Journal of Inclusion Phenomena and Macrocyclic Chemistry **37:** 299–307, 2000.

A Study of Sulfadimidine-β-Cyclodextrin Mixtures

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(Received: 1 April 1999; in final form: 12 August 1999)

Abstract. A physical mixture and a kneaded product containing sulfadimidine and β-cyclodextrin were prepared. The morphology of these products and of the sulfadimidine bulk substance were studied by scanning electron microscopy (SEM). The thermoanalytical behaviour of the samples was investigated. The existence of an inclusion complex in the products could not be proved. However an increase in dissolution rate was observed. The reason in the case of the physical mixture lies in the regular distribution of the active agent crystals and the β-cyclodextrin crystals, and in the case of the kneaded product in the formation of new recrystallized particles.

Key words: sulfadimidine, β-cyclodextrin, physical mixture, kneaded product, scanning electron microscope (SEM), thermoanalysis, dissolution.

1. Introduction

The sulfonamides, including sulfadimidine, exhibit antibacterial activity. Sulfadimidine is a water-insoluble drug that is official in the different pharmacopoeias [1]. β-Cyclodextrin is an excipient frequently used to increase the solubility of active agents [2, 3]. β-Cyclodextrin-containing products can be prepared by different methods (physical mixture, kneading, etc.) [4]. It appeared interesting to examine the influence of β-cyclodextrin on the morphology, the powder rheological behaviour and the rate of dissolution of sulfadimidine, and additionally to study whether an inclusion complex is present in these products.

2. Experimental

2.1. MATERIALS

Sulfadimidine crystals (Ph. Hg. VII.) and β-cyclodextrin (Cyclolab Ltd., Budapest) were used as received.

2.2. PREPARATION OF PRODUCTS

The physical mixture (molar ratio 1 : 1) was prepared in a Turbula mixer (W. E. Bachofen, Basel, Switzerland) for 10 min at 50 rpm. (Before mixing the components were sieved through a sieve 0.8 mm in wire distance.)

The kneaded product (molar ratio 1 : 1) was prepared with aqueous-ethanol (1 : 1) solvent using a mortar and pestle. The mass was continuously stirred during evaporation under infrared lamps, kneaded through a sieve (1.2 mm), dried overnight at room temperature and sieved again (1.2 mm). This product consisted of granule particles similar to crust granules.

2.3. METHODS

The *morphological study* was carried out using a scanning electron microscope (Hitachi 2400S, Japan).

The *thermoanalytical measurements* were performed on a TA Instruments 2000 Thermal Analyser System, using the following modules:

- TA 2920 DSC cell (for enthalpy changes),
- TA 2050 Thermogravimetric Analyser (for mass losses)

Conditions. The initial sample masses were about 4–6 mg, depending on the technique used. A heating rate of 5 °C/min was applied for TG and DSC measurements (10 l/h argon purge).

The reliability of the enthalpy determination is ±3%.

The *dissolution rate* of sulfadimidine was studied with rotating basket methods:

Apparatus. Pharma Test PTW II.

Dissolution medium: 900 ml artificial gastric juice

Temperature: 37 ± 0.5 °C

Rotation speed: 50 rpm

Sampling time: 5, 10, 20, 30 mins

Number of tests: 6 samples

Method: UV spectrophotometer, λ = 244 nm

3. Results

Morphology. Typical crystals of β-cyclodextrin (Figure 1) [5] and sulfadimidine crystals of many different sizes in their original form can be seen in the physical mixture (Figures 2a, b; 3a, b). It can be concluded that crystal aggregate formation

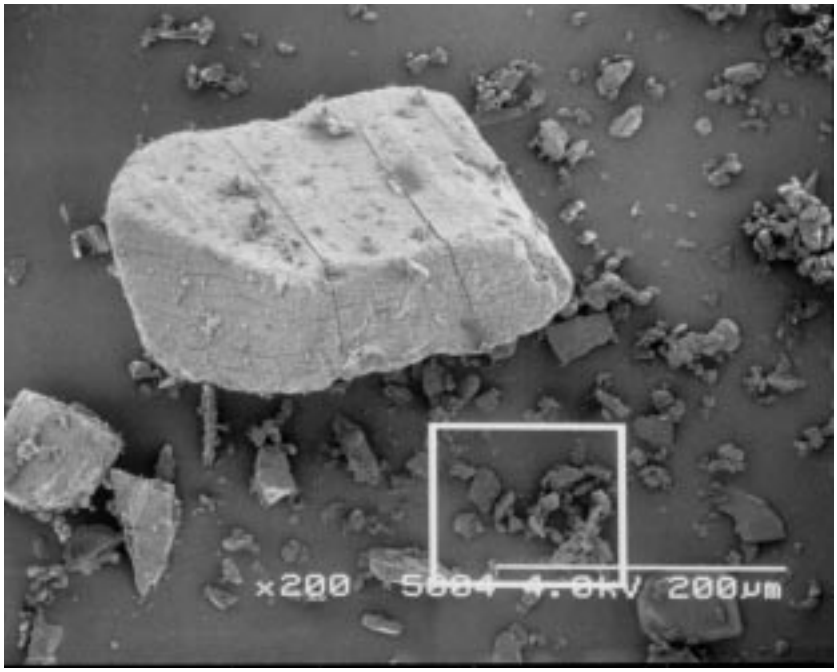

Figure 1. β-cyclodextrin crystal (SEM).

occured in the kneading process. Many small adhered crystals are to be observed in this product (Figures 4a, b).

Thermoanalysis. Sulfadimidine exhibits a sharp melting endotherm peak with an onset temperature of 198 °C, and a peak temperature of 200 °C (Figure 5). The heat of fusion is ΔH = 122 mJ/mg (± 3% accuracy). No mass loss or organic evaporation was observed before melting as proven by the TG analysis (Figure 6). Thermal decomposition starts at about 220 °C, with a 43% mass loss up to 350 °C and a 51% mass loss up to 400 °C.

The thermoanalytical behaviour of β-cyclodextrin can be divided into three main parts (Figure 6). The loss of crystalline water (12.5%) takes place from ambient up to 100 °C, followed by thermal decomposition above 280 °C. The mass loss of the primary and secondary decomposition products together up to 350 °C is 75%. The small endothermic peak in the DSC curve at about 220 °C reflects the solid-state transformation of the parent cyclodextrin (Figure 5).

The thermoanalytical curves of the physical mixture can be regarded as the superposition of the individual components. The sharp endothermic peak between 190–210 °C relates to the melting of the sulfadimidine (ΔH = 25 mJ/mg; ± 3% accuracy) (Figure 5). The water content of the sample is 9.1%. The evaporation and the thermal decomposition of the drug starts above 220 °C causing a 23% mass loss up to 280 °C, while the second part of the process of decomposition

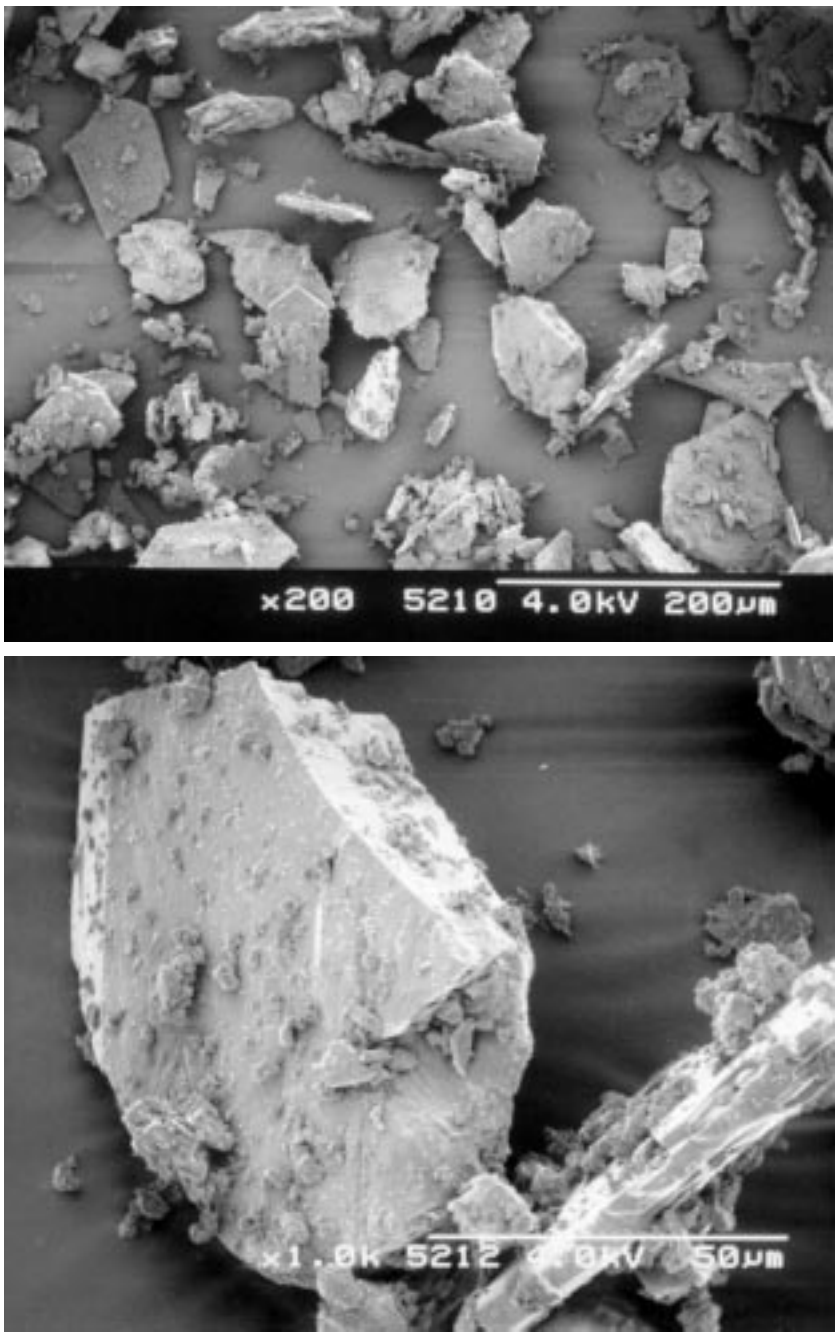

Figure 2. Sulfadimidine crystals (SEM).

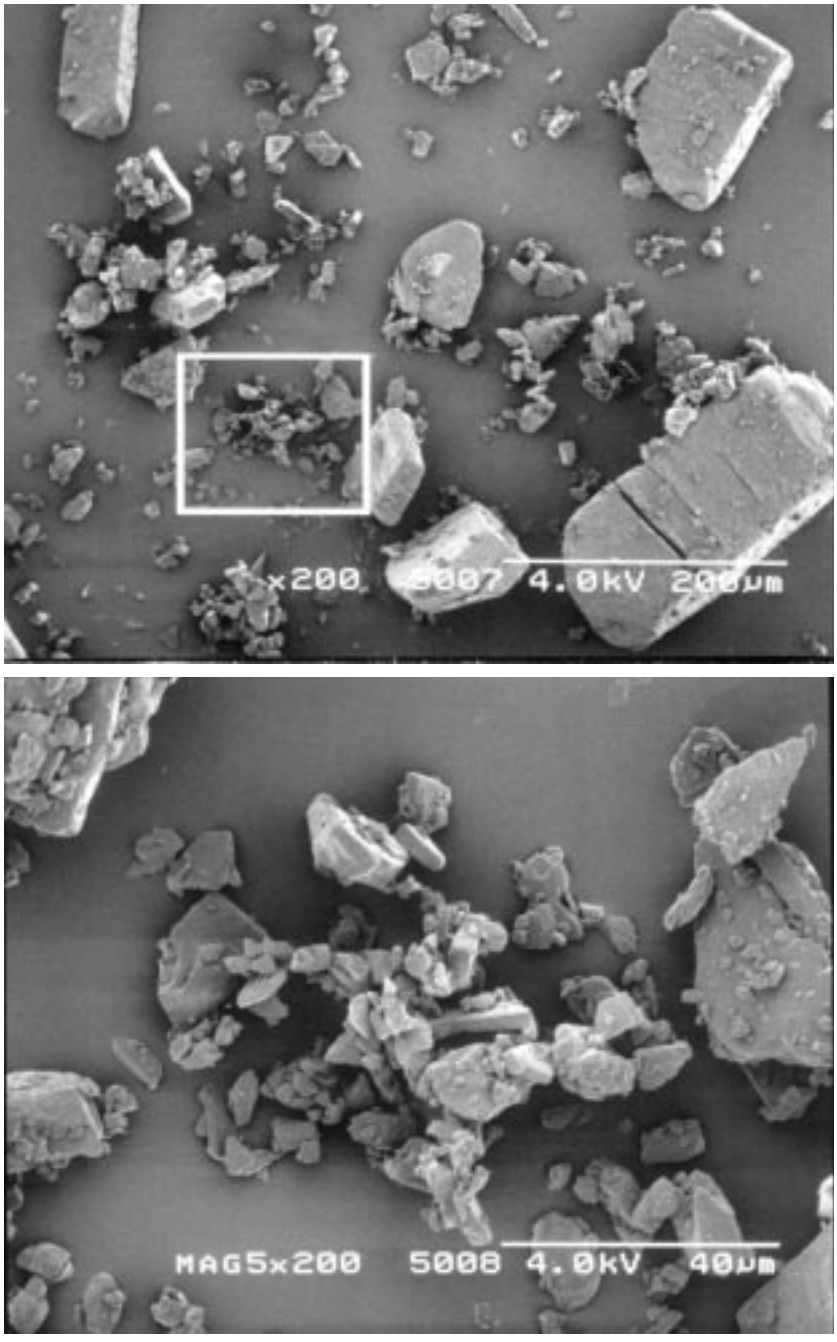

Figure 3. Sulfadimidine-β-cyclodextrin physical mixture (SEM).

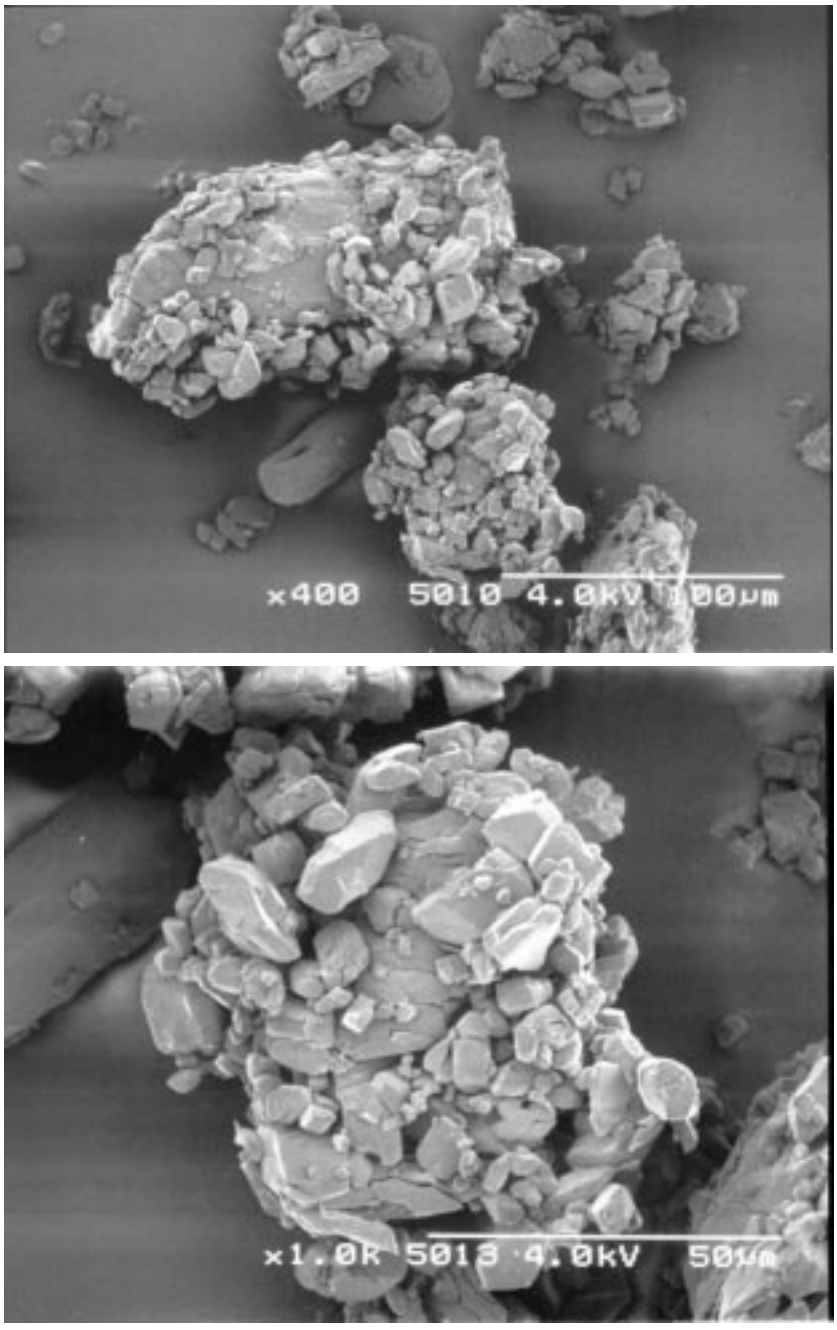

Figure 4. Sulfadimidine-β-cyclodextrin kneaded product (SEM).

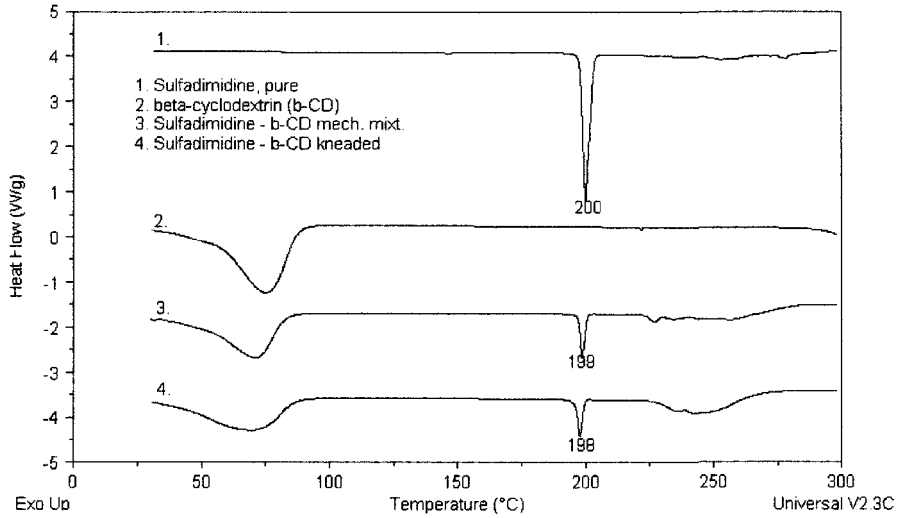

Figure 5. Thermoanalytical behaviour of the crystals and the products: DSC-curves.

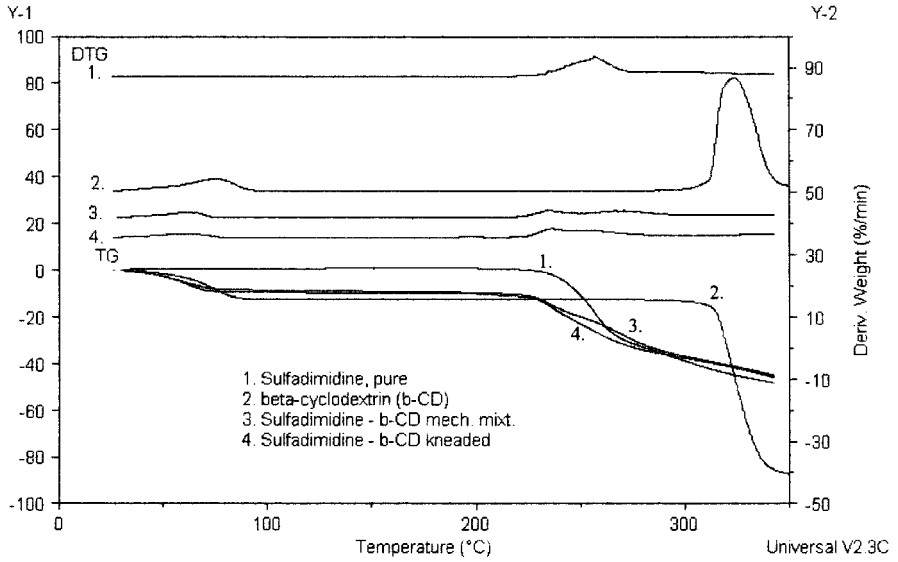

Figure 6. Thermoanalytical behaviour of the crystals and the products: TG and DTG-curves.

overlaps with the thermal degradation of the cyclodextrin, another 11% of weight loss was observed between 285–340 °C (Figure 6).

The DSC and the TG/DTG curves of the mechanical mixture and the kneaded product are practically identical. The melting peak of the guest component is still present after kneading indicating no formation of a real inclusion complex. The smaller calculated enthalpy change (ΔH = 23 mJ/mg; $\pm$ 3% accuracy) corresponding to the endothermic peak at 198 °C is due to the decrease of crystallinity

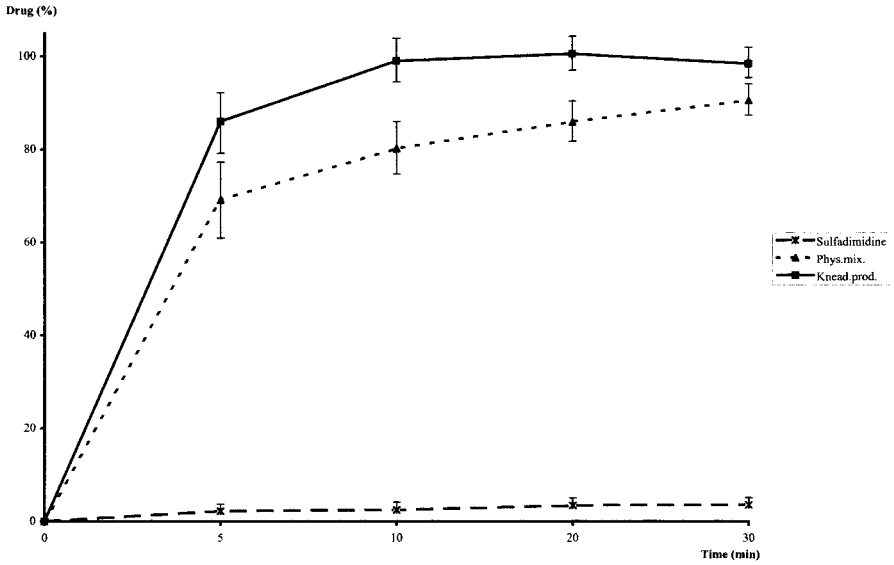

Figure 7. Dissolution rate of sulfadimidine, physical mixture and kneaded product.

of the sulfadimidine during the process of kneading (Figure 5). According to the TG curve this compound contains 8.3% of water. The decomposition of the sample starts at about 180 °C indicating the lower thermal stability of the kneaded product compared to the mechanical mixture. At the first main decomposition stage (between 180–270 °C) 23% and then between 280–340 °C 12% mass losses were determined (Figure 6).

To summarise the results of the thermoanalytical investigations no complex formation was observed between sulfadimidine and β-cyclodextrin in the physical mixture and when the kneading technique was used to prepare the sample.

Dissolution. The rate of dissolution of sulfadimidine is very poor (Figure 7). Only about 4% of the drug dissolved during 30 min. The rates of dissolution of sulfadimidine products containing β-cyclodextrin were much higher than that of the bulk substance. As concerns the two products, the dissolution of the kneaded product was faster. About 80% of the drug dissolved from the physical mixture during 30 min, whereas less than 10 min was enough for the total mass of the drug to dissolve from the kneaded product.

4. Conclusions

SEM was used to study the morphology (shape and surface) of the sulfadimidine-β-cyclodextrin physical mixture and kneaded product. For comparison, bulk sulfadimidine was used. The results showed that β-cyclodextrin influenced the rate of dissolution of sulfadimidine. Individual β-cyclodextrin crystals can be seen in

the SEM picture of the physical mixture. Furthermore, recrystallization took place during the kneading process, and new crystal aggregates can be observed in the kneaded products.

These findings correlate with the thermoanalytical results, which revealed no formation of an inclusion complex in the solid state. In spite of this, the dissolution is better and its rate is much higher. According to the literature, the mixing process could give rise to an ordered mixture [6]. The accelerating effect of β-cyclodextrin on the dissolution rate is connected with the regular distribution of the active agent, and the better solubility of β-cyclodextrin and the small crystals adhering to the surface. The better solubility of the kneaded product can be explained by the formation of granule particles, in which crystals of sulfadimidine and β-cyclodextrin are present together.

Overall, therefore, the application of β-cyclodextrin is of advantage as concerns the process of sulfadimidine dissolution.

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