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Application of finite inverse gas chromatography in hypromellose acetate succinate-water-acetone systems

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ABSTRACT

A modification of a GC was developed to investigate both infinitely dilute and finite concentrations of solvents in polymers. Thermodynamic properties of hypromellose acetate succinate (HPMCAS-L)-acetone-water systems are important for the optimization of spray-drying processes used in pharmaceutical manufacturing of solid dispersion formulations. These properties, at temperatures below the glass transition temperature, were investigated using capillary column inverse gas chromatography (CCIGC). Water was much less soluble in the HPMCAS-L than acetone. Experiments were also conducted at infinitely dilute concentrations of one of the solvents in HPMCAS-L that was already saturated with the other solvent. Overall the partitioning of the water was not significantly affected by the presence of either water or acetone in the polymer. The acetone partition coefficient decreased as either acetone or water was added to the HPMCAS-L. A representation of the HPMCAS-L structure in terms of UNIFAC groups has been developed. With these groups, the UNIFAC-vdw-FV model did a reasonable job of predicting the phase equilibria in the binary and ternary systems. The Flory-Huggins correlation with fitted interaction parameters represented the data well.

1. Introduction

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), i.e., to 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]. 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 of the solvent is altered by dissolved HPMCAS-L.

In this work, the solubilities of water and acetone in HPMCAS-L were studied in binary and ternary systems using a modified gas chromatograph and a careful mathematical analysis of the elution peak. The HPMCAS-L was coated on the inside walls of a capillary column. The IGC method has been extensively applied at infinite dilution in which case a very small pulse of the solvent is injected into a pure carrier gas stream [3–5]. There are some publications which discuss the use of IGC at finite concentrations in which case a small pulse of the solvent is injected into a carrier stream that contains a significant concentration of the solvent [6–8]. The current application required modification of the chromatograph so that a carrier gas containing a condensable solvent could be used without any condensation in the feed lines.

2. Experimental

The experimental apparatus used in this study is similar to that described by Tihminlioglu and Danner [9]. (See Fig. 1.) A Hewlett-Packard 5890 GC coupled with a thermal conductivity detector (TCD) was modified to enable studies of finite concentrations of condensable solvents in the carrier gas. It was essential that all inlet lines be heated to avoid any condensation. To accomplish this, a

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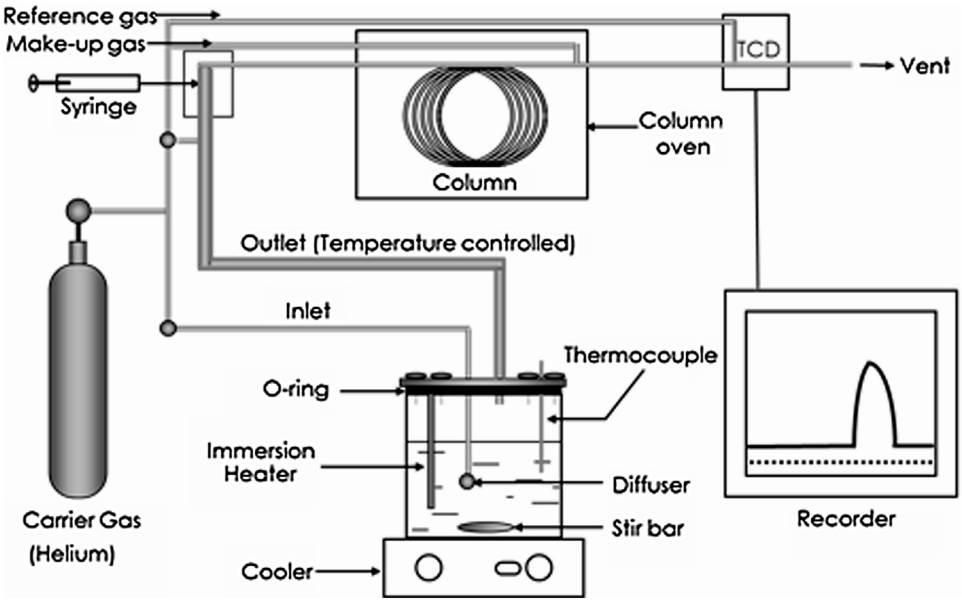

Fig. 1. Schematic of the modified inverse gas chromatograph apparatus.

temperature controlled manifold was built to enclose the inlet lines, ensuring no condensation occurred between the boiler and the column (See Fig. 2). An insulated cover was used over the normal inlet section. For temperature control, two small fans, a control heater, and a thermocouple were enclosed therein. Five on-off valves were used to allow various combinations of feed. Two other heaters and several thermocouples (a, b, and c) were incorporated to ensure uniform temperature was maintained throughout.

For infinitely dilute experiments only, the carrier gas, ultra-high purity (UHP) helium, was flowing through the capillary column at 2 ml/min. The makeup flow rate was adjusted such that the makeup and column flow totaled 5 ml/min. The injection port temperature was set to 50 °C above the boiling temperature of the solvent to ensure complete evaporation during the solvent injection. The TCD temperature was set at 160 °C. Air injects were used to determine the linear velocity of the carrier gas. This was followed by injections

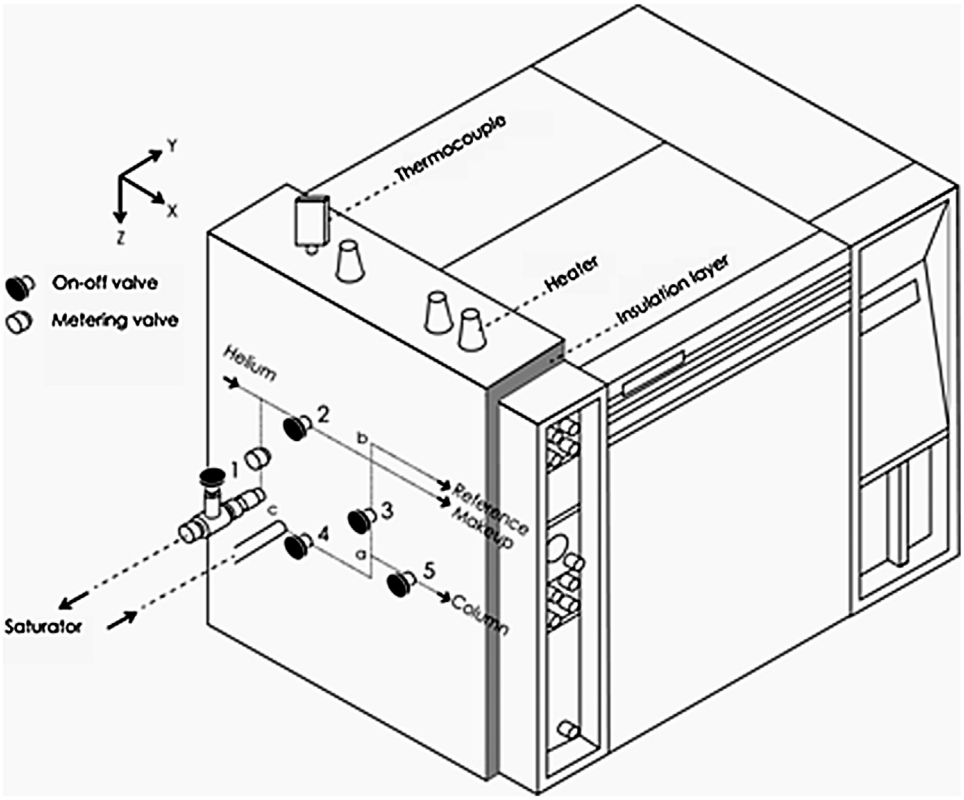

Fig. 2. The overview for the modified HP 5890 Gas Chromatograph.

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