REVIEW ARTICLE

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The Solid State Amorphization of Poorly Water Soluble Drugs

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This review addresses the issue of amorphization of poorly water soluble drugs in the solid state. Amorphous phase formation of the drugs is desirable for enhancement of dissolution rate, which can lead to a significant improvement of bioavailability. Grinding, a regularly used process in the pharmaceutical industry can bring about changes in molecular mobility and consequently induce amorphous phase formation. Sorbed water into the amorphous regions increases molecular mobility and subsequently affects physical and chemical stability. Adsorption and entrapment of drug molecules or amorphous molecular dispersion of drug into microporous carrier granules lead to an enhancement of physicochemical stability of the drug. Enthalpy relaxation experiments could be used to indicate relative molecular mobility and relative likelihood of reversion from amorphous to lower energy crystalline state.

An amorphous phase describes a condensed solid state without three-dimensional long-range molecular order in comparison to that observed in a crystal. Drugs generally have a higher enthalpy in the amorphous compared with crystalline state. Such amorphous materials are thermodynamically unstable and may recrystallize if molecular mobility within the region is high. Thus the rate of solid state degradation is increased when the crystalline form of the drug is rendered partially or fully amorphous[1-3].

The main expertise of formulation development is to improve the solubility and dissolution rate of poorly water soluble drugs. Amorphization of poorly water soluble drugs is thus desirable, which increases dissolution rate and can lead to a significant improvement of their bioavailability[4,5]. In a recent publication from our laboratory it has been reviewed that inhibition of crystal growth is possible by the addition of polymer in the liquid state[6]. Previous publications have reported drug dissolution enhancement from two component solid dispersion granules by solvent evaporation technique[7,8] wherein crystallinity of the drug has been decreased. Many amorphous dispersion techniques have been employed to enhance the dissolution rates of poorly water soluble drugs[9-11]. Three-component solid dispersion granules prepared by hot melt granulation have also been reported elsewhere for drug dissolution enhancement[12,13]. Changes in crystal structure may be observed during drug manufacturing processes and can lead to the instability in the pharmaceutical and biopharmaceutical performance of the drug[14,15]. Frequently used processes in the pharmaceutical industry such as grinding, spray-drying, freeze-drying, compaction, often induce at least a partial conversion of most substances to a high energy form[16-19]. This activated state[16-22] of the solid has been associated with increased solubility[20] and enhanced chemical reactivity[17-19]. In wet granulation process, particle growth occurs by liquid bridging of powders[23]. The study of moisture sorption phenomena in processed solids is especially difficult for the cases in which only a small amount of amorphous material is present, as experimental

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techniques are not readily available to measure small amounts of amorphous material in the presence of mostly crystalline substance[24]. Yet relatively, low percentage of amorphous material can absorb considerable amounts of moisture into their structure and act as the region that undergo considerable change and affect the overall properties of the bulk substance[16]. Significant changes can occur in certain regions of a solid containing low moisture, which may affect properties of the material influenced by molecular mobility[16]. Stabilization of the resulting amorphous state is therefore necessary for successful commercialization of the pharmaceutical product, an approach for improvement of dissolution of poorly water soluble drugs[25-26].

Amorphous phase formation by grinding:

Grinding is the mechanical process, regularly used in the pharmaceutical industry for the reduction of particle size of drugs. Sufficient strain has been generated in the solid particles by the high levels of mechanical energy so as to cause crystal lattice disruption (defect formation), followed by particle fracture. Large amounts of vibrational energy, heat and sound are also produced during grinding. The generation of excess energy can lead to additional physical and chemical changes in the crystal structure of the drug[28-41]. The theories of crystal to amorphous phase transformation are based on the concepts of mechanical and thermodynamic destabilization[32,33]. The mechanical mechanism describes how crystal lattice collapses to yield an amorphous structure under increased compression[32]. The thermodynamic mechanism declares that mechanical energy continuously increases the concentration of defects in a crystal lattice and ultimately transforms to the amorphous phase[33,34]. Amorphous phase formation on grinding can occur via a quench melting mechanism if increase in sample temperature takes place. Crowley and Zografi[35] demonstrated that indomethacin polymorphs and solvates could be made x-ray amorphous by cryogenic grinding. During ball milling, a combination of impact and attrition can bring about changes in molecular mobility and consequently induce amorphous phase formation. Gamma-polymorphs of indomethacin have been transformed to amorphous state during milling and this amorphous state has shown 60% higher solubility than the crystalline state[36].

Powder x-ray deffraction[37-39], differential scanning calorimetry[40] and Fourier transformed Raman spectroscopy[41] are conventional methods currently used to evaluate crystallinity. Recently, chemoinformetrical Fourier transformed near-infra red spectroscopy has emerged as an important technique for evaluating the degree of crystallinity[42,43]. Isothermal microcalorimetry[44-46], dynamic vapour sorption[47] and modulated-temperature differential scanning calorimetry[48] have enabled recently, detection of smaller amorphous quantities in terms of mechanical processing[44,46]. Inverse gas chromatography has allowed how mechanical processing influences the surface energies of a material[49,50]. An increase in disorder on the surface of salbutamol crystal indicated by simultaneous measurements of topographical and phase images as milling time was increased and the regions observed during phase images might be mechanically induced amorphous material on the surface[51].

Amorphization in presence of adsorbent:

The granules containing poorly water soluble drug, a solid dispersion carrier and an adsorbent have shown enhancement of drug dissolution[12,13]. An increase in the drug dissolution rate on storage of three component granules was due to drug hydrogen bonding onto the extensive surface of amorphous microporous granules of magnesium aluminosilicate[13,52-54]. Grinding with silicon dioxide, talc and a mixture of magnesium hydroxide-silicon dioxide increased the substantial amorphization of indomethacin[55]. Florite RE^R, a porous calcium silicate is capable of adsorbing a very large amount of oil through its numerous pores, and thus it has been used to prepare solid formulations of oily drugs such as Vitamin E[56]. Ethenzamide was melted and adsorbed on Florite^R in an amorphous state when the drug crystals were heated with Florite^R in a sealed glass ampoule without any solvent[57]. The drug dissolution was greatly increased compared with the drug crystals. Kinoshita *et al.*[58], in their recent study demonstrated melt adsorption of poorly water soluble drug on a porous calcium silicate using a twin-screw extruder as well as a glass ampoule for improving its dissolution and bioavailability. When a physical mixture of salicylimide and folded sheets mesoporous material (FSM-16) was heated at 120° for 3 h, amorphization of salicylimide was observed from the powder x-ray diffraction pattern[59]. Salicylamide molecules were dispersed into hexagonal FSM-16 channels during heating process as suggested by changes in fluorescence decay curve. The mesopores of folded sheet mesoporous silica acted as nanoscales not only for an interaction between chlorophyll molecules and the silica support but also for a nanospace interaction between the adsorbed chlorophyll molecules[60].

Effect of environmental moisture:

The effects of moisture on the properties of solid materials can be understood by the state of water in the solids and the different mechanisms of water sorption in the materials. There are specific pathways for diffusion of water into and within the crystal structure. Crystalline hydrates have been structurally classified into three broad groups namely isolated lattice site hydrates, lattice channel hydrates and metal-ion coordinated hydrates[61]. Ahlqvist and Taylor suggested that water has no fixed site in amorphous materials, or access to different parts of the molecule restricted[62]. Water sorbed into the bulk structure of amorphous material increases molecular mobility and subsequently alters variety of properties of drugs, such as bulk processing, handling characteristics, physicochemical stability[63,64] and eventually their pharmacological activity[65-67]. The existence of water molecules in the solid state of drugs can at least be divided into residual or sorbed moisture and pharmaceutical hydrate. In general, the water solubility of a drug hydrate is less than its anhydrate form because of its more thermodynamic stabilization by the interaction of water molecules[68].

Environmental moisture can interact with the crystalline solids in four different manners: (i) adsorption on the surfaces of the particles (ii) incorporation into microporous regions by capillary condensation (iii) formation of crystal hydrate and (iv) deliquescence[16,69]. Water sorbed into the amorphous regions can act as a plasticizer and increase molecular mobility due to the breakage of hydrogen bonds between molecules. Norfloxacin tablet with poor dissolution behaviour was improved to increase its dissolution rate after exposure to 75% relative humidity (RH) at room temperature. Hydrate formation of norfloxacin occurs in the anhydrate state[70]. Water content sorbed in the moisture-equilibrated norfloxacin was nearly to zero below 55% RH, but increased gradually with the external humidity and reached to a constant of one unit to form a hydrate after >75% RH[71]. Sorbed moisture from environmental humidity can induce the interaction between norfloxacin molecules from hydrogen bonding to ionic bonding by a proton transfer process in the solid state[71].

Molecular mobility and physicochemical stability:

The degree of molecular mobility within a particular amorphous material depends on a number of factors, such as temperature and solvent vapour pressure[72]. For example, sorption of a solvent into an amorphous region would increase molecular mobility and subsequently decrease the glass transition temperature (T_g). If the partial pressure of the solvent is high enough to lower the T_g below the experimental temperature, the region may recrystallize and expel the solvent[73] such a system is a dynamic process and will not reach a true equilibrium until it recrystallizes. Solid state transformation of creatine monohydrate has been categorized as[1,74] (i) physical transformations including polymorphism and desolvation, (ii) chemical transformation including chemical and photochemical reactions and (iii) thermal transformation. Creatine monohydrate dehydrates around 100° to form the anhydrous creatine. This dehydrated phase at temperatures above 230° loses another molecule of water and undergoes intramolecular cyclization to form creatinine. This cyclization event is supposed to be highly energetic and endothermic and attributed to melt-decomposition of creatinine[75].

Drugs generally have a higher enthalpy in the amorphous compared with the crystalline state. Inhibition of crystallization is possible by making amorphous molecular dispersion of drug among carrier molecules or adsorption and entrapment of drug molecules into microporous carrier granules. If the carrier used has a lower molecular mobility[76] than the drug, physical stability of the amorphous form may be enhanced[77-83]. Drug cyclodextrin complexes in solution have been studied widely to increase the stability[84-86] some studies have also focused on stability of drug cyclodextrin complexes in the solid state wherein drug crystallinity have been reduced[2,87-90]. An increase in the amount of chlorophyll adsorbed to the pores of mesoporous silica leads to an enhancement of the photostability accompanied by a shift in the absorbance maximum to a longer wavelength[77]. This is possible because even though thermodynamics still drives instability of the drug molecules in this state, kinetics may be altered to such an extent that crystallization occurs insignificantly slowly. The chemical degradation rate of amorphous drug was found to correlate with the molecular mobility well below its T_g[91]. Mass transport is the most critical factor in nucleation and crystal growth from the very viscous amorphous state and there lies the importance of mobility on physicochemical stability[92]. Andronis and Zografi[93] have reported the influence of thermodynamic parameters such as free energy (configurational entropy) on nucleation and crystal growth. Compounds with high T_gs, High configurational entropy barriers, and low molecular mobilities are supposed to show the greatest stability.

If the drug and excipients are rendered amorphous, the possibility exists for the formation of more specific effects, such as, acid-base equilibria or molecular complexation.

The presence of polyvinylpyrrolidone affects the less water soluble hydrate formation of theophylline anhydrate mainly by a mechanism that retards hydrate formation by competing with theophylline for water molecules[94]. The amorphous states of each of four drugs (ketoprofen, indomethacin, naproxen and progesterone) resulted by milling with neusilin were physically stable during storage at 40° and 75% RH for upto 4 weeks[95]. The acid base reaction between the carboxylic acid containing drugs and the silanol-containing neusilin proceeded via hydrogen bonded intermediate. The water of adsorption during storage at 75% RH plays the role of a medium in the conversion of the drug from crystalline state to the amorphous Neusilin-bound state on milling[95]. Tong *et al.* suggested that stronger electrostatic interactions between carboxylate group of indomethacin and counter-ions, such as sodium potassium, can increase the T_g of the amorphous salts resulting in higher physical stability of the salts in comparison with the acid at a particular storage temperature[96]. The T_g of the salt of indomethacin with monovalent lithium (139°)[96] was much higher than that of melt-quenched acid (44°)[97] and it was attributed that the T_g might be even higher for salts with divalent magnesium (present in neusilin), thereby improving the physical stability of amorphous salt of indomethacin[95]. In a very recent study, Watanabe *et al.* attributed the physical stabilization of indomethacin to its restricted molecular mobility due to mechanochemical reaction on milling with a mixture of $Mg(OH)_2$ and SiO_2 and the formation of bridging bonds[55]. Prolonged cogrinding of amorphous indomethacin with SiO_2 attained higher stability when compared to melt-quenching[54] of the two. This was explained by the stronger chemical interaction at the interface between indomethacin and SiO_2 by co-grinding, as revealed by ^{29}Si and ^{13}C solid state NMR.

Enthalpy Relaxation data may be used to indicate absolute physical stability for amorphous drugs by assigning a shelf life as the time required for 10% of material to have fully relaxed[98,99]. Enthalpy relaxation experiments provide an indication of relative molecular mobility in the materials while in the glassy state. For conventional or accelerated physical stability testing of amorphous form they may not be the adequate substitute[100].

CONCLUSIONS

Grinding of poorly water soluble crystalline drugs induces amorphous phase formation, which can lead to increased dissolution and consequently improved bioavailability. Higher stability of amorphous drugs is attained by storing with microporous adsorbent carrier by co-grinding or by melt adsorption technique without the use of solvents. Comparison of half-lives for enthalpy relaxation could be a successful and rapid indicator of relative molecular mobility and relative likelihood of reversion from amorphous to lower energy crystalline state.

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