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Crystalline mesophases: Structure, mobility, and pharmaceutical properties☆

Evgenyi Shalaev [a], Ke Wu [a], Sheri Shamblin [b], Joseph F. Krzyzaniak [b], Marc Descamps [c]

[a] Allergan plc, 2525 Dupont Drive, Irvine, CA 92612, USA
[b] Pfizer, Inc., Groton, CT 06340, USA
[c] University of Lille, UMET (Unité Matériaux Et Transformations), 59655 Villeneuve d'Ascq CEDEX, France

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ABSTRACT

Crystalline mesophases, which are commonly classified according to their translational, orientational, and conformational order as liquid crystals, plastic crystals, and conformationally disordered crystals, represent a common state of condensed matter. As an intermediate state between crystalline and amorphous materials, crystalline mesophases resemble amorphous materials in relation to their molecular mobility, with the glass transition being their common property, and at the same time possessing a certain degree of translational periodicity (with the exception of nematic phase), with corresponding narrow peaks in X-ray diffraction patterns. For example, plastic crystals, which can be formed both by near-spherical molecules and molecules of lower symmetry, such as planar or chain molecules, can have both extremely sharp X-ray diffraction lines and exhibit glass transition. Fundamentals of structural arrangements in mesophases are compared with several types of disorder in crystalline materials, as well as with short-range ordering in amorphous solids. Main features of the molecular mobility in crystalline mesophases are found to be generally similar to amorphous materials, although some important differences do exist, depending on a particular type of mobility modes involved in relaxation processes. In several case studies reviewed, chemical stability appears to follow the extent of disorder, with the stability of crystalline mesophase found to be intermediate between amorphous (least stable) and crystalline (most stable) materials. Finally, detection of crystalline mesophases during manufacturing of two different types of dosage forms is discussed.

Contents

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1. Introduction

Crystalline mesophases [1] represent a common state of condensed matter, occupying space between amorphous materials with short-range order and long-range *dis*order, from one side, and crystalline materials possessing long-range order on the lengthscale of tens of nms, from the other side. In this review, we adopt a broad definition of crystalline mesophases, which includes liquid crystalline structures, conformationally disordered crystals, and plastic crystals.

Disordered solids, which in pharmaceutical applications are generally associated with amorphous materials, have attracted major attention of pharmaceutical scientists for two main reasons. First of all, amorphous state can provide significant practical benefits, such as greater apparent solubility for small molecules, or better stability for protein drugs achieved by mixing protein and lyoprotector molecules on molecular level, provided that lyoprotector remains in the amorphous state. On the other hand, amorphous materials, being thermodynamically less stable than corresponding crystalline state, can undergo physical and chemical transformations, thus limiting their shelf life. Rates of chemical reactivity in the amorphous vs. crystalline materials are documented for many systems, with amorphous materials (including their glassy state, i.e., below the Tg) demonstrating significantly higher degradation rates [8–10]. Correspondingly, major efforts have been devoted to investigation of properties and stability of amorphous state. Dynamics of amorphous materials, which is associated with both the glass transition (Tg) and various sub-Tg mobility modes, such as Johari–Goldstein relaxation, has been investigated in many details [11–13]. Furthermore, structural aspects of amorphous pharmaceutical materials have attracted increasing attention recently [14,15]. Structural and dynamic properties of crystalline mesophases, from the other hand, have not been discussed at the same level of details in pharmaceutical literature, possibly due to some practical challenges associated with their detection and recognition. In many cases, it is not straightforward to distinguish crystalline mesophases from either crystalline or amorphous state, especially if experimental characterization is limited to a single method. E.g., X-ray powder diffraction (XRPD), which is a main solid-state characterization tool, would not allow distinguishing between a regular crystal and plastic crystal, because plastic crystals would also have sharp and strong diffraction lines. Furthermore, observation of the glass transition by DSC would not necessary be a unique signature of an amorphous material, because it is an inherent property of crystal mesophases as well.

The general relevance of mesophases to pharmaceutical systems has been recognized relatively recently [2,3], although the importance of liquid crystalline materials has long been known for some specific cases, such as topical formulations [4] and some drug delivery systems, e.g., liposomes [5]. In two earlier comprehensive reviews on crystalline mesophases in pharmaceuticals, both published in 2005 [3,16], the importance of crystalline mesophases for pharmaceutical R&D has been convincingly presented. In particular, numerous examples of active pharmaceutical ingredients were provided, including both small molecular weight compounds and macromolecules, and covering a range of therapeutic classes. It was also proposed [2], based on the original idea from [17], that milling-induced amorphization of crystalline materials can go through transient crystalline mesophase structures. If this is indeed the case, crystalline mesophases can be even more ubiquitous considering that milling (grinding) is a common industrial process. Furthermore, potential connections between crystalline mesomorphism and polyamorphicity – with the latter one also getting attention in pharmaceutical science – have been suggested. For example, a famous case of a polyamorphic form of triphenyl phosphite (so called "glacial phase") could indeed represent a plastic crystal composed of nanocrystals rather than a true polyamorphous state [18].

Similar to amorphous materials, mesophases can be converted to low temperature (and thermodynamically stable) crystal phase, although such transition can be kinetically hindered under typical experimental conditions. Upon deep-enough undercooling (also known as supercooling), mesophases exhibit a "freezing" of molecular motions similar to the liquid-to-glass transition. Correspondingly, they can be in a state with either dynamic disorder (above the calorimetric glass transition temperature, Tg) or static-frozen disorder (below the Tg). For example, a continuous cooling of a metastable disordered crystalline phase of ethanol, which represents a monotropic situation with the ordered stable phase, results in a freezing of disorder at temperatures below the Tg [6]. An important fundamental feature of mesophases, which separates them from amorphous glasses, is that the glass transition can take place in a thermodynamically stable crystalline state as indeed observed experimentally in orientationally disordered $SnCl_2 \cdot 2H_2O$ and $TlNO_2$ crystals [7].

In this review, fundamental properties of crystalline mesophases are summarized, covering both structural and molecular mobility aspects. Particular attention is paid to establishing a comparison with the nature of disorder existing in both conventional crystals and amorphous compounds, whereas a specific case of mesophases, i.e., orientationally disordered crystals, is considered in more detail. The structural overview is followed by the discussion of dynamic properties of crystalline mesophases, in which molecular mobility in mesophase is compared with the mobility in an amorphous state of the same molecule. Furthermore, general principles which determine relative thermodynamic stability of crystalline mesophases are presented, with the help of relevant phase diagrams. Finally, examples of instability of crystalline mesophases vs. amorphous and crystalline states of the same material are discussed. Several of the examples considered represent real situations encountered during development of novel drug candidates, covering both stability and formation of crystalline mesophases and change in their properties during pharmaceutical processing. The examples show that the chemical stability of crystalline mesophases is indeed intermediate between amorphous (least thermodynamically stable) and crystalline (most thermodynamically stable) forms. This conclusion is consistent with an early report which compared chemical stability of a crystalline mesophase with the same molecule in the crystalline state [19]. On the physical stability subject, we note that crystalline mesophases can be expected to crystallize much more easily above their Tg — provided that the mesophase is thermodynamically metastable in respect to the crystalline phase at a particular condition (e.g., temperature, pressure, solvent). We conclude that, while there is a growing awareness of pharmaceutical scientists about importance of the mesophases in pharmaceutical R&D and manufacture, potential pharmaceutical advantages of crystalline mesophases, such as their better stability than that of amorphous materials and higher apparent solubility/faster dissolution than crystalline structures, are probably under-explored.

2. (Dis)order in condensed phases and structure of crystalline mesophases

Structure and order hierarchy of different states of condensed matter is presented schematically in Fig. 1. Mesophases refer to those phases intermediate to crystalline and amorphous materials in terms of structural (dis)orders [20]. A number of mesophases have been discovered with various degrees of translational, rotational, and conformational disorder, and they are commonly classified as belonging to one of the three categories, that is, liquid crystal, plastic crystal, and condis phase (conformational disordered crystals) ([1,20]). Condis crystals, which possess translational and rotational order, but also have partial or complete conformational disorder [21], are the closest structurally to common crystalline materials. In condis crystals, different conformers are distributed randomly throughout of crystalline lattice, as, e.g., in pseudo racemic crystals (sometimes named pseudoracemate). Condis crystals are typically formed by macromolecules such as synthetic polymers with two or more conformers of similar overall molecular shapes, although conformational disorder can also exist in small molecules. A