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Modeling and Prediction of Drug Dispersability in Polyvinylpyrrolidone-Vinyl Acetate Copolymer Using a Molecular Descriptor

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ABSTRACT

The expansion of a novel *in silico* model for the prediction of the dispersability of 18 model compounds with polyvinylpyrrolidone-vinyl acetate copolymer is described. The molecular descriptor R3m (atomic mass weighted 3rd-order autocorrelation index) is shown to be predictive of the formation of amorphous solid dispersions at 2 drug loadings (15% and 75% w/w) using 2 preparation methods (melt quenching and solvent evaporation using a rotary evaporator). Cosolidified samples were characterized using a suite of analytical techniques, which included differential scanning calorimetry, powder X-ray diffraction, pair distribution function analysis, polarized light microscopy, and hot stage microscopy. Logistic regression was applied, where appropriate, to model the success and failure of compound dispersability in polyvinylpyrrolidone-vinyl acetate copolymer. R3m had combined prediction accuracy greater than 90% for tested samples. The usefulness of this descriptor appears to be associated with the presence of heavy atoms in the molecular structure of the active pharmaceutical ingredient, and their location with respect to the geometric center of the molecule. Given the higher electronegativity and atomic volume of these types of atoms, it is hypothesized that they may impact the molecular mobility of the active pharmaceutical ingredient, or increase the likelihood of forming nonbonding interactions with the carrier polymer.

Introduction

Amorphous solid dispersions (ASDs) are a proven formulation strategy, owing to the prevalence of water-insoluble molecules in current pipelines of the pharmaceutical industry.[1] There are, however, significant challenges with respect to the successful development of ASDs. This is evident from the relatively small number of formulations that have been approved for human use, since potential benefits to absorption were first observed,[2] and the pharmaceutical application of solid solutions was first proposed.[3] More recently, the number of ASDs that have successfully reached the market has increased, nevertheless, limited fundamental understanding, particularly with respect to issues surrounding their formation and physical stability, remains.[4]

Several specific and nonspecific interactions have been proposed to be of importance with respect to successful formation and persistence of ASDs, including crystallization inhibition due to a kinetic barrier for nucleation,[5] antiplasticization effects that reduce molecular mobility,[6] and specific nonbonded interactions, such as hydrogen bonding.[7,8] Reliable prediction of ASD dispersability, however, remains problematic, particularly with new chemical entities for which limited quantities are available during early development. It is ultimately necessary to perform extensive experimental studies to confirm that an active pharmaceutical ingredient (API) can successfully form an amorphous solid dispersion by intimate mixing with a carrier polymer, followed by

Abbreviations used: API, active pharmaceutical ingredient; ASD, amorphous solid dispersion; DSC, differential scanning calorimetry; HSM, hot stage microscopy; PDF, pair distribution function; PLM, polarized light microscopy; PVPva, polyvinylpyrrolidone-vinyl acetate copolymer; PXRD, powder X-ray diffraction; R3m, atomic mass weighted 3rd-order autocorrelation index; T_{m_API}, melting point of the active pharmaceutical ingredient.

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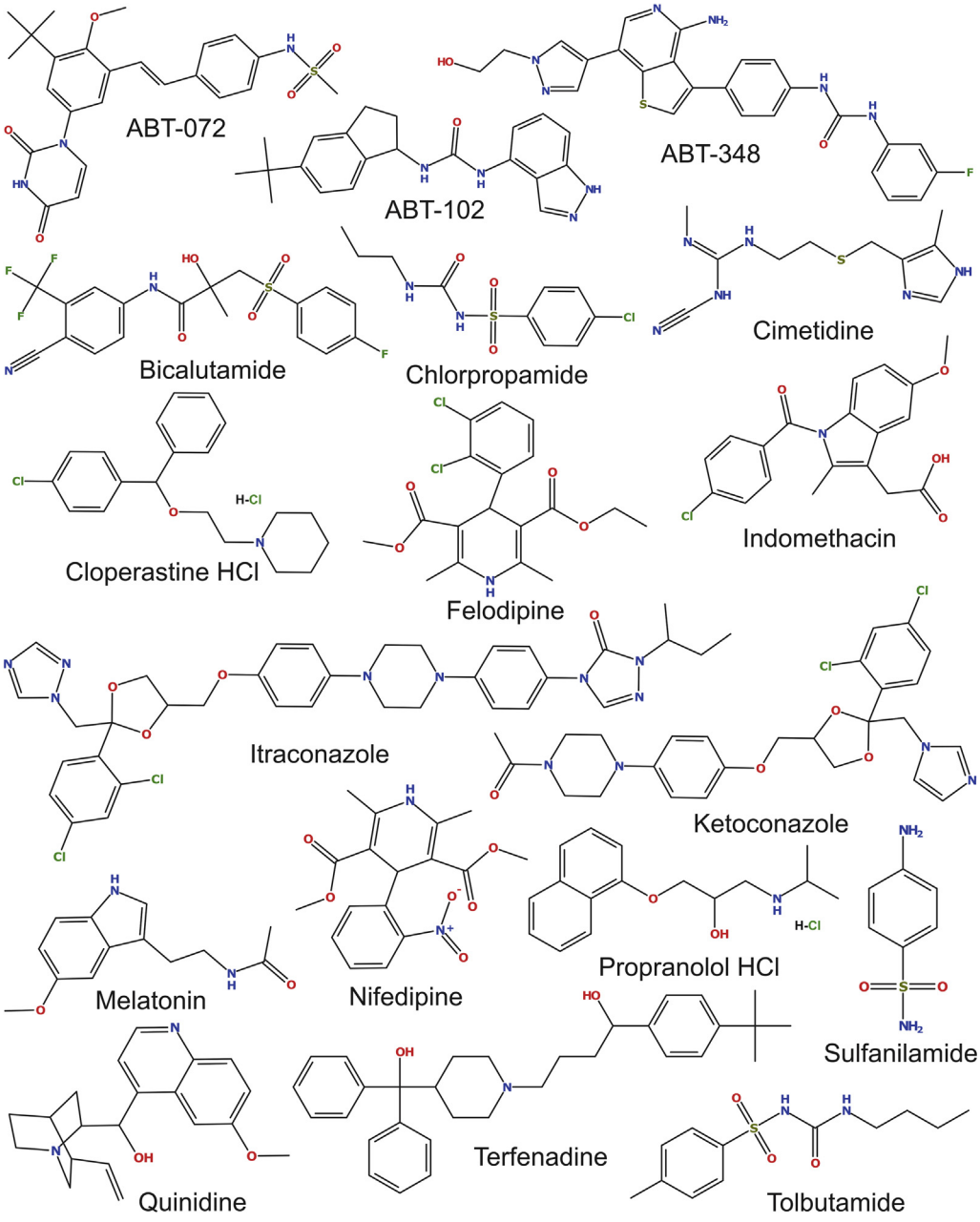

Figure 1. Molecular structures of API in the compound library.

cosolidification without recrystallization (herein referred to as 'dispersability'). In addition, confirmation that the formulation remains physically stable for pharmaceutically relevant periods of time is important for dispersible API to estimate product viability. Assessment of dispersability and physical stability by trial-and-error is costly, and may not be feasible, depending on the quantities of API available. Improved prediction of dispersability has the potential to reduce development costs by preemptively identifying promising binary mixtures, thereby reducing the experimental burden. If such a 'go/no-go' decision can be made before experiments are necessary by identifying attributes of an API essential for dispersability in a given polymer, it is expected that development costs and time-to-market will decrease.

Successful dispersability of an API molecule in a polymer matrix likely depends on a complex combination of material's properties that facilitate the interactions necessary to form an ASD. Molecular descriptors are being investigated to help elucidate those properties that are most important for dispersability. It is hypothesized that molecular descriptors most highly correlated with ASD formation are reflective of the combined attributes of the API molecule necessary for dispersion in a given carrier polymer, in this case, polyvinylpyrrolidone-vinyl acetate copolymer (a.k.a. PVPva or copovidone). Previous work showed that a single molecular descriptor (R3m) was predictive of solid dispersion potential for a 12-member API library in PVPva[9] prepared by melt quenching (M/Q) at a fixed drug loading (75% w/w). Although these initial results were promising, it remained uncertain if predictions made using R3m were more broadly applicable. The objective of this work was to further examine the usefulness of the R3m molecular descriptor as a predictive tool for dispersability of API in PVPva at different concentrations, prepared using different manufacturing processes.