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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

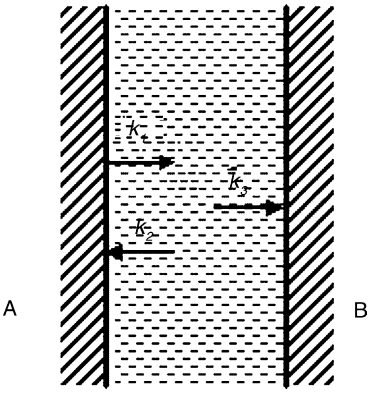

Fig. 1. A schematic diagram of the system considered in the model.

shown in Fig. 1. The plane in the left part depicts a part of the surface of molecular crystal, the plane to the right presents a part of the surface of the additive. The space between these planes is occupied by a solvent, which is water in the case under our consideration.

At the start of the process, the molecules of the drug pass into solution. A molecule that passes into solution can either return to the surface of the molecular crystal due to the reverse process (crystallization) or interact with calcium carbonate forming an easily soluble salt, water and CO_2. Having designated the concentration of the drug in solution as C_A and considering it as stationary, we can write down:

$$k_1 S_A = k_2 S_A C_A + k_3 S_B C_A,$$

where $k_1 S_A$ is the rate of passing into solution; $k_2 S_A C_A$ is the rate of reverse reaction (crystallization); $k_3 S_B C_A$ is the rate of interaction with calcium carbonate. The rate of transferring the drug into solution in the form of its salt can be expressed as $W = k_3 S_B C_A$. Expressing the concentration through

$$C_A = \frac{k_1 S_A}{k_2 S_A + k_3 S_B},$$

we obtain

$$W = \frac{k_1 S_A k_3 S_B}{k_2 S_A + k_3 S_B}.$$

So, if $k_2 S_A \gg k_3 S_B$, then, $W = K k_3 S_B$, where $K = k_1/k_2$, which means that the process rate will be determined by the reaction at the surface of B, as the limiting stage, and by the equilibrium between the direct and reverse reaction.

If, to the contrary, $k_2 S_A \ll k_3 S_B$, the rate will be unambiguously determined as $W = k_1 S_A$, i.e., by the dissolution of molecular crystal.

The above considerations are only the first approximation in describing the dissolution process: first, because we consider an extreme case of very large difference in the solubility of the components, which is true not in all the cases; second, this approach does not take into account the geometry of the system under consideration, i.e., relative positions of the surfaces of molecular crystal and additive; third, the molecular crystal is considered to pass into solution only in the form of molecules without taking into account their dissociation into ions.

A more detailed consideration evidently requires taking into account the diffusion processes that provide the transport of the molecules of substance A to the site of their reaction with the substance B. The diffusion flux of the dissolved molecules of A results in the concentration gradient between the surfaces of the particles of A and B. If at a definite moment of time maximally possible flux of A molecules turns out to be larger than the rate of dissolution of B, the substance A is in excess. In this case, the above-considered scheme is true, i.e., the rate of dissolution of A will be determined by the rate of reaction at the surface of B and will be independent on the concentration of dissolved particles. However, since the considered reaction between A and B proceeds through the dissociation stage, then, in fact, instead of the flux of molecules we are to consider the effective flux of ions (protons) which is proportional to the flux of molecules and to their dissociation degree. Gradual accumulation of salt of A in solution will lead to a decrease in the dissociation degree of A molecules. In order to maintain a constant reaction rate, the flux of protons should be maintained at a constant level. Hence, this will lead to gradual increase in the gradient of neutral A molecules. At a definite moment, the gradient of concentration of neutral molecules A will reach its maximum when the concentration of A in the vicinity of the particles composed of A becomes close to the solubility limit, while that in the vicinity of B particles is close to zero. Further accumulation of the salt and the consequent decrease in dissociation degree of A molecules lead to an inevitable drop in the gradient of protons and therefore, to a sharp decrease in their flux to the reaction surface. Since this moment, the rate of dissolution

of the substances will no more be determined by the dissolution of B and will be controlled by diffusion:

$$W = D_H S_B \frac{C_H}{d},$$

where D_H is the effective coefficient of proton diffusion; C_H is proton concentration in the vicinity of A particles; d is the distance between particles. Taking into account the fact that A particles should dissolve at the same rate

$$W = k_1 S_A - k_2 S_A C_A,$$

and the fact that the concentration of molecules is connected with the concentrations of ions by the equation describing the dissociation equilibrium

$$C_H C_I = K_A C_A,$$

(C_I is the concentration of acid anions; K_A is the equilibrium constant) we obtain the final equation for the dissolution rate

$$W = \frac{D_H k_1 S_A S_B}{D_H S_B + (k_2/K_A) S_A C_I d},$$

which predicts a sharp decrease in dissolution rate when high concentrations of the dissolved species are accumulated.

So, it follows from the proposed model that: (1) the presence of poorly soluble additive which however forms an easily soluble compound with the drug can cause the solubilization of this drug; (2) starting from a definite moment of time, the dissolution rate should decrease before the limit of solubility of the salt is achieved.

This model is in many respects similar with the model of dissolution of binary mixtures proposed in Wright and Carstensen (1986). The difference between the models is that our model relates to the systems, in which the second component of the mixture is poorly soluble, and the problem to solve is to intensify not the effervescency of drugs, but their solubility.

3.2. Dissolution of sulfathiazole single crystals in the presence of calcium carbonate

At the beginning, we have carried out a series of experiments aimed to demonstrate that the presence of calcium carbonate as an additive can really result in the solubilization of sulfathiazole due to the interaction of the sulfathiazole solution with calcium carbonate. For this purpose, we placed a single crystal of sulfathiazole into a micro-cell with water. Fine crystalline calcite powder was placed around the crystal at a distance of about 1 mm. After definite time intervals, we measured the dimensions of sulfathiazole crystal using its photographic images; thus we observed the propagation of the dissolution front from the surface into the depth of the crystal.

Changes in the crystal size with time were measured in three directions: along the largest face in the directions [1 0 0], [0 1 0], and normal to the plane in the direction [1 0 2]. It turned out that the crystal linear sizes in these directions decreased during dissolution at the same rate equal to $(3.5 \pm 0.4) \times 10^{-7}$ cm/s.

The changes in the crystal size versus time are plotted in Fig. 2. One can see, that in the case when calcium carbonate has been used as an additive, the

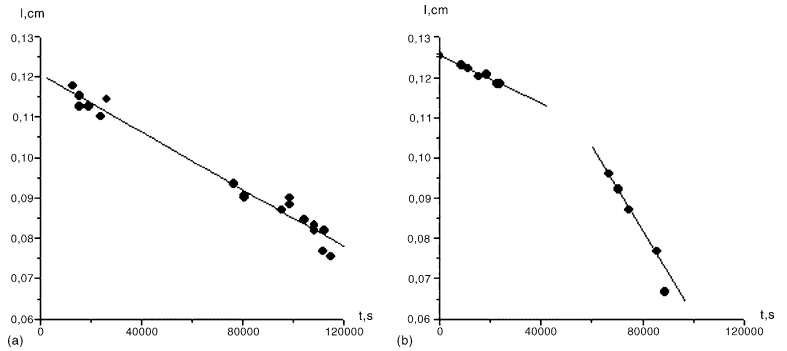

Fig. 2. The dissolution profiles (along [0 1 0] direction) of a sulfathiazole crystal alone (a) and with calcite additive (b).

dissolution process can be divided into two regions. The first one is likely to correspond to the establishment of a steady state in the model described above. The amount of solvent is large enough, so that the dissolution of sulfathiazole does not depend on the presence of calcium carbonate crystals. The rate of the process at this region almost coincides with that for the dissolution of a crystal without an additive. Starting from some moment of time, which is about 20 h in the case under our consideration, the process rate increases up to $(7.0 \pm 0.6) \times 10^{-7}$ cm/s. Such a jog is not observed when sulfathiazole crystal is dissolved without the additive. We believe that time corresponding to the jog of the curve relates to the moment when the steady state is established, after which the process rate starts to be affected by calcite additive, which forms a soluble salt with sulfathiazole thus shifting to the right the equilibrium of sulfathiazole passing into solution.

Acceleration of dissolution in experiments with single crystals can be considered as a confirmation of the above-formulated hypothesis concerning the mechanism of acceleration of the dissolution process with calcium carbonate additive. An evidence of the interaction between calcite and sulfathiazole in solution is ulceration of calcite surface in the sulfathiazole solution which is a result of reaction (Fig. 3).

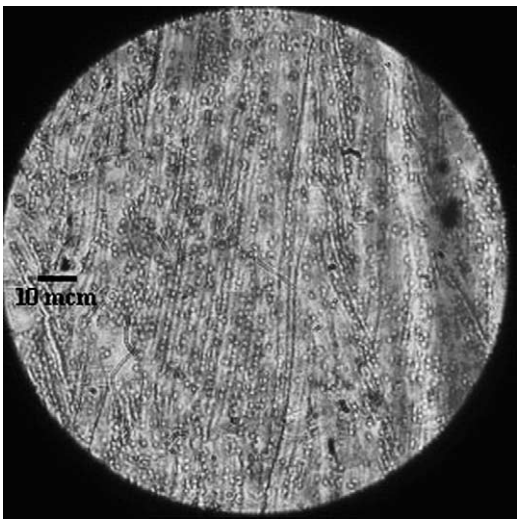

Fig. 3. The surface of a calcite crystal after it was kept in the solution with a sulfathiazole crystal placed in the same solution at 1 mm from the calcite crystal.

3.3. Dissolution of sulfathiazole–calcium carbonate powder mixtures

The results of experiments on dissolution of sulfathiazole–calcium carbonate powder mixtures are shown in Fig. 4.

One can see that the addition of finely ground calcite to sulfathiazole leads to substantial increase of both the dissolution rate and the amount of the drug passing into the solution. This effect is observed even after simple physical mixing of the components. For the mixture in which sulfathiazole particles are larger than calcium carbonate particles, solubilization is expressed to a higher extent than both in mixture with an inverse particle size distribution, and in the case of the mixture containing the two components as fine fractions. Judging from a stronger dependence of reaction rate on the size of carbonate particles than on the size of the particles composed of molecular crystals, it is likely that the limiting stage is the interaction of the solution of a molecular crystal with the calcium carbonate crystals; the process takes part at the carbonate surface.

Mechanical treatment of a mixture of components in activators (planetary mill AGO-2 and Spex-8000 mill) leads to a further enhancement of solubilization ef-

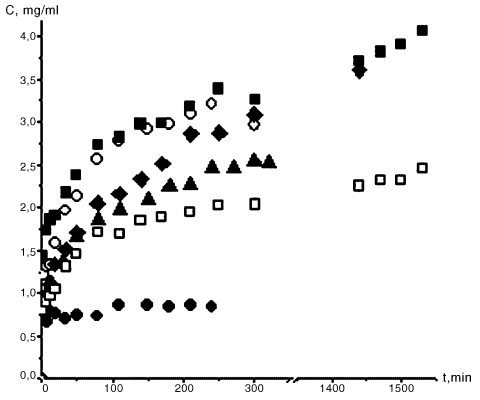

Fig. 4. The dissolution profiles of the sulfathiazole–calcium carbonate mixtures (2:1, by mole): (●) sulfathiazole alone; (□) a physical mixture of the components; the size of drug particles (80–110 μm) is smaller than the size of the calcite particles (320–800 μm); (▲) a physical mixture of the components; the size of drug particles (320–800 μm) is larger than that of the calcite particles (80–110 μm); (♦) a physical mixture of the components; the sizes of drug and calcite particles are within the range 80–320 μm; (◯) a mixture of the components mechanically activated in AGO-2 mill; (■) a mixture of the components mechanically activated in SPEX-mill 8000.

fect. The solubilization effect is almost similar for a high energy-strain AGO-2 device (in which the transition of the polymorph III into a metastable modification I is observed (Shakhtshneider and Boldyrev, 1993)) and for low energy-strain Spex mill (in which such a transition does not occur (Mikhailenko et al., 2004)). Taking this into account and keeping in mind the previously obtained results (Shakhtshneider and Boldyrev, 1994) providing an evidence that the III → I transition has no effect on the solubility of sulfathiazole, possibly due to the reverse transition occurring rapidly in solution (Lagas and Lerk, 1981), we think that the main reason of the enhancement of solubilization during mechanical treatment is the dispersion of the components and the improvement of contacts between them, that is, the formation of a mechanocomposite sulfathiazole–calcium carbonate.

One can conclude from Fig. 4 that after the transformation proceeds by 20–30%, the dissolution process slows down sharply in agreement with what follows from our model. The composition of solution at the moment of slowing down the dissolution is also in agreement with the proposed model. According to the data of chemical analysis, the solution contains about 3 mg/ml of the calcium salt of sulfathiazole, its solubility being 57 mg/ml, as we determined in independent experiments.

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