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PREPARATION OF THE DISPERSE SYSTEMS OF SULFATHIAZOLE-POLYVINYLPYRROLIDONE BY MECHANICAL ACTIVATION

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Abstract

The potential value of solid-state dispersions of insoluble drugs in water-soluble matrices is known to bring about enhancement of solubility, dissolution rate and bioavailability of the drugs. The conventional methods of preparation of solid dispersions such as fusion or solvent technique are somewhat limited. The method of mechanical activation analogous to that which is employed in the mechanical alloying method may be used in preparation of dispersions of organic solids. In this paper, the method of mechanical activation is applied to obtain a solid-state dispersion of sulfathiazole in polyvinylpyrrolidone. The mechanical treatment of sulfathiazole with polyvinylpyrro-

lidone in a planetary ball mill transfers crystalline drug into amorphous state, the process being accompanied by formation of hydrogen bonds of sulfathiazole with matrice. The apparent solubility and rate of solvation of sulfathiazole were greatly increased if it was previously mechanically treated with polyvinyl - pyrrolidone. The release of sulfathiazole from solid dispersions with polymer to drug ratio of 1:3, 1:1, 3:1 was examined, a polymer to drug ratio of 3:1 gave the highest solubility.

Introduction

The method of introducing medicinal substances into solid dispersions proposed by Sekiguchi and Obi (1) has been recently widely employed for increasing the bioavailability of poorly soluble medicinal substances, for preventing aggregation of particles which inevitably accompanies conventional fracturing methods, and as well for obtaining better contact between the surface of the substance being dissolved and the solvent. This method involves the co-fusion of a medicinal substance and a physiologically inert but easily soluble carrier followed by crystallization of the melt obtained. This results in the formation of an eutectic mixture, or, what is better, a solid solution which are characterized by better solubility in water or physiological solution (2).

A variety of other methods for obtaining of easily soluble disperse systems have been proposed later, including the co-dissolution of the drug and carrier in one and the same solvent followed by crystallization (3,4). Despite both these methods proved to be useful and promising in pharmaceutical chemistry,

they have some disadvantages such as the possibility of decomposition of pharmaceutical preparations during fusion, difficulties in dissolution of carrier, etc (4). Therefore, the search for new methods of obtaining disperse systems is of great importance.

For this purpose we have studied the method of mechanical alloying. Mechanical alloying is usually regarded as a method of obtaining compositional materials with controlled microstructure. It is carried out by periodical fracturing and rewelding of two or more powders in high energy ball mills. This method has received wide use in preparation of amorphous metastable metallic alloys, anomalous solid solutions and intermetallides with unusual properties (5,6).

In "mechanical alloying" of a mixture of organic solids, one might expect new effects, in particular, a greater role of "contact melting" (7), differences in mechanical properties and anisotropy of crystal structures. Besides, taking into account the results of the known works on modification of the properties of medicinal preparations by mechanical activation (8-11), one might expect that mechanical treatment would lead to mechanical activation of components of the mixture along with mechanical alloying.

As the subject of investigation we chose the system sulfathiazole-polyvinylpyrrolidone which had been studied in detail in works (12,13) where a disperse system had been obtained by co-dissolution of the components in alcohol followed by crystallization.

Experimental

In experiments, we used sulfathiazole obtained from Chemical pharmaceutical plant, Irbitsk, Russia and low-molecular (M = 12500 $\pm$ 2300) "medicinal" polyvinylpyrrolidone (PVP) purchased from Chemical synthetic half-product factory,Bolkhovsk, Russia.

Taking into account the dependence obtained (12), mixtures containing a sulfathiazole-to-PVP ratio of 3:1, 1:1, 1:3 were prepared. The mechanical activation of the mixtures was carried out in an AGO planetary-centrifugal mill with water cooling of vials. The volume of vials was 40 ml, the ball diameter was 6 mm and the ball feed was 70 g. The vials were filled with balls to 50%. The ratio of ball mass to sample charge was 35:1. The ratio of radii and the rotation speed was selected so that the load per a ball was of the order of 60g (g-the acceleration of 9.8 ms^{-2}).

The thermal analysis of the mixture before and after treatment was performed on a "Paulik, Paulik, Erdey" derivatograph at a heating rate of 10° per minute and a charge of 300 mg.

IR-spectra were taken on a "Specord-75 IR" spectrometer with KBr tablets.

X-ray phase analysis was performed on a "DRON-3" device using Cu K_{α}-radiation.

To study the rate of dissolution a sample charge taken so it contains 1,5 g of sulfathiazole was placed into a glass vessel fitted with a mixer and containing 100 ml of water. The temperature was monitored at 30°C. During the course of dissolution, the solution was sampled after definite periods of time

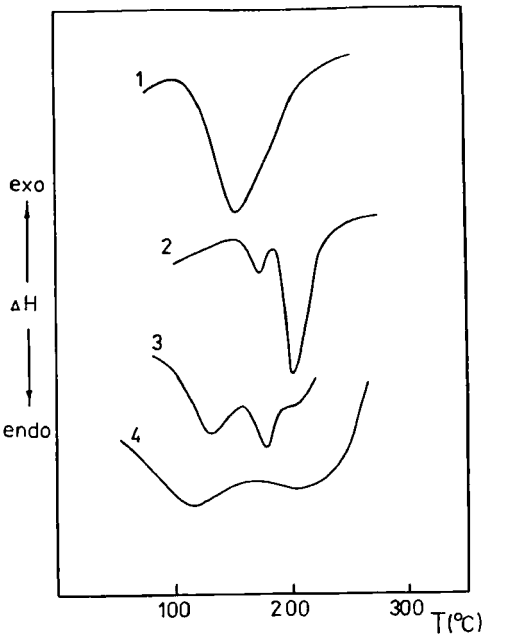

Fig.1. DTA curves of PVP (1); sulfsthiazole (2); physical mixture sulfathiazole - PVP (1:1) (3); sulfathiazole - PVP (1:1) mechanically activated for 12 min (4).

and filtered. The amount of sulfathiazole passing into the solution was determined from the intensity of a band at 283 nm on a "Shimadzu UV-240" spectrophotometer.

Results

The thermal analysis data (Fig.1) for the starting sulfathiazole, PVP and mechanically activated mixture of the components in a ratio of 1:1 show that under the action of powerful mechanical pulses

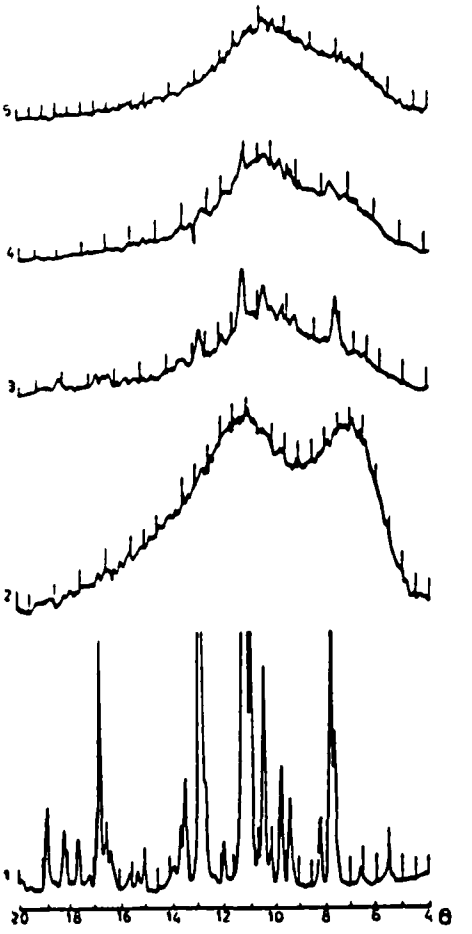

Fig.2. X-ray diffraction patterns of sulfathiazole (1); PVP (2); sulfathiazole - PVP (1:1) mechanically activated for 3 min (3), 6 min (4), 12 min (5).

on the mixture of components substantial changes take place. The derivatogram of the mixture after activation is not a superposition of the derivatograms of the starting components but indicates chemical changes occuring during the action of mechanical pulse.

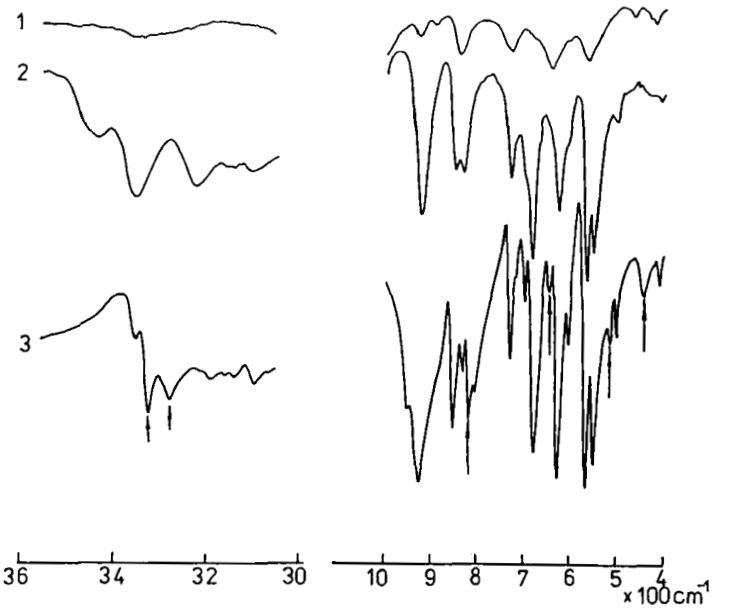

Fig. 3. IR-spectra of PVP (1); sulfathiazole - PVP (1:1) mechanically activated for 12 min (2); sulfathiazole (3).

After mechanical activation, substantial structural changes occur in the mixture, as shown by X-ray diffraction studies (Fig.2). In particular, during mechanical treatment, the continuous disappearance of peaks belonging to sulfathiazole takes place, which may be attributed either to amorphization as a result of mechanical activation or to chemical interaction with PVP.

The IR spectra of the sample after mechanical activation also show substantial chemical changes (Fig.3). Some bands corresponding to torsional oscillation (520 cm^{-1}), δ-deformational (820-807cm^{-1})

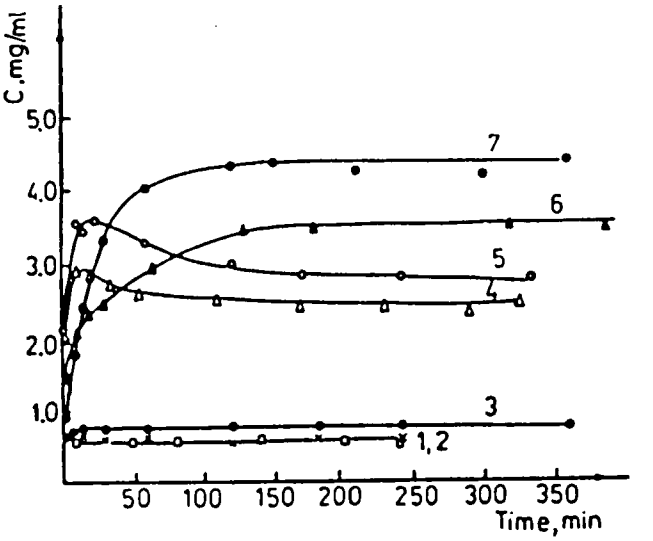

Fig.4. Dissolution curves of sulfathiazole intact (1); sulfathiazole mechanically activated for 12 min (2); sulfathiazole-PVP (1:1) physical mixture (3); sulfathiazole-PVP (1:1) mechanically activated for 4 min (4), 6 min (5), 8 min (6), 12 min (7).

and stretching vibrations (3320-3274 cm^{-1}) of the NH_2 and NH groups (14) of sulfathiazole disappear. At the same time, a new band at 3220 cm^{-1} appears, which corresponds to the interaction of the NH groups with the ketone ones (15).

Fig.4 gives the curves of the dissolution rate for the starting sulfathiazole being modification III, the sulfathiazole mechanically treated in an activator and a mixture of sulfathiazole with PVP subjected to mechanical activation for diferent pe-

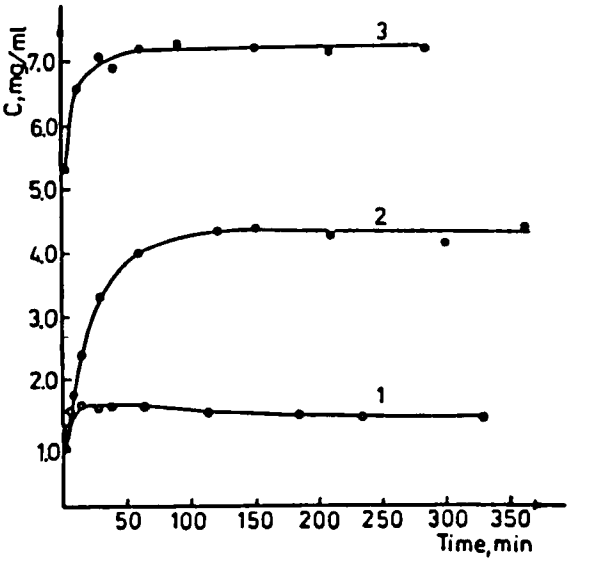

Fig.5. Dissolution curves of sulfathiazole-PVP mixtures mechanically activated for 12 min: sulfathiazole-PVP, 3:1 (1); sulfathiazole-PVP, 1:1 (2), sulfathiazole-PVP, 1:3 (3).

riods of time. It is seen that neither preliminary mechanical treatment of starting sulfathiazole lea - ding to the partial conversion of modification III into I (16) nor the physical mixture of sulfathiazole with PVP produce a substantial increase in the solubility of sulfathiazole.

On the contrary, the mechanical treatment of the mixture of sulfathiazole with PVP causes a considerable, almost 10-fold, increase in the solubility of sulfathiazole. It is interesting that the curves corresponding to the activation for 4 and 6 min leading to the formation of a mixture of amorphous and

crystalline phases differs in shape from those corresponding to longer activation times of 8 and 12 min, when a completely amorphous phase forms. First, the initial rate at small activation times is considerably higher than at large ones. Second, the form of the curves at 4 - 6 min is typical of metastable systems (17). In this case, the formation of an oversaturated solution initially occurs due to the dissolution of a metastable phase and then the system continuously comes to an equilibrium state. At longer activation times (8 - 12 min) the initial maximum disappears and the dissolution curve for the activated sample is a typical one.

Fig.5 shows the effect of the ratio between sulfathiazole and PVP in the activated mixture on the dissolution rate. It is clear that as the fraction of PVP increases the efficiency of mechanochemical action increases.

Discussion and conclusions

It is seen from the foregoing experimental data that the mechanical activation analogous to that which is employed in the mechanical alloying method may be used in preparation of high-disperse soluble medicinal remedics. A characteristic feature of the system sulfathiazole-PVP is that along with fracturing and activation of sulfathiazole, the chemical interaction with PVP also takes place. Thus, there is not one but several ways of increasing the dissolution rate during mechanical activation. This appears to be responsible for the features of the kinetics of dissolution of the mechanically activated

mixture. At the initial instance, mechanical activation appears to involve three basic ways: a) fracturing of sulfathiazole, b) its amorphization and conversion in metastable, more readily soluble form I (16), and c) chemical interaction of sulfathiazole with PVP. Since form I is little stable it appears to convert into starting form III under severe conditions of prolonged activation (16) and the main cause of mechanical activation in this case is apparently a solid state reaction between sulfathiazole and PVP leading to the formation of a soluble complex.

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