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Unintended and *in situ* amorphisation of pharmaceuticals☆

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ABSTRACT

Amorphisation of poorly water-soluble drugs is one approach that can be applied to improve their solubility and thus their bioavailability. Amorphisation is a process that usually requires deliberate external energy input. However, amorphisation can happen both unintentionally, as in process-induced amorphisation during manufacturing, or *in situ* during dissolution, vaporisation, or lipolysis. The systems in which unintended and *in situ* amorphisation has been observed normally contain a drug and a carrier. Common carriers include polymers and mesoporous silica particles. However, the precise mechanisms by which *in situ* amorphisation occurs are often not fully understood. *In situ* amorphisation can be exploited and performed before administration of the drug or possibly even within the gastrointestinal tract, as can be inferred from *in situ* amorphisation observed during *in vitro* lipolysis. The use of *in situ* amorphisation can thus confer the advantages of the amorphous form, such as higher apparent solubility and faster dissolution rate, without the disadvantage of its physical instability.

Contents

1. Introduction

Solid materials can exist in a crystalline state, where molecules are ordered in all three dimensions, or in an amorphous form with only short range order [1]. The transformation from the crystalline to the amorphous form, amorphisation, requires molecules to leave their place in the well-ordered crystal structure [2]. This can be achieved via mechanical activation such as milling or via phase transitions from the solid to a liquid or gaseous phase, i.e. either melting, dissolution, or vaporisation of the drug is necessary. The amorphous form has a higher apparent solubility and therefore potentially a higher bioavailability than the corresponding crystalline form. However, the amorphous form is thermodynamically unstable and will eventually recrystallise [3]. The kinetics of the recrystallisation process, i.e. how long does it take before recrystallisation has a pronounced effect on pharmaceutically relevant properties, determines whether amorphisation is a suitable formulation approach for a given poorly soluble drug or not. Amorphous products that have successfully been introduced into the market are mainly glass solutions consisting of a drug and a polymer [4]. However, drug solubility in polymers is normally low, and thus phase separation and recrystallisation may occur if the solubility limit is exceeded [5–7]. If the kinetics of these processes is slower than the shelf life of a pharmaceutical product, glass solutions were shown to be a good formulation approach. Nevertheless, the physical stability of these formulations has to be tested under various conditions in order to be sure that no stability issues will arise [8].

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Amorphous pharmaceutical solids."

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Unintended and *in situ* amorphisation can be understood as an amorphisation process that happens without any deliberate external energy input. If amorphisation can be induced just before the application of a formulation or even happens in the body after administration, it would allow the circumvention of stability issues of the amorphous form. Unintended and *in situ* amorphisation has been mainly reported in the fields of chemistry and physics and is also referred to as *in situ* amorphisation. It may occur as ion-induced, electron beam-induced, annealing-induced, or pressure-induced spontaneous amorphisation [9–12]. The materials that are amorphised in this way are often alloys and therefore they can endure harsh conditions under which small organic molecules such as drugs would degrade. In the pharmaceutical literature, unintended amorphisation has been mainly reported in case studies of manufacturing processes. It is regarded as a disruptive event in the supposedly well-planned and controlled manufacturing process and can negatively affect product performance. In other cases, *in situ* amorphisation was seen as a curious counterintuitive occurrence. In general, *in situ* amorphisation has not yet been investigated and explored to the extent to make it a useful formulation approach. Hence this review wants to provide an overview of unintended and *in situ* amorphisation in the pharmaceutical setting with the hope of advancing further studies in this field.

2. Unintended and *in situ* amorphisation

In many cases of unintended or unexpected amorphisation, there is a sudden change from an equilibrium state to a non-equilibrium state. For example, a drug sometimes precipitates out in an amorphous form, when a highly concentrated solution of a poorly water-soluble drug, which is dissolved in a water-miscible organic solvent, is added to water. It is important to note that such a change in the conditions induces a highly non-equilibrium (amorphous) state. During the sudden change in conditions, the amorphous form is the preferred form. However, when the conditions change again, e.g. after drying, this is of course no longer the case. In this review, we use the expressions "unintended" and "*in situ* amorphisation" if such a sudden change from an equilibrium state to a non-equilibrium state leads to the formation of an amorphous form, either unintended or intended. Unintended amorphisation can happen during manufacturing processes where it is an unintended event. However, recently, interest in intended *in situ* amorphisation has increased. Several paths can be used to create the amorphous form and similarly *in situ* amorphisation can also be achieved through different routes. Fig. 1 depicts the main approaches for intended *in situ* amorphisation

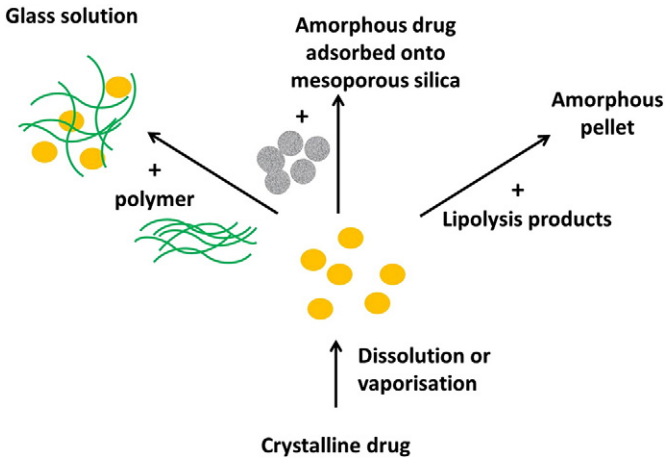

Fig. 1. Schematic of different approaches to achieve intended spontaneous amorphisation.

2.1. Process-induced, unintended amorphisation

Process-induced solid state changes can occur in the manufacturing processes of the pharmaceutical industry [13–15]. During manufacturing, the drug and excipients experience heat, mechanical stress, and moisture exposure. In all of the manufacturing steps, the solid state properties of the drug or the excipients can change: one polymorph may convert to another [16–18], hydrates may occur [19–21], amorphous material may crystallise [22–26], or crystalline material may amorphise. These changes in the solid state of a drug or excipient may have a substantial impact on the performance of a dosage form with regard to dissolution behaviour, degradation, and mechanical properties. Hence those changes have to be monitored and evaluated for their potential risk. A good example illustrating various process-dependent solid state changes is a study on theophylline tablets [27]. Theophylline can exist as stable anhydrate, metastable anhydrate, or as monohydrate. In order to prepare a tablet, the stable anhydrous form of the drug was mixed with microcrystalline cellulose and wet granulated with polyvinylpyrrolidone (PVP) solution. The granules were dried and compressed into tablets and stored at different humidities. During wet granulation on a laboratory scale, the stable anhydrous theophylline converted to the monohydrate form. In the subsequent drying step, the crystal water was lost, resulting in a mixture of both anhydrous forms. In order to avoid solid state transformations, the manufacturing process was further investigated. When the granulation step was performed in a fluid bed, the granules consisted only of the stable anhydrous form. However, after high shear granulation, a mixture of stable and metastable theophylline was produced. When a mixture of both anhydrous forms was stored over 33% relative humidity (RH), the metastable drug transformed to the stable anhydrate which was accompanied by decrease in dissolution rate.

Unintended amorphisation during manufacturing processes can lead to major changes in the performance of a product. The water adsorption and the molecular mobility are higher in disordered or amorphous regions than in the respective crystalline counterparts [28–30]. Therefore, chemical or physical instabilities, promoted by humidity, such as hydrate formation or hydrolysis, may be increased.

Asargan7016 is a commercial product containing acetylsalicylic acid and is manufactured via roller compaction. Asargan showed a higher water uptake between 10% and 80% RH in water vapour sorption analysis [31] than untreated crystalline acetylsalicylic acid [32]. Hancock and Zografi [33] suggested possible reasons for this behaviour, namely a very small particle size, an increase in microporosity, or partial amorphisation. The first two possibilities are not very likely to occur in the roller compaction process. However, amorphous material can adsorb more water than crystalline material [34]. This increased water adsorption into the amorphous regions leads to an increased interaction with water. The increased water adsorption, together with the higher molecular mobility of the amorphous from, resulted in faster hydrolytic degradation of acetylsalicylic acid into salicylic acid and acetic acid via ester cleavage. Hence process-induced solid state transformations changed the degradation profile of the drug.

Another example for increased degradation due to amorphisation is ABT-232. This drug can exist in a stable anhydrous form, a monohydrate, and the amorphous form which is highly hygroscopic [35]. The pure amorphous drug undergoes deliquescence and recrystallisation at ambient conditions within 10 min. ABT-232 in the stable anhydrous form was wet granulated with excipients, dried, and compressed into tablets. The monohydrate form converts rapidly to the anhydrate form at elevated temperatures. Therefore, after the drying step, the authors expected that the solid state form in the final compacts would be the anhydrate form. When these tablets were stored at high temperature and humidity, an unexpected loss of potency was found. The granules did not display the typical reflections of the drug when measured with X-ray powder diffraction (XRPD), indicating conversion of the drug to the amorphous form. During storage for 5 months at room temperature and ambient conditions, no recrystallisation occurred, even though the amorphous drug