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Perspectives on the amorphisation/milling relationship in pharmaceutical materials☆

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ABSTRACT

This paper presents an overview of recent advances in understanding the role of the amorphous state in the physical and chemical transformations of pharmaceutical materials induced by mechanical milling. The following points are addressed: (1) Is milling really able to amorphise crystals?, (2) Conditions for obtaining an amorphisation, (3) Milling of hydrates, (4) Producing amorphous state without changing the chemical nature, (5) Milling induced crystal to crystal transformations: mediation by an amorphous state, (6) Nature of the amorphous state obtained by milling, (7) Milling of amorphous compounds: accelerated aging or rejuvenation, (8) Specific recrystallisation behaviour, and (9) Toward a rationalisation and conceptual framework.

Contents

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1. Introduction

Mechanical activation of solids has a wide range of potential applications. It is used to modify the properties of materials, enhance their reactivity or produce new advanced materials [1–3]. Developed initially in the field of metallurgic and mineral science fields [4], mechanical activation of drugs started developing more recently [5–7]. Mechanochemistry has become an important subject of interest in pharmaceutical sciences for its role in the development of green synthesis [8,9], supramolecular structures [10] and cocrystal synthesis [11–13], as well as amorphous solid dispersions [14]. When a solid molecular compound is subjected to high energy milling, its structural and microstructural characters change considerably. The same holds true for molecular mobility and, consequently, for both the physical [15] and chemical stability. All these changes may have a considerable impact on biopharmaceutical properties e.g. enhanced solubility, hygroscopicity and dissolution capabilities [15–19]. Milling is commonly used during the processing of drugs. Accidental formation of disordered solids can dramatically undermine the expected stability and performance of the product. On the contrary the intentional use of mechanical activation to produce solids with increased dissolution capabilities can be of great interest in pharmaceutical formulation of active ingredients which are poorly soluble in the crystalline state [20].

It is thus of high importance to gain understanding in the possible modifications induced by high activation energy of molecular solids. Molecular compounds used for pharmaceutical applications have specific physical properties. There is a huge contrast between the strong intramolecular bounding and relatively weak interactions between molecules. Also molecular and crystallographic symmetry are in general very low. The consequences are: a rich crystalline polymorphism, a low melting temperature (Tm), slow kinetics of recrystallisation from the undercooled melt, good glass forming abilities and low glass transition temperatures (Tg). Tg is generally not far from room temperature either above or below. The specificities of molecular compounds induce specificities of their response to mechanical activation [21]. In particular the role of the relative position of the milling temperature with respect to the Tg of the amorphised compound is important [22]. The easiness to produce amorphous compounds by quench cooling of the melt has an equivalent in the capability of molecular compounds to have their structure and microstructure easily disorganised under milling. The formation of amorphous states, transiently or as an end product, is often observed or suspected. Such a formation of an amorphous intermediate can play a dramatic role in the processes by which occur mechanically induced chemical reactions [13,23]. This paper will briefly summarise and discuss some recent findings in the mechanical activation of one component molecular systems with specific interest in the generation and potential role of amorphous states.

1.1. Is milling really able to amorphise crystals?

It has long been claimed in the literature that many pharmaceutical compounds can be amorphised upon extensive milling [24,25]. In order to talk properly about an amorphous solid state, reference should be made to the glassy state which is conventionally obtained by undercooling a liquid which has avoided crystallisation. Structurally, the amorphised product has no long range crystallographic periodicity (i.e. X-ray diffraction does not show any Bragg peaks) so that it is more or less equivalent to a frozen liquid. Dynamically, it must show a glass transition (Cp jump in calorimetry) at a temperature T_g which marks the release of the molecular motions. Since a glass has specific dynamical properties [26–28] (non Arrhenius, non exponential, non linear main relaxations, specific sub-Tg β relaxations, etc.), additional useful markers of real amorphisation can be provided by spectroscopies (Dielectric, Raman, dynamic mechanical, enthalpic, etc.). These techniques must often be used in combination to distinguish a real amorphous solid state from a highly defective crystalline state. In a number of cases the identification of the real amorphous state obtained by milling is straightforward as it is the case for budesonide (Fig. 1). However, it can be sometimes difficult to determine whether a solid sample is actually converted to a real amorphous state. Two representative and common examples of the difficulty to identify an amorphisation induced by milling are presented below.

1.1.1. Apparent lack of glass transition

Recently, the non observation of a glass transition in some milled materials has led some authors [29–31] to bring into question the reality of a solid state amorphisation upon milling. This is, for instance, the case of griseofulvin [29–31] which does not show any sign of glass transition after a one hour cryomilling process. Instead, a two step exothermic process is observed on either side of the expected Tg. Facing these unusual features, it has been proposed that the milling of griseofulvin leads to the formation of a highly defective nanocrystalline powder and not to the formation of a glassy amorphous state. However, X-ray experiments show a total absence of Bragg peaks and a diffuse scattering halo fully similar to that of the quenched liquid [32]. Furthermore, three deeper investigations have revealed that milled griseofulvin has in fact an effective glassy amorphous character which is hardly detectable because the Cp jump at Tg is masked by a sub Tg recrystallisation process (Fig. 2). First, dielectric relaxation experiments have revealed the existence of β-relaxations characteristic of conventional glasses in the milled materials (Fig. 3). These relaxations are characteristic of glassy amorphous materials and do not exist in the crystalline state. Second, DSC experiments using high heating rates (200 °C/min) were able to shift the exothermic recrystallisation event toward the high temperatures (Fig. 4). This shift was strong enough to detect a Cp jump in the expected glass transition domain. Third, a very short milling (a few seconds) of the glass itself (as obtained by melt-quenching) was found to make the recrystallisation pattern identical to that of the milled crystal. In particular, the recrystallisation becomes bimodal and is depressed in the glass transition domain making nearly impossible the observation of a Cp jump at Tg. That proves that a powder of the glass behaves exactly as the milled crystalline sample.

1.1.2. Too short life time of the amorphous state

If the life time of the amorphous state produced by milling is short and if the analysis is carried out too late, the amorphised material may recrystallise before to be analysed. In that case, it may thus be wrongly concluded that milling did not amorphise the material. The case of glucose is particularly illustrative. Fig. 5 shows the X-ray diffraction pattern of the crystalline form of glucose before and after a 14 h milling process. Milling was performed at two different temperatures: at room temperature (25 °C) which is not far below Tg ≈ 40 °C and at −15 °C by placing the mill in a cold room. No amorphisation can be detected after milling

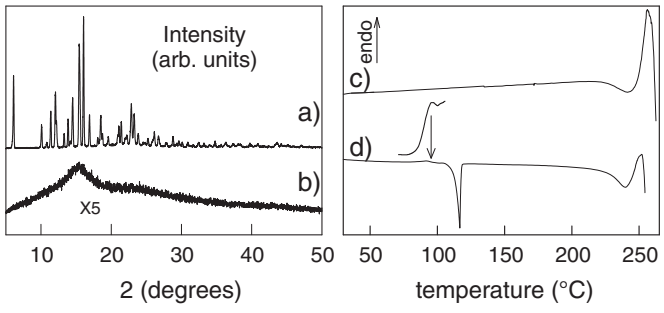

Fig. 1. X-ray diffraction patterns of budesonide recorded at room temperature before milling (a) and after a 15 h milling process. (b). DSC heating curves (5 °C/min) of crystalline budesonide before milling (c) and after a 15 h milling process (d). The inset shows a close up view of the glass transition domain appearing in the MDSC reversible heat flow (modulation of ±0.796 °C/min). (From Ref. [22]).