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An investigation into the crystallization tendency/kinetics of amorphous active pharmaceutical ingredients: A case study with dipyridamole and cinnarizine

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ABSTRACT

Amorphous drug formulations have great potential to enhance solubility and thus bioavailability of BCS class II drugs. However, the higher free energy and molecular mobility of the amorphous form drive them towards the crystalline state which makes them unstable. Accurate determination of the crystallization tendency/kinetics is the key to the successful design and development of such systems. In this study, dipyridamole (DPM) and cinnarizine (CNZ) have been selected as model compounds. Thermodynamic fragility (m_T) was measured from the heat capacity change at the glass transition temperature (T_g) whereas dynamic fragility (m_D) was evaluated using methods based on extrapolation of configurational entropy to zero ($m_{D_{CE}}$), and heating rate dependence of T_g ($m_{D_{Tg}}$). The mean relaxation time of amorphous drugs was calculated from the Vogel–Tammann–Fulcher (VTF) equation. Furthermore, the correlation between fragility and glass forming ability (GFA) of the model drugs has been established and the relevance of these parameters to crystallization of amorphous drugs is also assessed. Moreover, the crystallization kinetics of model drugs under isothermal conditions has been studied using Johnson–Mehl–Avrami (JMA) approach to determine the Avrami constant '*n*' which provides an insight into the mechanism of crystallization. To further probe into the crystallization mechanism, the non-isothermal crystallization kinetics of model systems were also analysed by statistically fitting the crystallization data to 15 different kinetic models and the relevance of model-free kinetic approach has been established. The crystallization mechanism for DPM and CNZ at each extent of transformation has been predicted. The calculated fragility, glass forming ability (GFA) and crystallization kinetics are found to be in good correlation with the stability prediction of amorphous solid dispersions. Thus, this research work involves a multidisciplinary approach to establish fragility, GFA and crystallization kinetics as stability predictors for amorphous drug formulations.

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1. Introduction

The solid state is preferred for drug formulations due to reasons of stability and ease of handling at different stages of drug product manufacture. The majority of drugs can exist in different solid-state forms such as amorphous or crystalline (hydrates, solvates and polymorphs) or both [1]. The amorphous form has the advantage of a higher apparent aqueous solubility compared to their crystalline counterpart [2]. However, inherently lower physical and chemical stability poses challenges in view of product performance and efficacy [3]. Phase transitions such as conversion of amorphous to crystalline forms are thermodynamically and kinetically driven by higher free energy and molecular mobility, respectively [4]. Given the increasing importance being attached to the stability of amorphous drug products during unit operations such as spray drying and melt extrusion (non-ambient conditions) or upon normal storage (where the conditions remain more or less constant), a robust crystallization prediction protocol may facilitate the prompt development of amorphous drug formulations with better life expectancy [5].

Crystallization tendency describes the properties related to crystallization behaviour of amorphous drugs. Different factors such as chemical structure, molecular weight, number of aromatic rings, symmetry of the structure, number of rotatable bonds, presence of intermolecular interactions, number of electronegative atoms and number of branches have been suggested to affect crystallization tendency [6]. In addition, physicochemical properties such as glass transition and melting temperature, melting and

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Nomenclature

m_T	thermodynamic fragility
T_g	glass transition temperature
T_o	Vogel temperature
m_D	dynamic fragility
$m_{D_{CE}}$	dynamic fragility from extrapolation of configurational entropy to zero
$m_{D_{Tg}}$	dynamic fragility from heating rate dependence of T_g
GFA	glass forming ability
JMA	Johnson–Mehl–Avrami
APIs	active pharmaceutical ingredients
MDSC	modulated differential scanning calorimeter
DPM	dipyridamole
CNZ	cinnarizine
PVP K30	polyvinyl pyrrolidone K 30
α	extent of crystallization
KWW	Kohlrausch–Williams–Watts
k	rate of crystallization
T	temperatures
D_T	diffusion coefficient at temperatures T
D_{Tg}	diffusion coefficient at temperatures T_g
Γ	mean relaxation time
VTF	Vogel–Tammann–Fulcher
R	universal gas constant
ΔC_p^{conf}	configurational heat capacity
ΔC_p	heat capacity change at T_g
T_K	Kuazmann temperature
T_m	melting temperature
D	strength parameter
T_{crys}^{Onset}	crystallization onset temperature
T_{crys}^{peak}	crystallization peak temperature
T_{red}	reduced crystallization temperature
β	heating rate
n	Avrami exponent
K	Avrami constant (or crystallization rate constant)
α	fraction of drug crystallized
T_c	crystallization temperature
E_a	crystallization activation energy
C	Kissinger constant

crystallization enthalpy/entropy, molecular mobility and viscosity of the supercooled and glassy states have been suggested to correlate with crystallization tendency of amorphous compounds [7]. Fragility is a measure of deviation of these physical properties from Arrhenius behaviour and is considered to correlate with glass forming ability (GFA) [6]. "Fragile" glass formers exhibit a large variation in properties such as molecular mobility, viscosity and/or heat capacity around the glass transition temperature, T_g, unlike "strong" glass formers. Sufficient kinetic stabilization of fragile amorphous drugs may lead to the development of robust products with enhanced dissolution rates. Therefore, a systematic examination of the crystallization kinetics is a critical part of formulation development of amorphous drug products.

Measurement of phase transitions from relaxation behaviour by perturbing equilibrium permits direct assessment of molecular mobility. However, powdered active pharmaceutical ingredients (APIs) are not always amenable to such measurements; for example, measurement of shear viscosity or dielectric spectroscopy requires sample manipulation or long experiment times which may result in unwanted changes (either physical or chemical or both). Fortunately, conventional and modulated differential scanning calorimeter (DSC) overcomes both of these limitations. It can be used to study the effect of temperature on structural relaxation (characterized by the mean relaxation time, Γ) and its impact on the crystallization tendency/kinetics of amorphous drugs. Herein, we report an investigation on the role of molecular mobility on crystallization tendency and compare isothermal and non-isothermal crystallization kinetics. The applicability of different solid-state crystallization kinetic models to identify the crystallization mechanism is probed. Insights gained from molecular mobility/crystallization studies and a thorough understanding of the mechanism of amorphous to crystalline transformation are expected to provide formulation scientists with a road map towards more effective stabilization of glassy drug products.

2. Materials and methods

2.1. Materials

Dipyridamole (DPM), cinnarizine (CNZ) and polyvinyl pyrrolidone (PVP) K30 were purchased from Sigma Aldrich (Ireland) and used as received.

2.2. Preparation of the amorphous drug form

Amorphous DPM and CNZ were prepared by heating the crystalline drug in a vacuum oven to a temperature 5 K above the melting point. The temperature was held at this point for 5 min and then quench cooled by dropping into liquid nitrogen. The thermal stability of amorphous drugs was established by high-performance liquid chromatography and thermogravimetric analysis which indicates that no degradation occurred during the preparation of the amorphous form.

2.3. High Performance Liquid Chromatography (HPLC)

A reverse phase HPLC method was developed for thermal stability studies of DPM and CNZ. For DPM, analysis was performed on a Water's Symmetry® C18 column (150 mm × 3.9 i.d., 5 μm) at 25 °C and a flow rate of 0.75 mL/min. The mobile phase consisted of 75:25 aqueous (0.1% v/v ortho-phosphoric acid):acetonitrile mixture. Detection was by UV at a wavelength of 283 nm and an injection volume of 40 μL was used. For CNZ, analysis was performed on XTerra® C18 column (250 mm × 4.6 i.d., 5 μm) at 25 °C and a flow rate of 1 mL/min. The mobile phase consisted of 50:50 aqueous (0.1% v/v of trifluoroacetic acid):acetonitrile mixture. Detection was done by UV at a wavelength of 251 nm and an injection volume of 20 μL was used. The linearity was demonstrated in the range of 1–20 μg/mL for DPM and CNZ.

2.4. Preparation of the amorphous solid dispersions

Amorphous solid dispersions (ASDs) of DPM and CNZ using PVP K30 as carrier matrix at 1:1 drug–polymer weight ratio were prepared in two steps. First, physical mixtures of drug and polymer were dissolved in sufficient volume of methanol and the solvent was removed under reduced pressure at 313 K using a rotary evaporator followed by drying at room temperature under vacuum for 24 h. In the next step, the dried mixtures were melt quenched and the ASDs were stored (at 25 °C and 0% moisture).

2.5. Heat capacity measurements

The heat capacities of crystalline and amorphous DPM and CNZ were measured using modulated DSC (MDSC) in accordance with the previously published protocols [8,9]. The modulation

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