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An Investigation into the Crystallization Tendency/Kinetics of Amorphous Active Pharmaceutical Ingredients: A Case Study with Dipyridamole and Cinnarizine

Authors : Shrawan Baghel, Helen Cathcart, Biall J. O'Reilly

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 lowers the activation energy barrier for crystallization and thermodynamically drives it 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) has been selected as model compounds. Thermodynamic fragility (m_T) is measured from the heat capacity change at the glass transition temperature (Tg) whereas dynamic fragility (m_D) is evaluated using methods based on extrapolation of configurational entropy to zero □(m□_(D_CE)), and heating rate dependence of Tg □(m□_(D_Tg)). The mean relaxation time of amorphous drugs was calculated from Vogel-Tammann-Fulcher (VTF) equation. Furthermore, the correlation between fragility and glass forming ability (GFA) of 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 was also analysed by statistically fitting the crystallization data to 15 different kinetic models and the relevance of model-free kinetic approach has been established. In addition, 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 is 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.

Keywords : amorphous, fragility, glass forming ability, molecular mobility, mean relaxation time, crystallization kinetics, stability
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