

Supercritical CO₂ and highly selective aromatase inhibitors: Experimental solubility and empirical data correlation

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ABSTRACT

The solubility of highly selective and potent third-generation aromatase inhibitors includes the non-steroidal agents letrozole and anastrozole and the steroid exemestane in supercritical carbon dioxide (SC-CO₂) has been investigated. The experiments were carried out using the simple and static method at pressures in the range of 12.1–35.5 MPa and temperatures ranging from 308 to 348 K. The mole fraction solubilities ranged from 0.22×10^{-5} to 1.88×10^{-4} . Solubility data were correlated using six empirical models (Chrastil model, dV–A model, K–J model, Bartle model, Yu model and Gordillo model). The results showed that these models can be applied to satisfactory solubility predictions at different pressures and temperatures. A comparison among the six models revealed that the K–J, and Gordillo models gave much better correlations of the solubility data with an average absolute relative deviation (AARD%) ranging from 0.2 to 2.3 and from 1.6 to 2.5%, respectively. Using the correlation results, the heat of drug–CO₂ solvation and that of drug vaporization was separately approximated in the range of –17.3 to –17.5 and 93.0–112.1 kJ mol^{–1}.

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1. Introduction

The bioavailability of pharmaceuticals presented in a solid formulation strongly depends on the size, particle size distribution and morphology of the particles [1,2].

Recently drug processing by using supercritical fluids (SCFs) has been proposed as an alternative to conventional processes as they allow improving the performance of these processes in terms of reduction of particle size and control of morphology and particle size distribution, without degradation or contamination of the product [3,4]. These techniques have received much attention during the last years, and their feasibility and performance have been experimentally demonstrated for many substances. One of the main pending tasks is the development of a systematic procedure for the design and scale-up of these processes [2,5–7]. Solubility data in supercritical fluids are the most important information and first step for the design of pharmaceutical processes, such as particle size reduction of drugs, preparation of drug-loaded microspheres

and microemulsions and development of drug delivery systems [4,7–10].

Non-steroidal aromatase inhibitors, such as anastrozole (ANA) and letrozole (LET) are very powerful inhibitors of oestrogen synthesis and exemestane (EXE) is a novel oral steroidal aromatase inactivator that acts by binding irreversibly to the breast cancer that is one of the most prevalent types of cancer observed in women [11]. ANA, LET and EXE have been introduced for the adjuvant treatment of hormonally responsive breast cancer in post-menopausal women [12]. They inhibit the aromatase enzyme, which is responsible for converting androgens (produced by women in the adrenal glands) to oestrogen [13].

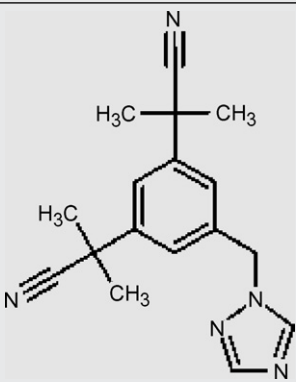
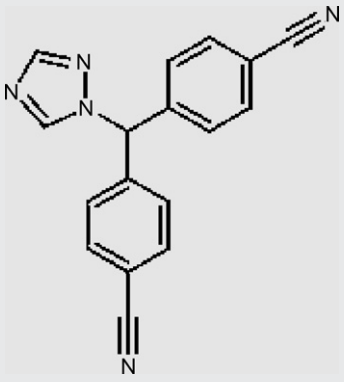
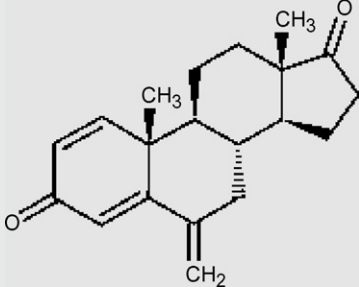
Supercritical carbon dioxide (SC-CO₂) is the greenest solvent that characterized by high solvent power, high diffusivity, low viscosity, low surface tension, and low critical temperature and pressure (304 K and 73.7 bar, respectively). It is widely and maturely applied to pharmaceutical processing due to its non-toxicity, non-residual, non-combustibility, non-explosive and ready availability at low cost [14].

Solubility is a good measurement of the interaction between species, and the accurate determination of the influence of pressure and temperature on the solubility provides insight into the influence of these variables on extraction and particle formation behavior [14,15]. Hence correlation and predictive techniques are needed to model solubility behavior. Currently used models include

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

Compound	Formula	Structure	MW (g mol ⁻¹)	T _m (K) ^a	λ _{max} (nm)	Solvent
Anastrozole	C ₁₇ H ₁₉ N ₅		293.37	354.2	226	C ₂ H ₅ OH
Letrozole	C ₁₇ H ₁₁ N ₅		285.31	454.2	246	C ₂ H ₅ OH
Exemestane	C ₂₀ H ₂₄ O ₂		296.40	428.3	246	CH ₂ Cl ₂

^a T_m is the melting point of the drug.

the application of the solubility parameter concept, equation of state methods, computer simulations, neural networks and an array of thermodynamic models, in addition to purely empirical methods to account for the solubility behavior of a solute in pure supercritical fluids.

Models derived from equations of state need complicated computational procedures that are not provided in commonly used commercial software. Also, these models employ the solute properties, such as critical properties, acentric factor, molar volumes and vapor pressure, which have not often been well established [16,17]. As an example, in a recent paper [18,19], the authors demonstrated that the large deviations between experimental and calculated solubilities are due to an error in sublimation pressure. Using 21 data sets of hydrocarbon solubilities in SC-CO₂, the average percentage error lies between 15.3 and 35.1% [18].

The empirical models are based on simple error minimization using least square method and, for most of them; there is no need to use physicochemical properties [20].

In the present study, the solubilities of ANA, LET and EXE have been determined in SC-CO₂ over a wide range of temperatures and pressures. Another goal of this work was to correlate the exper-

imental data using empirical models available in the literature [21–29].

2. Experimental

2.1. Materials

ANA, LET and EXE were supplied by Betapharma Company (Shanghai, China). All of the drugs were of reagent grade (with purity >99.5%) and thus were used without any further purification. Extra pure ethanol (Daru Pakhsh, Tehran, Iran) was used as a collection solvent. Carbon dioxide with 99.99% minimum purity was purchased from Sabalan Co. (Tehran, Iran) and used for all extractions. The molecular structures and properties of drugs used are shown in Table 1. Melting point (T_m) of the drugs was measured using a melting point measurement instrument from SANYO Gallenkamp PLC Company (Leicestershire, UK).

2.2. Apparatus and procedure

A Suprex (Pittsburgh, PA) MPS/225 integrated SFE/SFC system equipped with a modified static system for the solubility determi-

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