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Solubilities of four macrolide antibiotics in supercritical carbon dioxide and their correlations using semi-empirical models

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ABSTRACT

Accurate experimental determination of a solid drug's solubility in supercritical fluids and its correlation is crucially important to the development of supercritical technologies for the pharmaceutical industry. In the present work, the solubilities of azithromycin, erythromycin, clindamycin and clarithromycin in supercritical carbon dioxide were measured at temperatures ranging from (308 to 348) K and pressures from (12.2 to 35.5) MPa using a static method. The mole fraction solubilities ranged from 2.7×10^{-5} to 11.46×10^{-5}. The crossover region was observed for azithromycin, clarithromycin, clindamycin and erythromycin from 13.8 to 14.0 MPa, 15.0 to 15.2 MPa, 14.8 to 15.2 MPa and 16.8 to 17.1 MPa, respectively. Solubility data were correlated using four semi-empirical density-based models (Chrastil, Kumar, Johnston, Bartle and Mendez-Santiago and Teja models). The average absolute relative deviations ranged from 1.7 to 7.4; 2.07 to 8.1; 7.21 to 10.37 and from 5.13 to 9.44 for Chrastil, Bartle, K–J and M–T models, respectively. The results showed that by using three temperature-independent parameters these models can be applied for satisfactory solubility predictions at different pressures and temperatures. A comparison among the four models revealed that the K–J and Chrastil models gave much better correlation of the solubilities in comparison with other models. Using the correlation results, the heat of drug–CO_2 solvation and that of drug vaporization was separately approximated in the range of −13.56 to −23.12 and 33.07–47.65 kJ mol^{-1}. The correlation results showed good agreement with the experimental data.

1. Introduction

The macrolides are a group of drugs (typically antibiotics) whose activity stems from the presence of a macrolide ring, a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. Macrolides are large complex molecules consisting of 8- to 38-membered macro lactone with a number of stereo centers [1–3]. Azithromycin (AZI), a second generation macrolide, broad-spectrum antibacterial, has received increasing attention in recent years because of additional effects on host-defence reactions and chronic human diseases. Azithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, and thus inhibits translation of mRNA. Azithromycin is used to treat or prevent certain bacterial infections, most often those causing middle ear infections, strep throat, pneumonia, typhoid, gastroenteritis, bronchitis and sinusitis [4–7]. Erythromycin (ERY) is a macrolide antibiotic that has an antimicrobial spectrum similar to or slightly wider than that of penicillin, and is often prescribed for people who have an allergy to penicillin. For respiratory tract infections, it has better coverage of typical organisms, including mycoplasma and legionellosis. Although this medication is not particularly toxic, an overdose could cause diarrhea, stomach pain, upset stomach, hearing loss, dizziness, fainting, irregular heartbeat, etc. [8,9]. Clindamycin (CLI) usually used to treat infections with anaerobic bacteria, but can also be used to treat some protozoal diseases, such as malaria. It is a common topical treatment for acne and can be useful against some methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The most severe common adverse effect of clindamycin is *Clostridium* difficile-associated diarrhea (the most frequent cause of pseudomembranous colitis). Although this side effect occurs with almost all antibiotics, including beta-lactam antibiotics, it is classically linked to clindamycin use [10]. Clarithromycin (CLA) is a macrolide antibiotic used to treat pharyngitis, tonsillitis, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, pneumonia (especially atypical pneumonias associated with *Chlamydophila* pneumoniae), skin and skin structure infections. In addition, it is sometimes used to treat legionellosis, *Helicobacter pylori*, and lyme disease. Recently there has been research toward whether Clarithromycin can be used to effectively treat idiopathic hypersomnia [11,12].

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Supercritical fluid (SCF) technology has gained a rapid growth for the past few decades, and are presently considered as a viable environmental friendly alternative to several traditional industrial processes with conventional organic solvents [13,14]. This greener technology has several applications in food processing, pharmaceutical industries, separation processes, chemical reaction and a variety of extractions. supercritical carbon dioxide ($scCO_2$) is the most commonly used in SCF technology because it is inexpensive, nontoxic, readily available in relatively pure form, and has moderate critical constants (7.38 MPa and 304 K) [15–17]. SCFs have diffusivities between that of gases and liquids, compressibilities comparable to gases; densities comparable to liquids and in comparison with conventional organic solvents, SCFs have several interesting properties like high diffusivity, low viscosity and low surface tension [18,19]. These unique properties make $scCO_2$ an attractive solvent for many industrial separation and purification processes, especially in the pharmaceutical industry. Among the several applications of SCFs reported in the literature, particle micronization with $scCO_2$ offers a unique technology for producing micron and submicron particles with controlled size and purity. It is important to consider the phase behavior of supercritical fluid systems in selecting the most appropriate supercritical methods for pharmaceutical material separation, micronization and purification. Many recent literature have reviewed the solubility data of solid compounds in $scCO_2$ [15–17]. However, except erythromycin no solubility data of pure azithromycin, clarithromycin and clindamycin in $scCO_2$ have been listed in previous literature. Because the determination of equilibrium solubilities of solids in SCFs at different temperatures and pressures is time consuming; hence, the modeling of the solubilities is essential [15,20]. Several models have been proposed to correlate and predict the solubility of the component in SCF.

Models used for correlating the solubility data can be broadly classified as equation of state (EoS) based models and semi-empirical models. EOS models require many physical properties, which are estimated by group contribution methods leading to erroneous correlations [20–22]. To overcome this limitation, semi-empirical and empirical models, like density based models, have been proposed. Semi-empirical equations, only need available independent variables like pressure, temperature and density of pure SCF instead of solid properties [23,24]. They are based on simple error minimization. Recently, many semi empirical models such as Bartle [25], Chrastil [26], Gordillo [27], Mendez Santiago and Teja (M–T) [28], Sparks [29], Adachi and Lu [30], and Kumar and Johnston (K–J) models [31] were used for correlating the equilibrium solubility data of solid compounds in $scCO_2$.

In this study, the equilibrium solubility of AZI, ERY, CLI and CLA was measured in supercritical carbon dioxide with static method in the pressure range from (12.2 to 35.5) MPa and at temperatures equal to (308, 318, 328, 338 and 348) K. Then four semi-empirical models (Chrastil, Bartle, K–J and M–T models) were applied for the correlation and prediction of the solubilities of drugs in supercritical carbon dioxide at different conditions.

2. Experimental

2.1. Materials

HPLC grade methanol from Merck (Darmstadt, Germany) was used as received. Carbon dioxide with 99.99% minimum purity was purchased from Sabalan Co. (Tehran, Iran) and used for all extractions. The drugs, AZI, ERY, CLI and CLA (with purity of >99.5%) were obtained from the Department of Pharmaceutics of Tehran University (Tehran, Iran) and used without further purification. However, prior to the measurement of solubilities, small quantities of volatile impurities were extracted by dynamic supercritical fluid at P = 12.2 MPa and T = 308 K for a duration of 10 min at a supercritical flow rate of 0.5 mL min^{-1}. It is worthy to note that crystallization process can be applied to increase the purity of the drugs before solubility determination experiments.

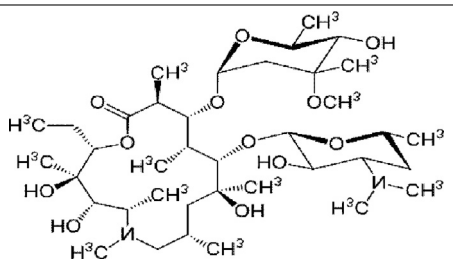
The chemical structures and physical properties of the drugs are summarized in Table 1. Maximum wavelength for each compound was obtained using a model Cecil Aquarius CE 7200 Double Beam UV–vis spectrophotometer (London, UK) with 1-cm pass length quarts cells.

2.2. Apparatus and analysis

A Suprex (Pittsburgh, PA) MPS/225 system equipped with a modified static system for solubility determination in the supercritical fluid extraction mode was used [32]. A detailed description of the apparatus and operating procedure is given elsewhere [16,32]. Solubility measurements were accomplished with a 1-mL extraction vessel in the pressure range from 12.2 to 35.5 MPa at the temperatures of 308–348 K for duration of 20 min to ensure that equilibrium condition was attained. Approximately, 300 mg of the solid solutes were mixed with some 1 g of glass beads and packed into the extraction vessel. This procedure prevents channeling, increases the contact surface between the sample and the supercritical fluid, and, consequently, reduces the equilibration time. Sintered stainless steel filters (5 μm) were used to prevent any carry-over of the solutes. The equilibrium temperature and pressure were measured with accuracies of ±1 K and ±0.1 MPa, respectively.

$scCO_2$ was pressurized and passed into the extraction vessel by a syringe pump. After equilibrium at the desired temperature and pressure, an 82.84 μL portion of the saturated $scCO_2$ was loaded into the injection loop by means of a 10-port, 2-position valve. Then, the loop was depressurized into the collection vial containing a known volume of the proper solvent (methanol) by switching the injection valve. In order to prevent solvent dispersal, a micro-adjusting valve adjusted the depressurizing rate of the sample loop.

Table 1
Structure of the drugs used and their physicochemical properties.

Compound	Formula	Structure	MW/g mol^{-1} [a]	T_m/K [b]	λ/nm [c]
AZI	$C_{38}H_{72}N_2O_{12}$		748.984	393–403 [33]	210