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Cryomodification of Solid Drug Substances

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Cryomodification of Solid Drug Substances

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The possibility to affect the size, structure, composition, and stability of solid-state particles for drug applications through the preparation of metastable solid-phases from the vapor phase at low temperatures is discussed in the context of drug delivery systems. Some of the important conditions for the cryogenic modification of the solid-state are determined. Examples involving two important drugs are presented, which led to the formation new polymorphs that could be used to create new drug formulations.

Keywords: drug delivery systems; metastability; solid state

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INTRODUCTION

It is well known that the chemical and biological activities of solid substances depend not only on their chemical formula, but also on the physicochemical properties derived from their solid-state structure. Since most drugs are solids, drug design must consider solid-state properties such as supramolecular structure, the degree and type of dispersivity, and drug and excipient combination efficiency. Modification of these properties may influence the solubility and the chemical stability of the drug. The most common approaches to solid-state drug modification are based on milling, melting the drug with excipients, formation of liposomes, absorption of the drug on a polymer or another support material, rapidly changing the solvent, rapid solvent evaporation, and fast freezing followed by evaporation of the solvent under vacuum (freeze-drying). These methods modify the solid state properties of substances at the macroscopic and

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microscopic levels by using conditions that are not far from thermodynamic equilibrium.

Solid-state metastability is one of the best initial points for the preparation of modified structures. An important aspect of metastability is that there may be several starting metastable states for any given system and there may be also many different final states. In principle, each metastable state may have its own final state. The preparation of metastable sample by cryogenic methods is convenient. There are several experimental variables that can be manipulated. For example, the speed of cooling of the initial system could be an important way of affecting polymorphic structure and the faster the cooling the more metastable states may be possible to trap. In this paper we discuss an approach towards the preparation of metastable solids for drug applications based on deposition from the vapor phase at low temperatures.

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RESULTS AND DISCUSSION

In our earlier work, a kinetic model was developed to account for the formation of metastable solid structures by vapor deposition on cooled surfaces [1]. The following assumptions were used:

- The temperature of the sample during vapor deposition is equal to the temperature of the cold surface.
- Molecules deposited on the surface have some mobility for a certain time after they are uncovered by removal of the adjacent layer of molecules.
- The formation of external layer carries out through formation and growth of the two-dimensional nucleating centers.
- The rate of formation of nucleating centers is described by atomic theory of nucleus formation.
- The time of mobility is inversely proportional to the rate of vapor deposition.

Several investigations [2,3] support this model and have allowed us to conclude that the preparation of samples by vapor deposition opens many possibilities for influencing the solid state structure of the initial metastable state, as well as the structure of the final state. When urea and thiourea are used, clathrates can be obtained which are impossible to prepare by other methods. The urea crystals were prepared with cyclic molecules and the thiourea ones with linear molecules. Sometimes the diameter of these molecules was greater than the typical diameter of the thiourea channels. Access to these exceptional

clathrates was attained through variations in the speed of vapor deposition and other experimental parameters. In some cases, two different guest molecules were included in the clathrate structures where the type of molecular packing and the nature of the channels can be influenced. When the experimental parameters are changed using tetraphenylcyclopentadiene and maleic anhydride, either a metastable solid solution or mixture of crystals can be obtained [4,5].

In this article we describe an approach where we apply the cryogenic method to a drug substance with the hope of exploring novel delivery systems. Several different drugs, including gabapentine, moxonidine, glibenclamide, carvedilol, and fluticasone propionate were modified in this manner to get answer on several questions: (a) Is it possible to prepare drugs in micronized form? (b) Is it possible to obtain metastable solids? (c) Is it possible to affect the degree of micronization and the structure of samples consisting of only one substance?

Our investigation revealed that all the drugs analyzed so far can be made in a glassy state, which can be crystallized upon heating [6]. Optical microscopy showed that all drugs are microcrystalline after heating to room temperature, with particle variations of 0.5 to 4 μm, depending on the experimental conditions. Gabapentine and fluticasone propionate were investigated more thoroughly.

The cryomodification of gabapentine was realized by vapor deposition on a cold surface at temperatures varying from 77–273 K. The samples were then heated to room temperature. When deposition was performed at surface temperatures of 77–180 K, the samples were obtained in a glassy state. Formation of microcrystals occurred by heating to 200–210 K. When the initial surface temperature was 77 K the final crystal sizes were 0.5–1.0 μm. When the temperature of vapor deposition was increased to 180 K, the size of the crystals increased to 3.5–4.0 μm. In the range of 240–273 K, gabapentine was obtained in a microcrystalline form with particle sizes of 2.5–3.0 μm. Figure 1 shows the results of micronization at a surface temperature of 140 K. The micronization of fluticasone propionate proceeded like that for gabapentine, as shown in Figure 2.

Apart from micronization, the cryomodification of gabapentine and fluticasone propionate were accompanied by structural modifications. Figures 3 and 4 illustrate the IR–spectra and X ray diffraction data, respectively, obtained before and after the cryomodification treatment of gabapentine.

From the IR spectra of gabapentine, it is clear that the initial spectrum at 77 K **(1)**, which corresponds to the glassy state, converts at room temperature to spectrum **(2)**. Spectrum **(2)** is different from the spectrum of the starting crystalline gabapentine **(3)** and corresponds

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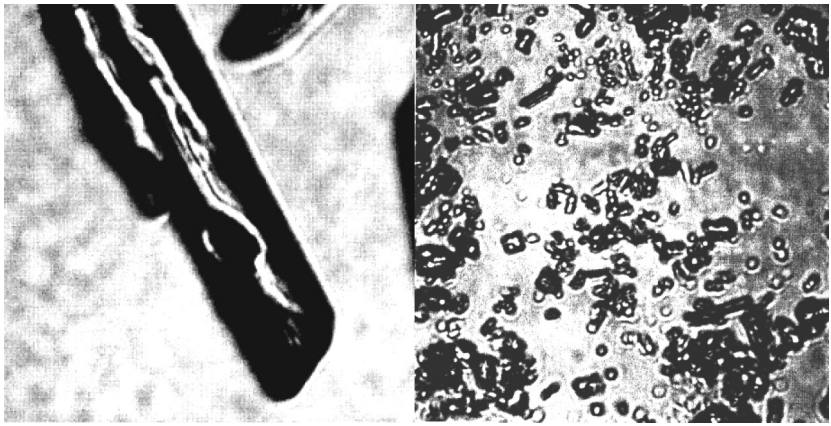

FIGURE 1 (Left) Starting gabapentine crystals; (Right) Micronized gabapentine at a surface temperature of 140 K (the horizontal size of the picture is 70 μm).

to that of a polymorphic modification described in the literature. When the vapor of gabapentine was deposited onto the surface at 273 K, the resultant IR spectrum **(4)** is different from all the previous ones. The main difference is the appearance of a new peak at 850 cm^{-1} and the disappearance of the peak at 1350 cm^{-1}. The new spectrum **(4)** is assigned to a previously unknown polymorph of gabapentine and was verified by X-ray diffraction data, which shows shifted peaks with much lower scattering intensities. The lower intensity of the scattering signals indicates a lowering of crystalline order for the modified

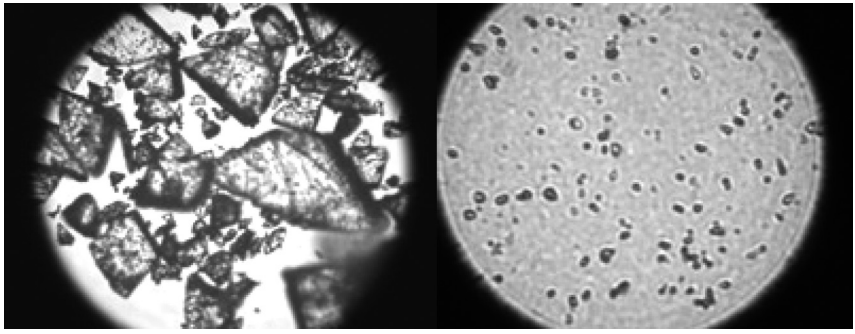

FIGURE 2 (Left) Starting fluticasone propionate crystals; (b) Micronized fluticasone propionate deposited on a cold surface at 100 K (The views are 150 μm on the left frame and 70 μm on the left).

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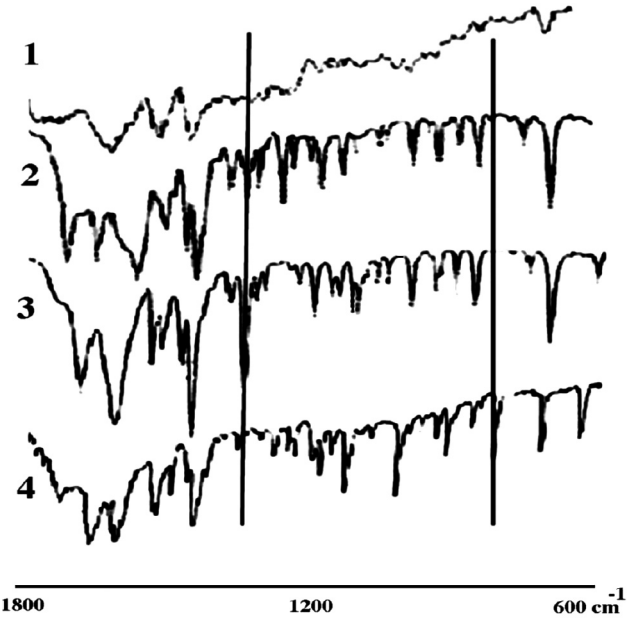

FIGURE 3 IR Spectra of gabapentine in: 1. Glassy state at 77 K; 2. Heated to 293 K; 3. Starting sample; 4. Temperature of vapor deposition of 273 K.

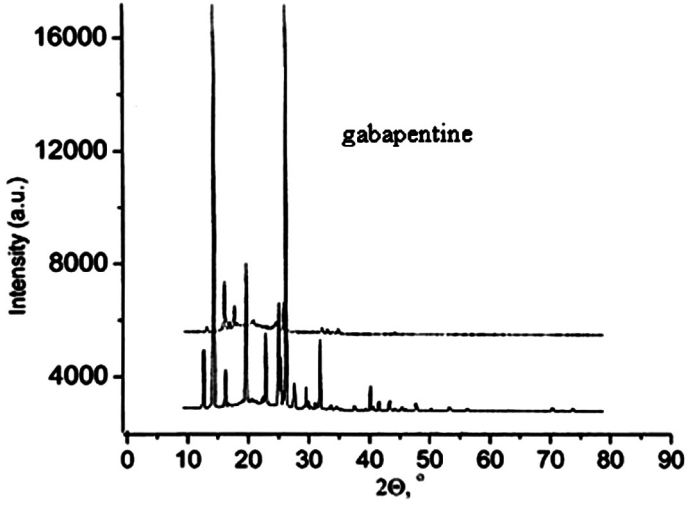

FIGURE 4 X-ray diffraction data for gabapentine micronization.

gabapentine structure. This result may be not only of scientific interest, but also for the development of other drug delivery systems, such as inhalation, where a high speed of dissolution is important.

The cryomodification of fluticasone propionate, like that of gabapentine, showed a strong dependence on experimental conditions as determined by the nature of the final structure. The variability of the IR spectra in the case of fluticasone propionate under different experimental conditions is illustrated in Figure 5. The IR spectra suggest that the glassy sample prepared at surface temperatures of 77 K converts upon heating to the structure of the starting fluticasone propionate crystals, as indicated by the arrow leading to the frame in the bottom right portion of Figure 5. The X-ray diffraction data shown in Figure 6 provides additional evidence. While the scattering signals of the modified samples have some peaks absent, the positions and intensities of the main peaks are unchanged as compared to those of the stable form of fluticasone propionate. An interpretation of this

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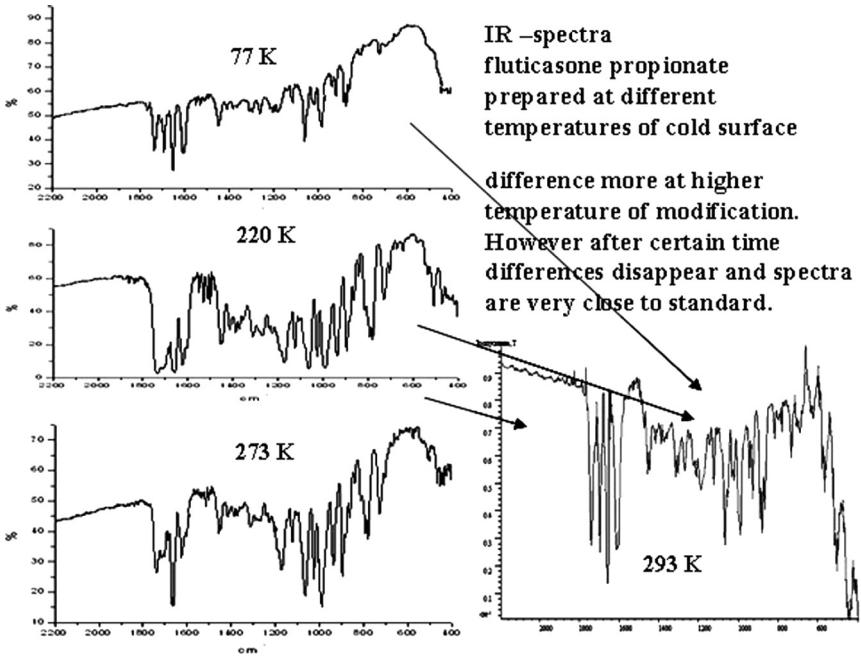

FIGURE 5 IR spectra of fluticasone propionate deposited at temperatures of cold surface 77 K, 220 K, 273 K and heated to 293 K. Spectrum at 293 K are obtained right away for first sample (77 K) and 7 days later for other samples (220 K, 273 K).

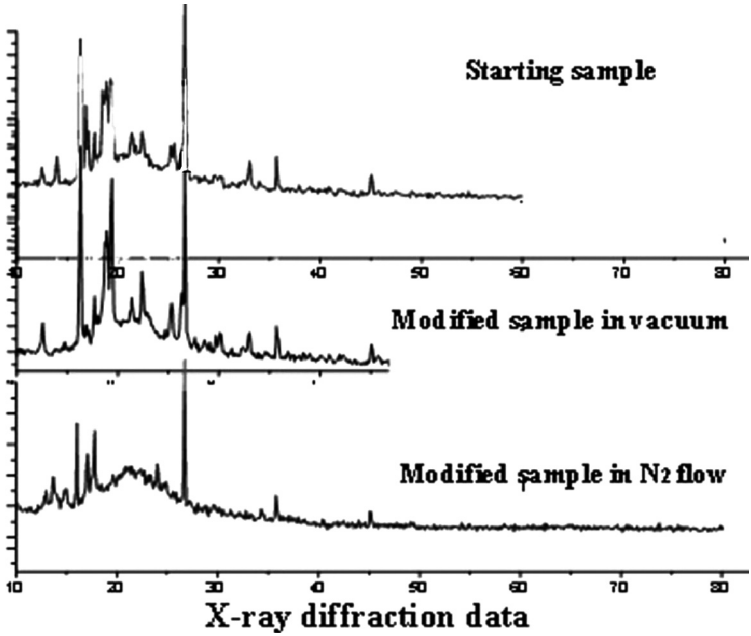

FIGURE 6 X-ray diffraction data for fluticasone propionate.

result is that modified fluticasone propionate has the same solid state structure, but that the orientation of its molecules is disordered in the crystal lattice.

When the temperature of the vapor deposition was higher (220 K and 273 K), the IR spectrum of fluticasone propionate right after deposition was different from that of the starting sample (Fig. 5). However, after several days, the spectrum changed and became closer to that of the starting sample, suggesting that a previously unknown metastable polymorph of fluticasone propionate may have formed. As illustrates in Figure 7, changes in the range 1600–1750 cm^{-1} can be recorded over a period of 5–7 days with samples deposited at 273 K and heated to 293 K.

Deposition experiments using nitrogen gas, rather then deposition from the vacuum, suggested that the metastable form of fluticasone propionate can be trapped in a metastable state. The bottom spectrum of Figure 7 **(4)** shows the IR of fluticasone propionate prepared by deposition with a stream of heated nitrogen gas at 77 K, and taken three month later. That this sample is kinetically trapped was also suggested by the X-ray data shown in Figure 6.

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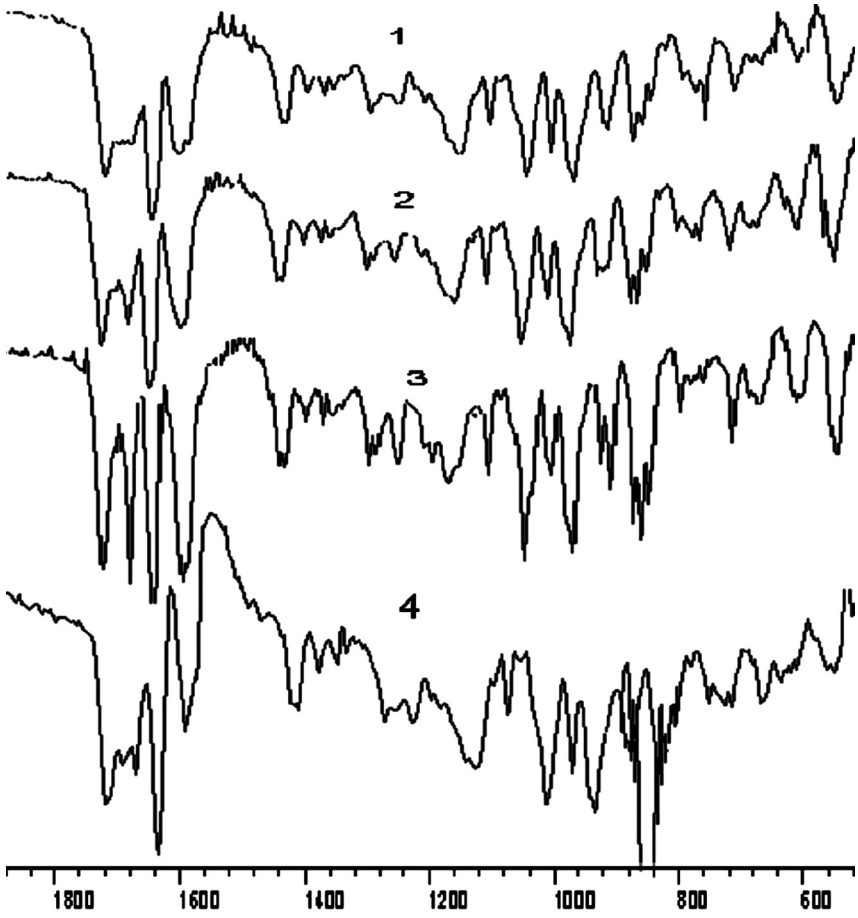

FIGURE 7 IR spectra of fluticasone propionate deposited on cold surface at 273 K and heated to 293 K (1–3): 1. Two days later, 2. Four days later, 3. Seven days later; and 4. Evaporated by a hot nitrogen flow, deposited on the surface at 77 K, and after 90 days at 293 K.

CONCLUSION

The present results suggest that the cryomodification of solid samples offers new possibilities to change the properties of drugs. This work can be continued in many directions towards new drug delivery systems as cryomodification drastically extends the range of influence on the solid state properties of organic solids.

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