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On the mechanism of solubilization of drugs in the presence of poorly soluble additives

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Abstract

A model is proposed which describes the solubilization of a poorly soluble drug in the presence of an insoluble excipient which forms an easily soluble compound with the drug. For sulfathiazole–calcium carbonate system as an example, it is demonstrated using sulfathiazole single crystals and powdered samples that the presence of insoluble additive causes an increase in dissolution rate and solubility of the drug.

Keywords: Drug solubilization; Insoluble excipient; Sulfathiazole; Calcium carbonate

1. Introduction

Solubilization of poorly soluble drugs is an important problem in pharmaceutical science and technology (Yalkowsky, 1981; Dubinskaya, 1999). One of the methods of the solubilization of a drug is to convert it from the molecular form into a salt form (Berge et al., 1977). Another common method of increasing the dissolution rate, and, in some cases, also the solubility of a drug, is to mix the drug with a well soluble excipient. This can be achieved either by co-crystallization of a drug–excipient mixture from a common solvent, or by co-melting components (Sekiguchi et al., 1964; Chiou and Riegelman, 1971), or by mechanical treatment of the mixture (Yamamoto et al., 1974; Shakhtshneider and Boldyrev, 1999). The dissolution of a drug is facilitated due to the formation of an unstable drug–excipient complex.

Recently, a method of solubilization of drugs was proposed, that combines the two approaches mentioned above. A 'mechanocomposite' of a drug with an additive is formed. In the composite, the drug is in its molecular form, but transforms easily into its salt form as the composite is brought into contact with the solvent (Dushkin et al., 1994). This approach is based on the phenomenon of the co-

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dissolution of two compounds (Higuchi et al., 1963; Corrigan, 1991; Healy and Corrigan, 1996; Shaw et al., 2002). The only difference is that there is a chemical interaction between the components in the process of their dissolution. Usually, an easily soluble compound is used as an additive (e.g., sodium carbonate or bicarbonate). It was interesting to use such an additive which itself is insoluble in water but interacts with the drug at the moment of dissolution forming an easily soluble compound, thus providing solubilization of the drug. Results of such an experiment are reported in the present paper. At first, a model of the system under investigation is discussed; then the results of the experimental test for the existence of the effect itself are presented.

In order to verify the model, we made experiments on the dissolution of sulfathiazole in the presence of calcium carbonate as an additive. According to Kanke and Sekiguchi (1973), the solubility of sulfathiazole in water at 25 °C is 0.47 mg/ml (at 35 °C it is 0.79 mg/ml). Calcium carbonate is practically insoluble in water (Reeder, 1983).

2. Materials and methods

2.1. Materials

Sulfathiazole was obtained from the Chemical Pharmaceutical Plant, Irbitsk, Russia. The substance was recrystallized from water–ammonia solution, in order to obtain modification III of sulfathiazole (Kanke and Sekiguchi, 1973) as a coarse crystalline powder. The fraction with definite particle size was obtained by sieving. Sulfathiazole III single crystals were grown from a mixture of solvents: acetonitrile–methanol (1:1). Single crystals were shaped as hexagonal plates with the best developed face (1 0 2).

Calcium carbonate fractions with definite particle size were prepared by grinding calcite crystallites and sieving.

2.2. Dissolution studies

2.2.1. Preparation of the samples

Physical mixtures of the components with the variable particle size were prepared: (1) the size of drug and calcite particles within the range 80–320 μm; (2) the size of drug particles 80–110 μm, and the size of calcite particles 320–800 μm; (3) the size of drug particles 320–800 μm, and the size of calcite particles 80–110 μm.

Mechanical activation was performed with the activators AGO-2 (Russia) and Spex-mill 8000 (USA). The parameters of activation in AGO-2: vial volume, 40 ml; the ratio of load mass to ball mass, 1:30; the diameter of steel balls, 6 mm; ball loading, 20 g; treatment time, 15 min. Activation parameters for Spex-mill 8000: the ratio of load mass to ball mass, 1:10; the diameter of steel balls, 6 mm; treatment time, 30 min.

2.2.2. Dissolution procedure

In order to investigate solubilization effect, the sulfathiazole single crystal, about 0.2 cm × 0.2 cm × 0.02 cm in size, was placed into a micro-reactor thermostated at 37 ± 0.5 °C containing 7 ml of water, together with macrocrystalline calcite powder, so that the distance between calcite and sulfathiazole crystal was not more than 0.1 cm. The process was observed and photographed after definite time intervals with NU-2E optical microscope (Karl-Zeiss Jena) and digital camera Power Shot G1 (Canon). The size of sulfathiazole crystals in [1 0 0], [0 1 0] and [1 0 2] directions was measured using the photographs, and thus the rate of dissolution of the crystal in these directions was determined.

To investigate the rate of dissolution and the extent of passing into solution, a weighed portion of the drug–calcite (2:1, by mole) mixture was placed into a vessel thermostated at 37 ± 0.5 °C, which contained 50 ml of water (pH 6) and was equipped with a mixer. The solution was sampled after definite time intervals; the concentration of the dissolved drug was measured with Shimadzu UV 240 spectrophotometer (Japan) using absorption at 283 cm^{-1}. Each experiment was repeated three times and the three curves were averaged.

3. Results and discussion

3.1. Model of the system

Let us imagine a system containing poorly soluble molecular crystals and a poorly soluble additive which is used for solubilization according to the scheme