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Solubility and partitioning of carbamazepine in a two-phase supercritical carbon dioxide/polyvinylpyrrolidone system

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ABSTRACT

Supercritical carbon dioxide ($scCO_2$) processing of drug/polymer mixtures is an environmentally friendly means of creating an impregnated polymeric carrier to enhance the aqueous dissolution rate of drugs that exhibit poor water solubility or are thermally labile. However, the role of drug solubilization and its interaction with the polymer during $scCO_2$ processing on the extent and rate of dissolution has been ambiguous. In this study, we examine the rate of dissolution of carbamazepine (CBZ), a hydrophobic drug for treating epilepsy, in $scCO_2$ (90–200 bar, 35 °C and 45 °C) and its partitioning into polyvinylpyrrolidone (PVP, 10 and 29 K MW) using *in situ* UV–vis spectroscopy. Our results show that partitioning occurs by surface adsorption and impregnation within the polymer matrix. These processes are linked to plasticization, which is dependent on PVP molecular weight, and temperature and pressure during treatment. The rate and extent of CBZ solubility is also controlled by treatment condition. The ability to tune polymer and drug simultaneously can be used to control the nature and extent of drug loading.

1. Introduction

Formulation of a water insoluble drug faces several challenges owing to the inherent properties of the drug itself, including crystallinity and hydrophobicity, which restricts free dissolution in water. Non-crystalline amorphous forms can be formed, which improve the dissolution rate, but these forms are thermodynamically unstable and ultimately convert back to more stable crystalline forms (Craig et al., 1999). Carbamazepine (CBZ), a class II compound as per the Biopharmaceutics Classification system (Lőbenberg and Amidon, 2000), is one such crystalline drug that would greatly benefit from an improved dissolution rate as its absorption from the gastrointestinal tract is dissolution-limited (Nair et al., 2002). In order to circumvent thermodynamic instability posed by amorphous forms, another common route that is adopted to enhance the solubility and rate of dissolution of drugs is to combine them with water soluble, pharmaceutically acceptable polymer excipients. This is commonly achieved using melt dispersion, spray drying, or film coating techniques (Hancock et al., 1995; Hancock and Zografi, 1997). Amorphous forms, if generated, are stabilized by co-solidifying the drug with the polymer excipients. This hampers the molecular mobility of the drug and prolongs the amorphous to crystalline conversion (Yoshioka et al., 1995; Hancock et al., 1995).

In the case of CBZ, a remarkable increase in aqueous CBZ dissolution has been reported when formulated with water-soluble polymer solid dispersions, which led to increased bioavailability (El-Zein et al., 1998). Examples of the polymeric pharmaceutical excipients used include polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG). However, a major limitation associated with utilizing such polymers is that conventional processing techniques generally require the use of organic solvents that pose a toxicological threat. Also, some drugs are thermally labile and the formation of drug–polymer mixtures must be accomplished using non-thermal processes. This limits the types of processing techniques that can be employed.

Liquid or supercritical carbon dioxide-based solvent systems can be used as an alternative method to prepare and process drug-impregnated polymer mixtures without the use of organic solvents. There are several advantages to employing carbon dioxide as a solvent; it is non-flammable, chemically inert, inexpensive, and has an accessible critical temperature (31 °C) and critical pressure (73.8 bar) (Hyatt, 1984; McHugh and Krukonis, 1994). CO_2 is also environmentally friendly as it can be removed from the atmosphere and recycled in a closed-loop process. A key property of $scCO_2$ is the ability to tune solvent strength and mass transfer properties with slight changes in the pressure or temperature (Mukhopadhyay, 2004). CO_2 is widely applicable in the pharmaceutical industry and it can plasticize amorphous polymers, which mimics heat-induced plasticization (Kazarian et al., 1997; Kazarian, 2000, 2004). Hence, CO_2-based processes for creating drug–polymer mixtures are of great interest (Moneghini et al., 2001; Sethia and Squillante, 2004;

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Nomenclature

CBZ	carbamazepine
PVP	polyvinylpyrrolidone
$A_{280\,nm}$	absorbance at 280 nm
a_D	molar adsorptivity (mol mol^{-1} cm^{-1})
b	light pathlength (cm)
K_D	drug (CBZ) partition coefficient (mole fraction basis)
$m_D^{CO_2}$	mass of drug in CO_2
m_D^{PVP}	mass of drug in PVP
M_D	total mass of drug
MW_D	molecular weight of drug
$MW_{N\text{-}VP}$	molecular weight of PVP monomer (N-vinylpyrrolidone)
$x_D^{CO_2}$	mole fraction of drug in CO_2
x_D^{PVP}	mole fraction of drug in PVP

Kikic and Vecchione, 2003; Kazarian and Martirosyan, 2002; Guney and Akgerman, 2002; Senčar-Božič et al., 1997).

CO_2 plays a dual role in forming drug-impregnated polymer mixtures. It plasticizes the amorphous polymer (Kikic et al., 1999; Kikic and Vecchione, 2003; Shieh et al., 1996) and it fully or partially solubilizes the drug, as illustrated in Fig. 1. For a given polymer, the impregnation of a drug within the polymer is influenced by its degree of plasticization by CO_2, which is a function of the polymer molecular weight, the drug solubility in CO_2, and the drug partitioning between CO_2 and the polymer phase. These properties are functions of temperature and pressure, and further influenced by the processing duration. If ample time is given for plasticization and drug solubilization, a drug that exhibits a high affinity for the polymer phase can quickly sorb into the polymer matrix. Alternatively, if the drug shows a greater affinity for the scCO_2 phase, impregnation of the polymer often occurs by drug deposition within the plasticized matrix upon depressurization. This could result in the re-crystallization of the solute rather than yielding the desired molecularly dispersed solute within the polymer matrix (Kazarian and Martirosyan, 2002), which can impair aqueous drug dissolution.

Results from our previous work (Ugaonkar et al., 2007), where PVP–CBZ mixtures were processed as a function of PVP molecular weight (10 and 29 K) in near- and supercritical CO_2, suggest that a combined effect of PVP plasticization and CBZ dissolution in CO_2 are critical in controlling the nature of the PVP–CBZ interaction and achieving enhanced aqueous dissolution of CBZ. In this work we have measured CBZ scCO_2/PVP partition coefficients as functions of temperature (35 °C and 45 °C) and PVP MW (10 and 29 K) using *in situ* UV–vis spectroscopy. Our objective was to examine the relationship between PVP morphology and CBZ partitioning to determine whether CBZ partitioning was driven by absorption or adsorption.

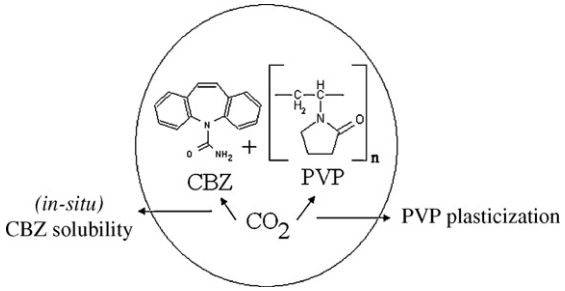

Fig. 1. Schematic of depicting the effects of *in situ* CO_2 processing of CBZ/PVP.

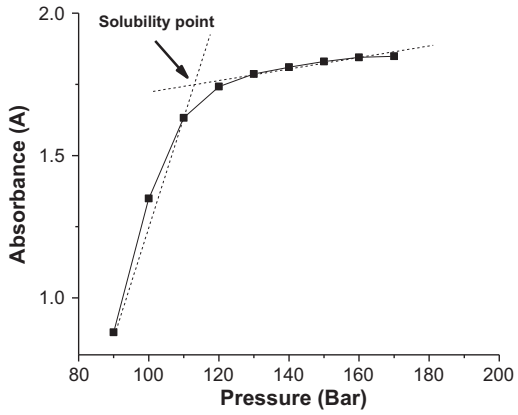

Fig. 2. Representative plot depicting the graphical method used to determine equilibrium solubility. UV absorbance of CBZ (0.2 mg in 12 ml of CO_2) is plotted as a function of pressure at 35 °C. A solubility of 4.26×10^{-6} mol/mol is taken from the solubility point intercept at the set pressure.

2. Materials and methods

2.1. Materials

Carbon dioxide (99.8% purity, bone dry grade) was procured from Airgas (East Greenwich, RI). Carbamazepine in monoclinic form was a gift from Hitech Pharmacal (Amityville, NY). Polyvinylpyrrolidone 10 K and 29 K were purchased from Sigma–Aldrich (St. Louis, MO).

2.2. CBZ dissolution, solubility, and partitioning behavior

The *in situ* high-pressure UV–vis spectroscopy technique used to measure CBZ absorbance was adapted from Ngo et al. (2001). The advantages of this technique are that it does not require external sampling, it is particularly useful for solutes at low concentrations, it eliminates the need to account for density dependent changes in solute molar absorptivities in scCO_2 (Rice et al., 1995), and it does not require prior knowledge of molar absorptivity to obtain solute concentration. The effects of temperature, pressure, and the presence of PVP on the rate of dissolution of CBZ in the scCO_2 phases are clearly demonstrated using this method.

CBZ solubility measurements were conducted by placing a known amount of dry CBZ powder in a high-pressure spectroscopic cell (~12 ml internal volume; Thar Technologies, Pittsburg, PA). The cell was sealed, placed inside a UV–vis spectrophotometer (Cary 50, Varian Inc., Palo Alto, CA), and slowly loaded with liquid CO_2 using an ISCO syringe pump (model 500D, Teledyne-ISCO, Lincoln, NE). The liquefied CO_2 was then heated to 35 °C to reach supercritical conditions. The pressure range tested was 90–200 bar. The cell was heated to the same temperature as that of the pump using heating tape and the temperature of the optical cell was controlled using a separate PID temperature control unit. Starting at a low constant pressure, the absorbance at $\lambda = 280$ nm of CBZ was measured as a function of time until equilibrium was reached. Equilibrium was taken at the point where the absorbance values at $\lambda = 280$ nm remained constant. The pressure was increased by increments of 10 bar and the absorbances were measured at each pressure until equilibrium. The final equilibrium absorbance was determined when an increase in pressure did not affect absorbance, which denoted the point at with all the CBZ in the cell was solubilized. The graphical method for determining the equilibrium solubility point from a plot of absorbance as a function of pressure is depicted in Fig. 2 for 0.2 mg CBZ loaded into the optical cell. As seen from Fig. 2, an increase in pressure causes an increase in