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ORIGINAL ARTICLE

Differentiating amorphous mixtures of cefuroxime axetil and copovidone by X-ray diffraction and differential scanning calorimetry

Utilisation de la diffraction des rayons X et de l'analyse calorimétrique différentielle à balayage dans la différenciation des mélanges amorphes formés entre le céfuroxime axétil et la copovidone

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Summary The amorphous, molecular solid dispersion of cefuroxime axetil and copovidone with the mass ratio 71/29 is compared to its pure components in the amorphous state and to an amorphous mechanical mixture with the same mass ratio. Calorimetric studies demonstrate that all these materials are vitreous. By using X-ray diffraction profiles, a clear difference can be observed between the local order of the solid dispersion and that of the mechanical mixture. More generally, it is shown how the presence or absence of additivity in the diffraction data can be used to distinguish between different amorphous mixtures.

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MOTS CLÉS
Dispersion solide ;
État amorphe ;
État vitreux ;
Ordre local ;
Interaction principe actif—excipient

Résumé La dispersion solide amorphe moléculaire, formée par le céfuroxime axétil et la copovidone dans le rapport massique céfuroxime axétil/copovidone = 71/29, est comparée à ces deux constituants purs amorphes et à leur mélange mécanique dans le même rapport. Les examens calorimétriques montrent que tous ces matériaux sont vitreux. Les profils de diffraction des rayons X montrent que la dispersion solide est différente du mélange mécanique. Plus généralement, on montre comment la notion d'écart à l'additivité peut être utilisée pour caractériser l'originalité des dispersions solides.

Introduction

Molecular glasses are generally prepared by quenching the melt of molecular compounds. However, in certain cases molecules decompose in the molten state. By spray drying, decomposition is circumvented through dissolution in a suitable solvent at room temperature. The resulting solution is sprayed at a moderately increased temperature far below the melting point of the dissolved compound. The solvent evaporates quickly and an amorphous material results in the form of solid glassy spheres with diameters depending on the size of the droplets (typically ranging from a few micrometers to a few hundred micrometers) [1—5].

Glassy solids are thermodynamically out of equilibrium and are therefore not stable. They tend to crystallize over time; e.g. antique inorganic glasses turn opalescent or even opaque because they are slowly recrystallizing over more than 2000 years. As far as molecular solids are concerned, some of them recrystallize within a few days at room temperature or even more quickly, while others remain glassy for years. To prevent glasses from spontaneous crystallization in pharmaceutical applications, drug formulators add polymers in the solution for spray drying, resulting in a solid dispersion. Such a glass, a two-component single-phase material, is generally stable enough for marketing. The polymers, which often remain amorphous because the long chains diminish their ability to crystallize, function as molecular barriers limiting molecular displacements and as a result suppress crystallization of the active pharmaceutical ingredient. Moreover, dispersing a drug molecularly in a homogeneous glassy matrix often improves its bioavailability.

An interesting example of such a solid dispersion was reported in 1981 by Sato et al. [6]. It concerned an antibiotic (9,3″-diacetylmidecamycin) [7] in the crystalline state, whose solubility in biological media was too low; therefore it was not suitable for marketing, despite its promising in vitro antibiotic activity. To increase the bioavailability, the authors increased the dissolution rate and reached a greater solubility by preparing amorphous particles of the antibiotic by spray drying. Unfortunately, while in contact with aqueous solutions, these particles recrystallized within a few hours rendering them unsuitable for the market. The authors decided to add 0.2% hydroxypropylmethylcellulose in the solution for spray drying. The resulting material consisted of two-component microspheres that did not recrystallize in contact with water. Later on, it was demonstrated that the microspheres are glassy, because they exhibit a glass transition between 99 and 106 °C [8]. The bioavailability and the solubility of the drug in the microspheres had even increased, thus leading to a high in vivo activity. As a result, 9,3″diacetylmidecamycin was (and is still) marketed as tablets containing a glassy solid dispersion of the active pharmaceutical ingredient.

In this paper, calorimetric and X-ray diffraction studies are presented for another non-crystalline glassy antibiotic, cefuroxime axetil, mixed with the polymer copovidone. A comparison is made between a mixture consisting of a solid dispersion made of a single vitreous state and a mixture consisting of a physical dispersion (obtained by grinding) of a vitreous active pharmaceutical ingredient (API) in a vitreous polymer. The comparison is based on the additivity of diffraction profiles in the absence of interactions. This approach can be useful for the development of amorphous or vitreous drugs to increase bioavailability.

When comparing amorphous states of the same material, it becomes clear that they are not all the same. The most obvious cause may be the particle size of the amorphous material, as it is known that particle size lowering through mechanical dispersion increases the surface area in contact with the dissolution medium increasing the dissolution rate and improving the bioavailability [9]. However, the molecular organization in the amorphous material can be different too, the so-called short-range or local order.

A diffuse diffraction profile is related to the local order, because of the property of electrons to act as scattering centers, i.e. electrons behave as secondary X-ray emitters. Therefore, the scattering or diffraction profile depends on the relative positions of the atoms in the (amorphous) solid or liquid. Thus, differences in local order in a material will have an effect on the diffraction profile, which in turn makes it possible to compare local order by comparing the diffraction profiles of different amorphous materials. In principle, the pair distribution function $G(r)$ can be obtained by mathematical transformation, i.e. the Fourier transform, of a diffuse diffraction profile making use of the structure factor (or interference function) $S(Q)$, in which $Q = (4\pi/\lambda) \sin \theta$ (λ is the wavelength of monochromatic radiation, and θ is the Bragg angle as a function of which powder diffraction profiles are recorded). However, the same information is necessarily present in the diffuse diffraction profiles. Their use to obtain information about amorphous materials is not very frequent in pharmaceutical preformulation.