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Solubility of water and acetone in hypromellose acetate succinate, HPMCAS-L

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ABSTRACT

Thermodynamic properties of a hypromellose acetate succinate (HPMCAS-L)-acetone-water system at temperatures below the glass transition temperature of HPMCAS-L were investigated. The solubility of water and acetone in HPMCAS-L is important for the optimization of spray-drying processes used in pharmaceutical manufacturing of solid dispersion formulations. Finite concentration data of each component were obtained separately using gravimetric sorption, differential pressure decay, and capillary column inverse gas chromatography. Results of thermodynamic properties were compared with prediction models based on the UNIQUAC functional-group activity coefficients (UNIFAC) method as well as the correlation model of Flory-Huggins. UNIFAC interaction parameters, modified to account for the interactions of water with the monosaccharide type groups in HPMCAS-L, had to be used in order to generate reasonable predictions. Overall, the Flory-Huggins model provided the best representation for both binary systems.

1. Background

Knowledge of phase equilibria for small molecules in polymers is of considerable importance in industrial applications, such as polymer synthesis, devolatilization, and drying of polymer films. The total amounts of these components remaining in the final product are determined by the chemical phase equilibria between the gas and polymer phase. In the pharmaceutical industry, hypromellose acetate succinate (HPMCAS-L), a synthetic polymer derived from cellulose, has been widely used as a polymer to kinetically stabilize the amorphous phase of active pharmaceutical ingredients (API) and prevent them from recrystallizing to their more thermodynamically stable form [1]. Within these amorphous solid dispersions (ASDs), the APIs are intended to be well dispersed throughout a polymer matrix and therefore sterically hinder the formation of crystalline nuclei. Due to their higher energy state, ASDs can have higher apparent solubility and faster dissolution rates than crystalline API while maintaining good physical stability [2]. Amorphous solid dispersions are frequently prepared by the spray-drying process and several commercial examples exist [3]. In a spray drying process, API is mixed with the desired stabilizing polymer through dissolution in a common solvent, frequently acetone, water, or mixtures thereof. The homogeneous solution is atomized through a nozzle where, upon mixing with heated gas in the spray drying chamber, the solvent is evaporated yielding ASD powder. Knowledge of solvent solubility in the ASD is useful in various aspects of the process design including determination of whether particles reach equilibrium with the gas stream or on how the vapor liquid equilibrium (VLE) of the solvent is altered by dissolved HPMCAS-L.

2. Experimental

In the current work three techniques were used to measure the phase equilibria in the acetone-water-HPMCAS-L systems: gravimetric sorption (GS), differential pressure decay (DPD), and capillary column inverse gas chromatography (CCIGC). GS and DPD are generally used to measure the phase equilibria at finite concentrations of solvent while CCIGC is predominantly applied to the region of highly concentrated polymer, where the solvent

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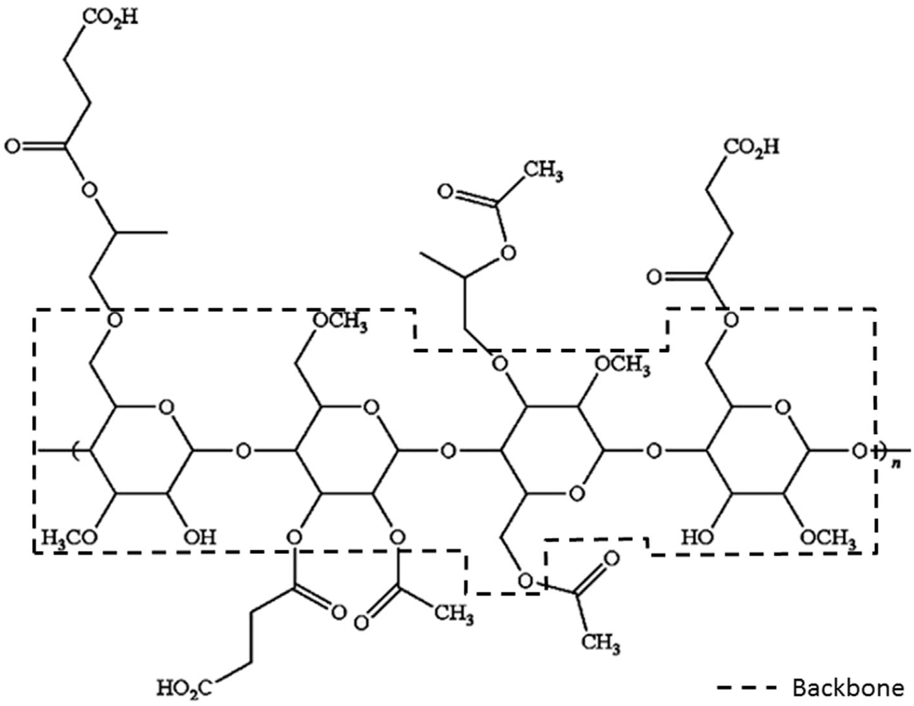

Fig. 1. HPMCAS molecular structure.

concentration is virtually zero. In this work, however, the CCIGC method was modified to allow the study of binary polymer-solvent systems at finite concentration of solvents [4].

All three of these experimental methods and the relevant data analyses have previously been described in the literature. In the GS approach the polymer is exposed to the vapor pressure of the solvent and the uptake is measured by observing the extension of a calibrated quartz spring [5]; in the DPD method the pressure drop is measured in a constant temperature, constant volume chamber as the solvent is sorbed into the polymer [6]; and in the basic CCIGC method the elution profile is modeled to determine the partition coefficient [7]. An extension of the CCIGC approach was made in the current work to allow the determination of finite concentrations of solvent [4].

3. Materials

High purity acetone designated for use in gas chromatography and distilled water were used as the solvents without further purification. HPMCAS-L was sourced from Shin-Etsu Chemical Co., Ltd. Since hypromellose acetate succinate, HPMCAS-L, is a synthetic polymer derived from random substitution of cellulose hydroxyl groups, there is no exact formula for its monomer. A generalized structure was proposed by Lyon et al. [8] as shown in Fig. 1. The HPMCAS-L molecule can be visualized as a cellulose backbone with 2-hydroxypropyl groups (-$OCH_2CH(CH_3)OH$), methoxy groups (-OCH_3), acetyl groups (-$COCH_3$), and succinoyl groups (-$COCH_2CH_2COOH$) as well as residual hydroxyl groups. The HPMCAS-L has a density of 1.314 g/cm^3 with a weight averaged molecular weight 55000 g/mol and a glass transition temperature of 118 °C. The HPMCAS-L was coated as the stationary phase on the inner wall of a capillary column using the static coating technique [9]. The film was uniform with a thickness of 3 µm as confirmed by SEM pictures [4]. For GS and DPD, films were made by dissolving the HPMCAS-L in tetrahydrofuran (THF), followed by slow evaporation of the THF. They were then evacuated in a vacuum at 65 °C for 10 days. The final samples sizes were 256.0 mg for the acetone GS studies,165.7 mg for the water GS studies, and 249.3 mg for the DPD studies.

4. Thermodynamic models

4.1. Flory-Huggins model

The polymer-solvent system was modeled by the well-known lattice theory of Flory and Huggins [10] taking into account both combinatorial and residual effects.

Table 1
Modified interaction parameters for the H_20-HPMCAS groups of Ming and Russell [14].

	H_2O	CH_2O[a]	OH[a]
H_2O	0	193.1	171.3
CH_2O	2007	0	237.7
OH	−189.7	28.06	0

[a] In monosaccharides.

Table 2
Group representation used to model HPMCAS.

Subgroup	Number
CH_3	6
CH_2	5
CH	6
CH_3O	3
CH_2CO	3
CHO	2
COOH	3
CH_2O[a]	4
CHO[a]	14
OH[a]	2

[a] Modified groups for H_2O-HPMCAS.