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Measurement and correlation study of silymarin solubility in supercritical carbon dioxide with and without a cosolvent using semi-empirical models and back-propagation artificial neural networks

Gang Yang [a,1], *Zhe Li* [a,1], *Qun Shao* [b], *Nianping Feng* [a,*]

[a] *Department of Pharmaceutical Sciences, Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, China*

[b] *Open Innovation, University of Bradford, West Yorkshire, BD7 1DP, UK*

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ABSTRACT

The solubility data of compounds in supercritical fluids and the correlation between the experimental solubility data and predicted solubility data are crucial to the development of supercritical technologies. In the present work, the solubility data of silymarin (SM) in both pure supercritical carbon dioxide ($SCCO_2$) and $SCCO_2$ with added cosolvent was measured at temperatures ranging from 308 to 338 K and pressures from 8 to 22 MPa. The experimental data were fit with three semi-empirical density-based models (Chrastil, Bartle and Mendez-Santiago and Teja models) and a back-propagation artificial neural networks (BPANN) model. Interaction parameters for the models were obtained and the percentage of average absolute relative deviation (AARD%) in each calculation was determined. The correlation results were in good agreement with the experimental data. A comparison among the four models revealed that the experimental solubility data were more fit with the BPANN model with AARDs ranging from 1.14% to 2.15% for silymarin in pure $SCCO_2$ and with added cosolvent. The results provide fundamental data for designing the extraction of SM or the preparation of its particle using $SCCO_2$ techniques.

* *Corresponding author*. Shanghai University of Traditional Chinese Medicine, Shanghai, 201203, China. Tel.: +86 21 5132 2198.
E-mail address: npfeng@hotmail.com (N. Feng).

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[1] These two authors contributed equally to this study.

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1. Introduction

In recent years, supercritical fluids (SCF) have been widely applied in the fields of pharmaceuticals, food nutrition, and industrial materials [1–3] owing to their non-toxic, non-flammable, non-explosive and recyclable properties. On the other hand, working with SCF requires high-pressure processes which imply high investment costs for the machinery and the training of skilled staff [4]. For the application of SCF in extraction, reaction, waterless dyeing processes and particle preparation [5–8], the solubility of compounds in SCF is a key parameter in process design. Since experimentally acquiring solubility data is time consuming and laborious, understanding and ultimately predicting the solubility of related compounds are very helpful in supercritical process design or election parameter [9]. Supercritical carbon dioxide ($SCCO_2$) is the most widely used SCF for its temperate critical conditions, low cost, quick diffusion, and excellent dissolving capacity [10]. There are several studies on solubility data of substances in $SCCO_2$ [11–14]. However, there have been only a few studies on the solubility of flavonoids [15,16], and no solubility data for silymarin has been analyzed thus far.

Silymarin (SM), a hepatoprotective agent obtained from the herb *Silybum marianum* (L.), is widely used in the treatment of liver diseases such as cirrhosis, hepatitis, and fatty infiltration due to alcohol and toxins [17]. A mixture of flavonolignan isomers, namely silybin, isosilybin, silydianin, and silychristin, collectively constitute SM. Among these isomers, silybin is the major component of SM, representing approximately 60–70%, and is responsible for its pharmacological activity [18–21]. Extraction of SM using $SCCO_2$ has many advantages, such as lower extraction temperature, shorter extraction time, and no remains of toxic solvents [22,23]. Moreover, $SCCO_2$ can be utilized to produce SM nanoparticles, solid dispersion and liposomes that may improve the bioavailability of SM, in which the supercritical antisolvent (SAS) and solution-enhanced dispersion by supercritical fluids (SEDS) methods were often utilized [24–26]. Thus, the solubility of SM in $SCCO_2$ is important for all of these processes. Among the factors responsible for the limited acceptance of SCF technologies, the insufficiency of supercritical solubility data has been frequently cited.

However, the measurement of equilibrium solubilities of solids in SCF at different temperatures and pressures is experimentally expensive and time consuming; hence, the modeling of the solubilities is essential. The models classically used to fit with the solubility of solid solutes are semi-empirical equations such as Chrastil [27], Bartle [28], Mendez-Santiago and Teja (MST) [29] models. Semi-empirical models only need independent variables like pressure, temperature and density of SCF instead of solid properties [30,31]. They are based on simple error minimization. Nowadays, application of BPANN has been considered a promising tool because of their simplicity toward simulation, prediction and modeling. One of the characteristics of modeling based on BPANN is that it does not require the mathematical description of the phenomena involved in the process, and might therefore prove useful in simulating and up-scaling complex systems. So, it is preferable to use a nonparametric technique such as a neural network model to make reliable prediction of silymarin solubility in the $SCCO_2$ and co-solvent system [32].

The purpose of this study is to provide fundamental data for the extraction and particle preparation process of SM using the $SCCO_2$ technology, and to find a way of predicting the solubility of SM in $SCCO_2$. During our research, the equilibrium solubility of SM was measured in $SCCO_2$ with a static method in the pressure range of 8 to 22 MPa and at temperatures equal to 308, 318, 328 and 338 K. The influence of ethanol, acetone and dichloromethane as cosolvents on solubility was also investigated. Finally, three semi-empirical models (Chrastil, Bartle, and Mendez-Santiago and Teja models) and a back-propagation artificial neural networks (BPANN) model were applied to fit with the experimental solubility data and predict the solubility of SM in $SCCO_2$ at different conditions

2. Material and methods

2.1. Materials

Silymarin and oridonin were purchased from Dalian Meilun Biotech Co., Ltd. (Dalian, China). CO_2 with a purity of 99.99% was obtained from SJTU chemical store (Shanghai, China). Ethanol, acetone and dichloromethane were purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd. (Shanghai, China).

2.2. Apparatus and procedure

The solubility of SM in $SCCO_2$ was measured by a semi-dynamic technique, as shown by the schematic (Fig. 1). Solubility measurements were taken in the pressure range of 8 to 22 MPa at temperatures of 308 to 338 K. A certain amount of SM powder was preloaded in the saturation cell and the procedure of solubility measurement was as follows: Before the experiment, CO_2 was delivered by a high pressure piston pump into the saturation cell for air removal by adjusting the pressure relief valve V_R. The high pressure CO_2 then passed into the system, heated and kept at the desired temperature with a temperature sensor. After the desired conditions were achieved, the valves V_R and V_1 were closed. The $SCCO_2$ was made to circulate in the system by the circulating pump. Based on pre-experimental results, the circulating time was set for 90 min. When the system reached equilibrium, the valves V_2 and V_C at the inlet and outlet of the 50 ml U-sample collector were closed, and the certain amount of $SCCO_2$ with dissolved solute was sealed inside. The amount of $SCCO_2$ can be calculated using the CO_2 density corresponding to the operating conditions and the inner volume of the collector. Finally, the U-sample collector was taken down, cooled, and depressurized very slowly by releasing the CO_2 into a 100 ml beaker containing 20 ml of ethanol, to precipitate the dissolved SM precipitated inside the U-sample collector. The U-sample collector was then washed with ethanol more than three times, and the washing solvent was combined with the solution of the beaker. All experiments were performed in triplicate.

The procedure of measuring the SM solubility in $SCCO_2$ with a cosolvent at a mole fraction of 0.02 was similar, except that at the beginning, a calculated amount of solvent was injected into the system in advance.