab

Solubility studies. Solubility of carbamazepine in stearic acid was demonstrated by means of differential scanning calorimetry (DSC) (Perkin Elmer model DSC-4). The experimental conditions are shown on the traces (Figs. 4–6).

The solubility of carbamazepine in stearic acid was further investigated by means of assay (HPLC) of saturated solutions at different temperatures. The chromatographic conditions were:

Column: 250 × 4.6 mm packed with Nucleosil $10C_8$
Mobile phase: Methanol/water (750 : 250)
Detection: UV at 285 nm.
Flow rate: 0.7 ml/min

All standard and test solutions were prepared in methanol.

Identity of crystalline material. The crystals were examined microscopically at 150 × and compared with carbamazepine crystals grown from solution in molten stearic acid.

In addition, the melting point of the crystalline material was determined using a capillary melting point apparatus (Gallenkamp, Loughborough, U.K.) and compared with values for each of the tablet ingredients.

TABLE 3

Light microscopy results

Formulation	Storage time	Storage temp.	Surface appearance
1. Without stearic acid	0, 5 days, 6 weeks	35 °C, 50 °C	Smooth glossy tablets
2. With stearic acid	0	–	Smooth glossy tablets
	0, 5 days, 6 weeks	35 °C	Smooth glossy tablets
	5 days	50 °C	Matt tablets. No crystals visible
	5 days	80 °C	Matt tablets. Slightly crystalline.
	6 weeks	50 °C	Marked crystallinity
	6 weeks	80 °C	Very marked crystallinity.

Results

The results for light microscopical inspection are given in Table 3.

Scanning electron microscopy at 6 weeks showed no surface crystal growth on tablets containing no stearic acid stored at 35 °C and 50 °C nor on tablets containing stearic acid stored at 35 °C.

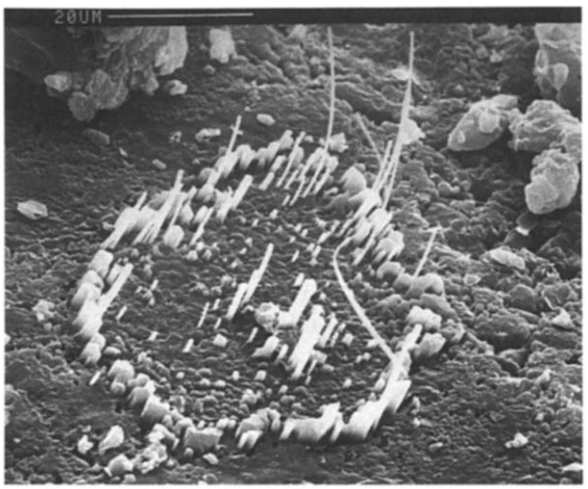

Fig. 1. Scanning electron micrograph of carbamazepine tablet containing stearic acid stored at 50 °C for 6 weeks showing crystals protruding from smooth tablet surface.

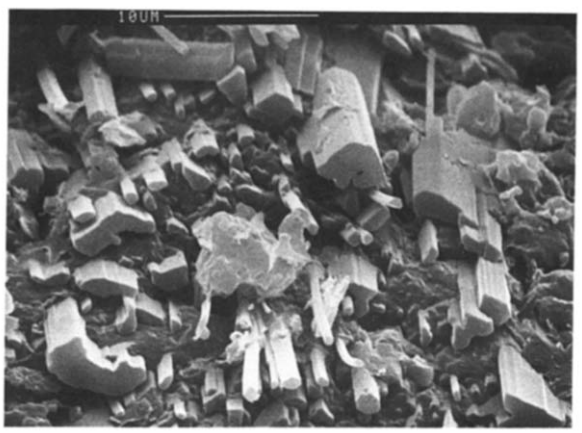

Fig. 2. Scanning electron micrograph of carbamazepine tablet containing stearic acid stored for 6 weeks at 50 °C and showing characteristic appearance of crystalline material.

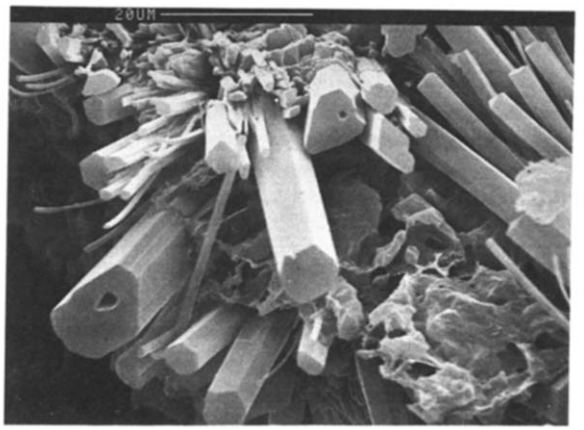

Fig. 3. Scanning electron micrograph of carbamazepine tablet containing stearic acid stored for 6 weeks at 80 °C.

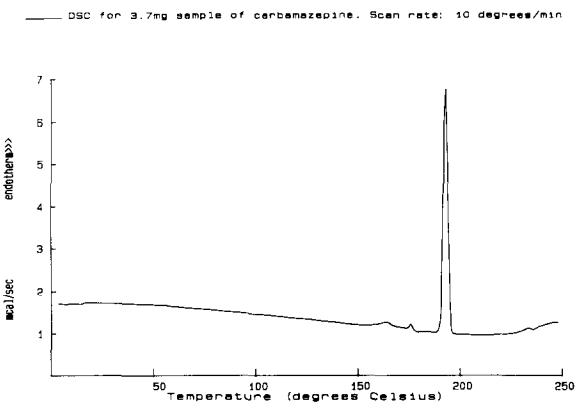

Fig. 4. DSC of carbamazepine.

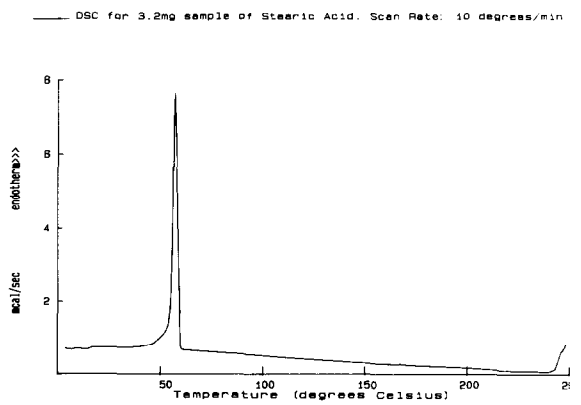

Fig. 5. DSC of stearic acid.

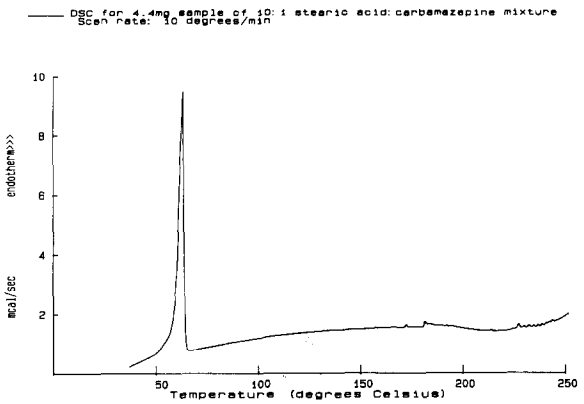

Fig. 6. DSC of 10 : 1 stearic acid : carbamazepine mixture showing absence of carbamazepine fusion endotherm.

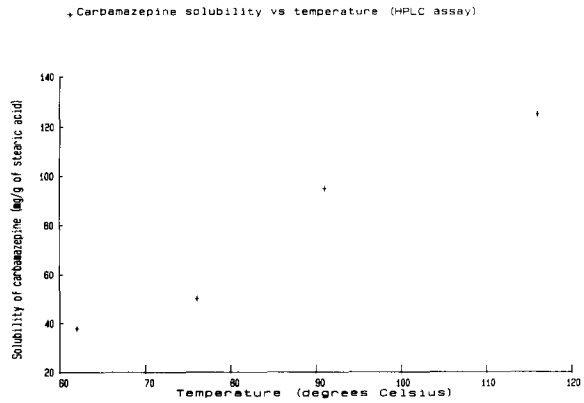

Fig. 7. Solubility of carbamazepine in stearic acid.

TABLE 4

Melting points of crystals and formulation excipients

Substance	Melting point (°C)	Comments
Crystalline material	186–187	Capillary MP apparatus
Carbamazepine	approx. 194	DSC. See Fig. 4.
Carbamazepine	187–188	Capillary MP Apparatus
Carbamazepine	190–193	Merck Index, 1983
Stearic acid	40–64	DSC. See Fig. 5.
Magnesium stearate	88.5	Handbook of Pharmaceutical Excipients, 1986

Extensive crystal growth was observed on tablets containing stearic acid stored at 50 °C and 80 °C. (See Figs. 1–3).

DSC demonstrated abolition of the carbamazepine fusion endotherm in mixtures of carbamazepine and stearic acid. This is indicative of the carbamazepine being in solution. These results are shown in Figs. 4–6.

The solubilities of carbamazepine in stearic acid at several different temperatures are shown in Fig. 7.

Microscopical study of the crystals showed them to be similar in form to crystals grown from carbamazepine solutions in molten stearic acid. The results of melting point studies are given in Table 4.

Discussion and Conclusions

The results show clearly that crystals only appear on the surface of tablets at elevated temperatures and in the presence of stearic acid. The crystals are of carbamazepine: neither magnesium stearate nor stearic acid can form crystals of the kind observed with the melting point observed.

The results also show that carbamazepine is soluble in molten stearic acid. Observable crystal growth only occurred in samples stored above the onset of stearic acid melting of about 40 °C (see Fig. 5). No crystal growth was seen in the presence of solid stearic acid at 35 °C. It therefore seems likely that the mechanism of crystal growth was by recrystallisation of carbamazepine from saturated solution in molten stearic acid.

The presence of crystal growth under such conditions is an interesting phenomenon both because it demonstrates the possibility of crystal growth in tablets due to a non-aqueous mechanism and because it illustrates the need for caution in interpreting high temperature storage results wherein components of a formulation may not be in the same physical state as at room temperature.

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