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Molecular Dynamics Simulation of Amorphous Hydroxypropylmethylcellulose and Its Mixtures With Felodipine and Water

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ABSTRACT

Understanding drug-polymer molecular interactions, their miscibility, supersaturation potential, and the effects of water uptake may be invaluable for selecting amorphous polymer dispersions that can maximize the oral bioavailability of poorly water-soluble drugs. Molecular dynamics simulations were performed using a model for hydroxypropylmethylcellulose (HPMC) resembling the substitution patterns found experimentally. HPMC at low and high water contents (0.9%-23.0% wt/wt) and mixtures with a hydrophobic drug, felodipine (FEL), were constructed. T_g values and densities after ~30 ns aging at 298 K were close to published results. Except for hydrogen bonds (HBs) between the 5-O- and a 3-OH group in a neighboring repeat unit, HPMC oxygen atoms have a low HB probability ($p < 0.1$) perhaps due to shielding by surrounding substituents. Water molecules tend to be isolated at low water content while clusters were prevalent at $\geq$10.7% water. The Flory-Huggins FEL-HPMC interaction parameter (-0.20 ± 0.07) predicts complete miscibility at all HPMC compositions, in agreement with experiments. However, HBs between the FEL-N-H and HPMC favoring miscibility are disrupted with increasing water. Apparent diffusion coefficients versus water content were generated for water and FEL and a theory for the non-Einsteinian nature of water diffusion is proposed.

Introduction

Formation of an amorphous solid can often lead to enhanced aqueous solubility and oral bioavailability of a poorly water-soluble drug candidate. However, because the pure amorphous solid forms of drugs are higher energetic states than their crystalline forms, they usually lack physical and chemical stability and are therefore rarely developed alone as commercial drug products. This problem has been largely remedied by combining amorphous drugs with excipients such as polymers that are themselves more stable and capable of promoting stability of the embedded drugs. Such formulations in which the drug is in a molecularly dispersed state are generally referred to as amorphous solid dispersions (ASD).[1-5] Hydroxypropylmethylcellulose (HPMC), a cellulose derivative consisting of a linear backbone of cellulose to which methyl and hydroxypropyl groups are attached by ether bonds (Fig. 1), is one of the most promising carriers because it is nontoxic and able to inhibit crystallization of drugs at high levels of drug loading. HPMC may also be used as a coating for hydrophilic carrier matrix systems to control drug release for oral drug delivery. In this regard, extensive research has been undertaken to explore the underlying transport mechanisms.[6-8]

The ability of a polymer to stabilize an amorphous drug is critically dependent on its miscibility with the drug on a molecular level. Intimate mixing on a molecular level is often verified by the collapse of T_gs for the amorphous drug and polymer into a single value as commonly observed by differential scanning calorimetry or by other techniques such as X-ray powder diffraction, solid-state nuclear magnetic resonance, and infrared spectroscopy.[9-11] According to the Hildebrand theory for the solubility of nonelectrolytes,[12] miscibility between a drug and polymer of interest is largely determined by the similarity of interaction energies between drug molecules and polymer molecules themselves as characterized by their solubility parameters.[13] However, this approach discounts specific interactions (e.g., hydrogen bonds [HBs]) that may often exist between the drugs and polymer carriers leading to underprediction of their miscibility. It is thus necessary to utilize a more accurate approach, such as the Flory-Huggins theory[14,15] that is capable of taking into account the effects of strong intermolecular interactions between drugs and polymer carriers of interest to verify their miscibility.[16,17] In addition to the thermodynamic driving force, drug-polymer intermolecular interactions

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may also exert a kinetic barrier to inhibit nucleation[9,18,19] or crystal growth[20] thereby improving drug dissolution rates.[4,21]

HPMC is somewhat hygroscopic, being capable of absorbing a large amount of water depending on the environmental humidity (e.g., up to ~25% water uptake by weight from 0% to 100% relative humidity[22]) or upon contact with aqueous solutions or biological fluids. Changes in water content in an HPMC-based drug product under storage could gradually alter the polymer structure (e.g., by reducing T_g and increasing drug mobility) and potentially undermine the physical and chemical stability of the drug product. During the drug dissolution process from an HPMC matrix tablet, water penetration plays a dominant role in instigating gelling, matrix expansion, and drug release most commonly via a diffusion mechanism.[23] While a variety of transport mechanisms based on swelling of HPMC and diffusion of water and drugs in HPMC matrices have been explored to predict drug release profiles,[7,23] few studies have been undertaken to investigate the mobility of water and drug molecules in HPMC polymers with varying water content. For example, Siepmann et al.[23] proposed that imbibition of water leads to polymer swelling and enhanced polymer mobility. With increased water content, drug diffusivity may increase and accelerate release from the HPMC matrix. However, these important phenomena have yet to be verified microscopically through atomic-level structural and dynamic investigation.

Thus, understanding polymer-drug molecular interactions, their effects on the mutual miscibility, and the effects of water on polymer/drug properties is imperative for the rational design of successful drug delivery systems that are stable under storage and exhibit optimal release characteristics upon administration. For this study, felodipine (FEL) was selected as a model poorly water-soluble drug having reported water solubility as the crystalline compound of 0.74 μg/mL at 25°C.[24] FEL is a dihydropyridine calcium antagonist (Fig. 1) widely used in the treatment of hypertension.[25] However, its poor solubility in water and extensive metabolism in the gut and liver lead to very low oral bioavailability. As a result, ASD technology has been promoted as a promising formulation strategy to enhance the solubility and dissolution rate of FEL.[4,26] FEL possesses a hydrogen bond (HB) donor > N-H and 2 HB accepting ester groups that are capable of forming various HBs with HPMC. Thus, amorphous mixtures of HPMC and FEL offer an opportunity to explore the power of both the solubility parameter and Flory-Huggins approaches for predicting miscibility.

Molecular dynamics (MD) simulations are well suited to explore atomic-level intermolecular interactions that are responsible for determining solubility, diffusivity, and other thermodynamic and kinetic properties in condensed materials. This is especially true for polymer/drug systems whose multidimensional spectra of molecular interactions and conformational dynamics could not be easily observed experimentally or predicted by existing mathematical models. Although *ab initio* computation has been applied to small molecular systems, MD simulation based on a classical mechanics force field remains the realistic choice for multimolecular and polymeric systems. In recent years, MD simulations have been increasingly utilized to investigate a broad range of drug/polymer properties of pharmaceutical interest including phase transitions,[27-29] molecular miscibility,[28,30-33] structural relaxation,[27,34,35] and solute diffusivity.[29,35-39] Nevertheless, computational studies on cellulose-based polymer derivatives such as HPMC are still rare perhaps due to the complex substitution patterns of methyl, hydroxypropyl, and other substituents on multiple sites of the cellulose backbone.

The main goal of this work was to develop molecular models for an HPMC polymer using Amber and Glycam force fields and use these models to construct HPMC systems and mixtures of HPMC and FEL containing different amounts of water. Similar to the method of hot melt extrusion used experimentally to form glasses,[40] these molecular systems were equilibrated in a molten state then cooled through the glass transition to form amorphous solids. A series of dynamic simulations from 30 to 100 ns was then performed to monitor certain structural and dynamic properties of the amorphous solids during aging. Molecular trajectories generated from these dynamic runs were primarily utilized to (1) calculate various thermodynamic, structural, and dynamic properties of interest such as density, T_g, and molecular mobility; (2) map the landscape of intermolecular interactions (e.g., HBs) and associated molecular distributions; (3) determine solubility and miscibility employing solubility parameters and Flory-Huggins interaction parameters; and (4) determine the apparent diffusivity of solutes (FEL and water) in amorphous HPMC containing different quantities of water.

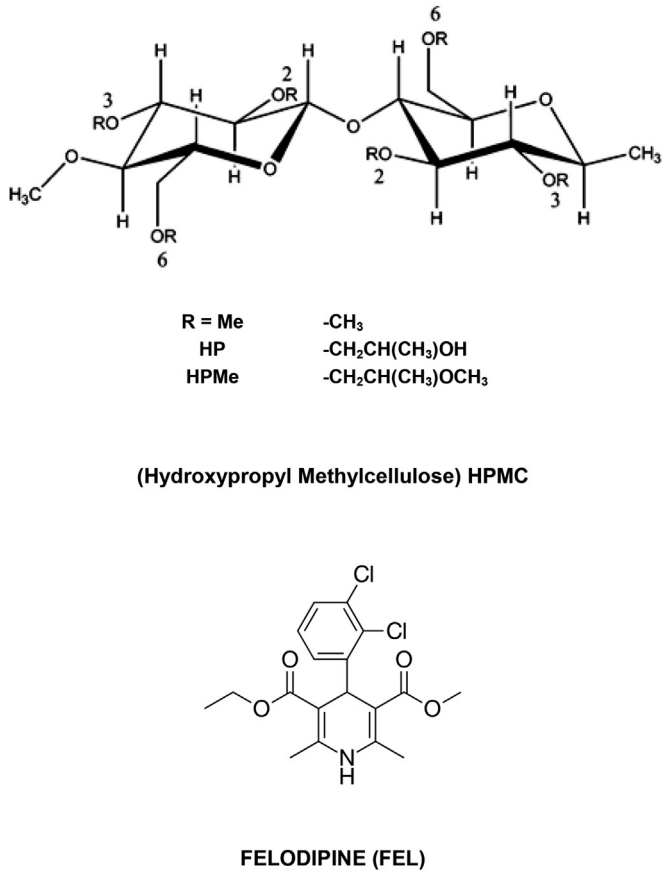

Figure 1. A schematic diagram of HPMC units and FEL.

Computational Methods

As shown in Figure 1, HPMC consists of a backbone of cellulose with or without substitution of Me, HP (2-hydroxypropyl), or HPMe (2-methoxypropyl) groups onto the glucose unit oxygen at positions O2, O3, or O6. A gas-liquid chromatography/mass spectroscopy study by Adden et al.[41] provided a detailed database of the molar% distribution for all the detectable monomer patterns. Those definitively defined patterns with molar% >0.2 as shown in Table 1 based on this dataset were used to build an HPMC molecular model within the framework of the Amber Molecular Dynamics Package (University of California, San Francisco, CA). To facilitate the process of building the polymer model, basic glucose unit structures with