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Probing the amorphous state of pharmaceutical compounds within mesoporous material using pair distribution function analysis

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ABSTRACT

Pharmaceutical compounds with poor solubility are loaded within mesoporous materials in order to understand the effect of mesoscale confinement on their dissolution behaviour. Structural and calorimetric characterization is combined with atomic pair distribution function analysis probing the interactions between the silica surface and the loaded amorphous compound. Whilst different degrees of amorphism are not identifiable from X-ray diffraction data or calorimetry techniques, the atomic pair distribution function analysis can help identify local ordering of the drug molecules. Together with a list of drug descriptors such as crystallization properties, molecular size and glass transition temperature the behaviour of encapsulated compounds and their release kinetics may be rationalized. Dissolution experiments confirm that different release rates can be achieved with small differences in mesopore design such as the presence of micropores in SBA-15, and loading amount.

1. Introduction

The focus in drug discovery on complex bimolecular targets with high potency has significantly increased the number of poorly soluble pharmaceutical compounds in clinical development with properties outside the confines set out by Lipinski's *Rule of 5* (1). There is a need to tackle the formulation of such compounds to improve their bioavailability, enhance their efficacy and reduce their potential toxicity. The preparation of a compound in its amorphous form can result in superior pharmacokinetics (2). The amorphous compound has higher free energy, enthalpy and entropy than the crystalline form (3). It is a metastable state however, limiting the number of pharmaceutical compounds developed using this approach.

Drug loaded mesoporous silica particles can stabilize the formation amorphous solid dispersions of a wide range of Class II and Class IV compounds (4-10). Thermodynamic nanoconfinement and restrictions in molecular mobility of the loaded compound are the driving forces for the suppression of crystallization within the pores (11, 12). The Gibbs-Thompson equation describes the largest pore diameter (d*) in which the energetic gain of crystallization is lower than the surface energy,