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PHASE TRANSFORMATIONS IN SULFATHIAZOLE DURING MECHANICAL ACTIVATION

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ABSTRACT

The effect of mechanical treatment in a planetary ball mill on the transformations of polymorphs of sulfathiazole were studied by means of X-ray diffraction analysis, infrared spectroscopy and differential scanning calorimetry. It has been shown that mechanical treatment initiates transitions of sulfathiazole polymorphs III $\rightleftharpoons$ I. In an initial period of mechanical treatment a part of the sulfathiazole was converted into a noncrystalline solid. Preliminary mechanical treatment of form III resulted in the reduction of III $\rightarrow$ I phase transition temperature by 20-30°C in the samples without form I and by 40-50°C in the samples where the part of the substance were transformed into form I during mechanical treatment.

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Single crystal thermomicroscopy studies showed that III → I phase transition proceeds via nucleation and a rapid advance of an interface through the crystal.

It seems that deformation of crystals during mechanical treatment and formation of noncrystalline solid with high extent of disordering make probable the initiation of phase transition of sulfathiazole during mechanical treatment.

INTRODUCTION

The phenomenon of polymorphism is of great importance in the modern drug technology since the efficacy and stability of a medicine depends on the content of one or another polymorphic form of the medicinal substance. In most cases, metastable polymorphic forms of medicinal substances show the largest pharmacotherapeutical activity (1,2). Mechanical treatment of a substance is known to be one of the methods for stimulating of polymorphic transitions in solids and leading to the formation of metastable polymorphic forms (3,4). The existence of numerous polymorphs of organic substances having pharmacotherapeutical activity suggests that mechanical treatment could be used for obtaining active forms of drugs. Mechanochemical studies developed recently in pharmacy have shown that some drugs undergo polymorphic transformations upon mechanical actions such as, for instance, grinding and compression (5).

The purpose of the present work was to study the effect of mechanical treatment on the polymorphism of sulfathiazole.

Three polymorphs of sulfathiazole have been reported (6-8), forms II and III being stable at room temperature and high-temperature form I obtaining from polymorphs II and III at 173-175°C. The main difference between these crystal forms lies in the types of hydrogen bonds present and their effects on the arrangement of molecules in the crystal. Modification I is the most suitable form of sulfathiazole for pharmaceutical use owing to its higher rate of dissolution and solubility (9).

Little has been accomplished as regards the effect of mechanical treatment on the polymorphism of sulfathiazole. Sekiguchi et al (10) reported that on grinding of sulfathiazole with a ball mill consisted of a porcelain cylinder with porcelain balls at 180 rpm no phase transformation in the substance have been observed. It has been noted, however, that retransition of the high-temperature form of sulfathiazole was facilitated by the mechano-chemical influences of grinding.

EXPERIMENTAL

Materials

Single crystals of polymorph III were grown as colourless hexagonal plates by slow evaporation of a dilute ammonium hydroxide solution at room temperature. Polymorph I was obtained by heating of form III crystals at 170°C for 30-40 min, and also by recrystallization of commercial sulfathiazole from n-butanol.

Testing

The mechanical treatment was conducted in a mechanical activator consisted of a planetary cen-

trifugal ball mill with water cooling using steel balls. The ratio of balls to the sulfathiazole sample was 20:1 in weight.

The IR spectra of tablets with KBr were recorded on a "Specord-75IR" spectrometer. The differential scanning calorimetry curves (DSC) were measured with a "Setaram DSC 111" in an argon atmosphere with a heating rate of 10°/min, and a sample weight of about 100 mg. X-ray phase analysis was carried out on a DRON-3 apparatus using Cu K_α radiation. For a qualitative estimation of sulfathiazole modifications present in the samples under study, LiF was used as an internal standard material. The calibration plots of the ratio of the peak heights at θ=7.7° due to form III or at θ=8.8° due to form I to the height of LiF peak at θ=19.3° versus the content of the given form in the sample were constructed.

Microscopic observations were performed using a NU-2E polirazing microscope. Crystals were placed on a thermostated plate heated to a definite temperature.

RESULTS AND DISCUSSION

Effect of mechanical treatment on the polymorphism of sulfathiazole

After mechanical treatment in the mechanical activator (acceleration 200 m/s^2, a ball diameter 8 mm) for 1 min, the X-ray diffraction pattern showed a broadening of the peaks and a decrease in their intensity (Fig.1). After 5 min of mechanical treatment, the appearance of new diffraction peaks was observed. These peaks may be assigned to the high-temperature phase I of sulfathiazole. The

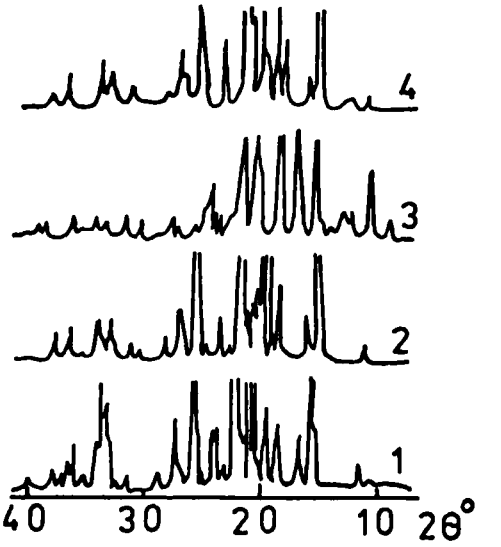

Figure 1 - Diffraction patterns of sulfathiazole after mechanical treatment in the mill (200 m/s^2) :
1 - intact form III; 2 - 1 min;
3 - 40 min; 4 - 90 min of treatment.

presence of modification I in the samples mechanically treated is supported by the IR spectroscopy data (Fig.2). Upon further treatment, the intensity of diffraction peaks of the phase I increases for some time and then began decreasing to complete disappearance. Prolonged mechanical treatment (to 3 hr) did not lead to the new appearance of the high-temperature phase. However, if the treatment was conducted after an interruption for several hours the general pattern of the substance behaviour repeated. The conversion fraction of the starting substance into the phase I reached 50-80%. The use of balls of lesser diameter (5 and 3 mm) led to decreased con-

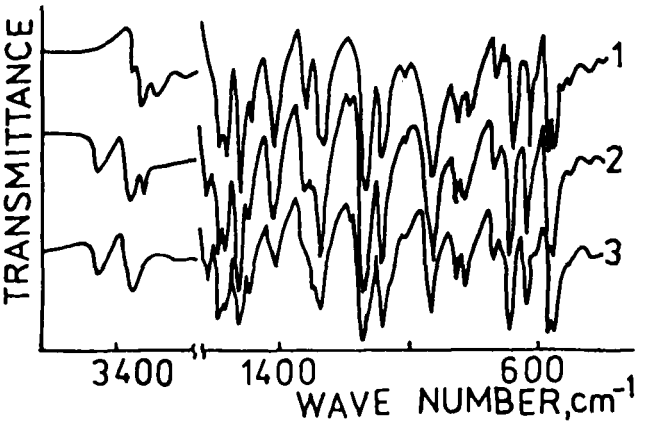

Figure 2 - IR-spectra of sulfathiazole: 1 - form III; 2 - form III after mechanical treatment for 10 min; 3 - form I obtained by heating III.

version fraction. Besides, the qualitative estimation of the content of sulfathiazole polymorphic forms in the samples showed that at the initial stage of mechanical treatment a part of the substance in the samples (up to 50%) appears to be in a noncrystalline state. This is also indicated by the broadening of diffraction peaks and by the decrease in their intensity after the first minutes of mechanical treatment. The DSC curves (Fig.3) of the samples obtained show two broad exothermic peaks in the range of 30-80°C, which is apparently due to the crystallization of the substance. These peaks were absent if after mechanical treatment the samples were subjected to annealing at 70°C. In this case, the amount of the form III was increased in the samples, while the content of the modification I did not change. The data obtained confirm the presence of the non-

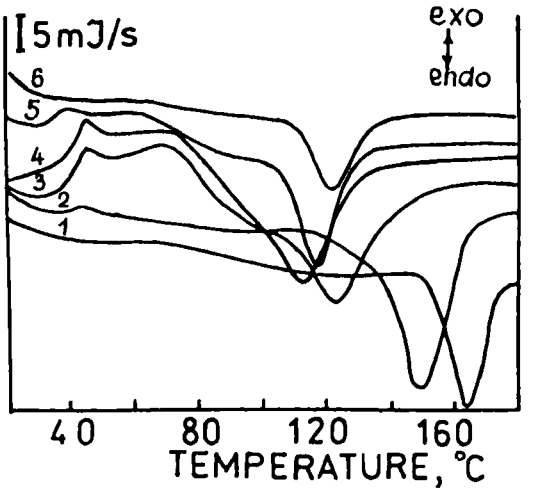

Figure 3 - DSC curves of sulfathiazole after mechanical treatment:
1 - intact form III, sample weight 47 mg;
2 - 1 min, 124 mg; 3 - 10 min, 120 mg;
4 - 20 min, 107 mg; 5 - 30 min, 78 mg;
6 - 45 min, 75 mg.

crystalline phase in sulfathiazole samples subjected to mechanical treatment. Prolonged mechanical treatment led to the recrystallization of the substance: a narrowing of the diffraction peaks and an increase in their intensity were observed.

It follows from the experimental data that the mechanical treatment of sulfathiazole initiates both the III → I and I → III transitions. In order to verify this, the form I obtained by heating of sulfathiazole III was treated mechanically. After 1 minute of mechanical treatment, the appearance of peaks attributable to form III was observed in the X-ray diffraction patterns of the samples. Prolonged

mechanical treatment led to complete disappearance of peaks of the high-temperature modification and formation of the sulfathiazole form III. Further behaviour of the substance was analogous to the above: after interruption, mechanical treatment led to the appearance of the phase I which disappeared upon prolonged mechanical treatment.

Analysis of the crystalline structures of sulfathiazole polymorphic modifications has shown (6,7) that in the forms I and III the number of hydrogen bonds per molecule and their strength are approximately equal (7), therefore the structures of these two modifications differ insignificantly. This apparently explains the relative easiness of the transitions III $\rightleftharpoons$ I (11).

The use of more severe operation conditions of the mill (acceleration 600 m/s^2, ball diameter 8 mm) brought about a repeated variation in the concentration of the high-temperature form to its complete disappearance and appearance again after 40-50 min of treatment (Fig.4). It is evident that in this case we deal not with mechanical equilibrium as observed for phase transitions during mechanical activation (3), but with variation of the activity of the solid relative to the phase transformation.

The presence of extremums on the curve of the properties of mechanically treated substance against the time of treatment has been discussed by Naeser and coworkers (12,13). The authors have suggested that deformations produced by mechanical treatment in the substance can be periodically cured partially, in this case the energy content of the solid would pass through maximums and minimums. The periodical

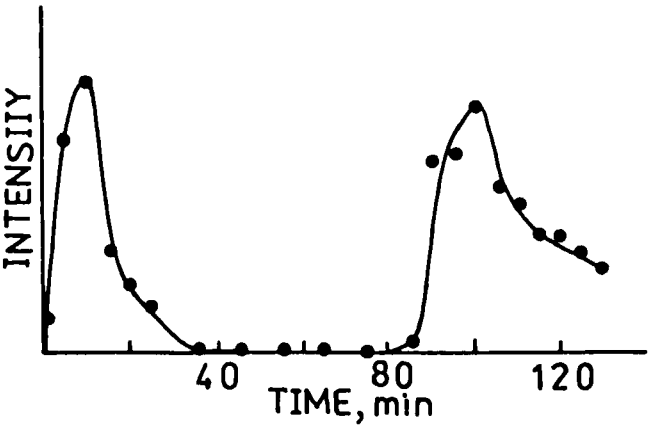

Figure 4 - Variation of intensity of sulfathiazole I diffraction peak (d=5.06 Å) with time of mechanical treatment in the mill (600 m/s^2).

annealing of the substance activated, in opinion of other authors (14), may be associated with temperature variations during mechanical treatment in high-energy activators. A mathematical model suggested in the work (14) for the description of mechano-chemical system as an open, possessing unlinear inherent dynamics enables to show the possibility of realization of different stationary regimes depending on conditions of mechanical treatment.

It is evident that in order to elucidate the causes of variations of concentration parameters of the system in our case, additional experiments are required. Investigation of such kind of phenomenon is of interest both for the understanding the peculiarities of mechanical activation of solids and for its technological applications.

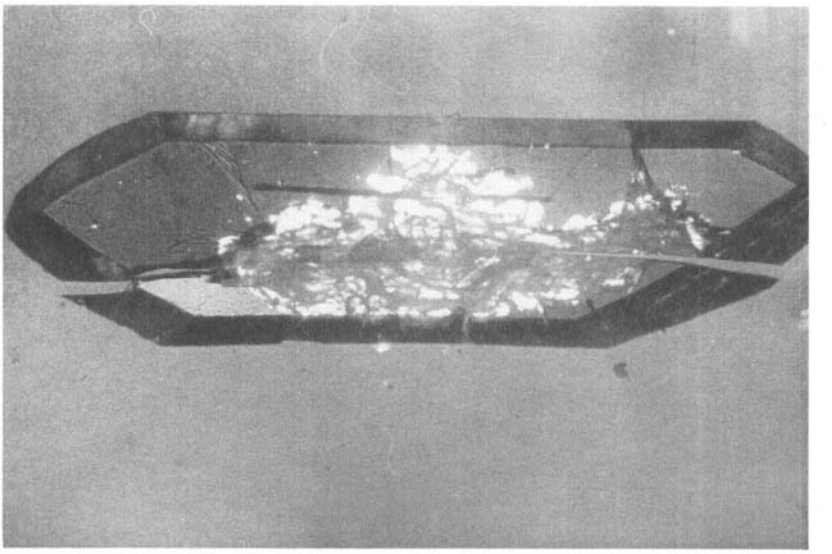

Figure 5 - Microphotograph of a sulfathiazole single crystal during III→ I phase transformation (x 20)

The phase transition III → I in sulfathiazole single crystals

Microscopic observations have shown that the III → I transformation proceeds topochemically, i.e. via the formation of a product phase and propagation of an interface formed through the crystal (Fig.5). The movement of the interface is of irregular character: a rapid propagation is accompanied by stopping of the reaction front. The cracking of the initial crystal and of the product phase is observed. The pseudomorphous product of the transformation is polycrystalline. Experiments on indentation of the crystals have shown that the sites of pricks with an indentor are the centres of nucleation of the product phase.

The course of the phase transformation in sulfathiazole may be apparently described as proceeding on a cooperative mechanism well-known for phase transitions (15). In contrast to per-atomic mechanism, the cooperative mechanism is characterized by the rapid propagation of the interface with irregular rate through the crystal. Such a behaviour of the interface is associated with the partial relaxation of elastic stresses at the interphase boundary and formation of a semicoherent interface. The phase relaxed is characterized by increased effective surface energy, which leads to an increase in the barrier for the nucleation. The nucleation at the sites of indentation suggests that the deformation of crystals leads to decreased energetic barrier for nucleation. Possibly, this is one of the factors responsible for initiation of phase transition during mechanical treatment in a mill.

It follows from the DSC data that the mechanical treatment in a mill leads to a decrease in temperature of phase transition in sulfathiazole. The extrapolated onset shifts by 20-30° in mechanically treated samples which do not contain the high-temperature phase and by 40-50° in the samples wherein a portion of the substance was subjected to the III—I transition during mechanical treatment. In the first case, the cause of the decreased temperature of transition is evidently the increase in the number of defects in sulfathiazole crystals upon mechanical treatment, in the second one, the regions of the new phase formed as a result of mechanical treatment appear to serve as nuclei during the thermal phase transition.

Summers et al (16) reported reduction in the transition temperature of polymorphic forms of sulfathiazole after compression. The authors postulated that this fact was due to the production of dislocations in the crystal and the distortion of the crystal at crystal boundaries formed in the compressed materials.

On mechanical treatment in activator, it seems that the formation of noncrystalline phase in the first stage of treatment plays an essential role in proceeding of phase transformation in sulfathiazole. Probably, it is the formation of noncrystalline phase with a high degree of disorder which makes possible initiation of phase transformation in sulfathiazole during mechanical treatment.

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