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International Journal of Pharmaceutics 308 (2006) 100–106
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Solubility of silybin in aqueous poly(ethylene glycol) solution

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Received 3 August 2005; received in revised form 21 September 2005; accepted 23 October 2005
Available online 29 November 2005

Abstract

Silybin is a main component in silymarin, which is an antihepatotoxic polyphenolic substance isolated from the milk thistle plant, *Silybum marianum*. A major problem in the development of an oral solid dosage form of this drug is the extremely poor aqueous solubility. In present work, the solubility of silybin in aqueous poly(ethylene glycol) 6000 (PEG 6000) solution at the temperature range from 293.15 to 313.15 K was measured by a solid liquid equilibrium method. The aim of this study is to investigate the possible effect of poly(ethylene glycol) concentration and temperature on the solubility of the drug, and to reveal the solubilization capacity of the polymer for the drug. Experimental results reveal that the solubility of silybin increases with the increase both in PEG's concentration and temperature. With the increase in PEG's concentration, the transfer enthalpy and entropy for silybin from water to aqueous PEG solution increases first in a positive region, and then decreases to a negative region. The transfer enthalpy is lower than the entropy term. A modified Universal Quasi Chemical (UNIQUAC) model was used to correlate solubility data.

Keywords: Silybin; Poly(ethylene glycol); Solubility; The Universal Quasi Chemical (UNIQUAC) model

1. Introduction

The solubility of biologically active compounds is often a limiting factor for their applicability. Drugs are mainly hydrophobic organic compounds. Therefore, the solubility enhancement of drugs is an important task in pharmaceutical technology, because it leads to a better bioavailability. A broad variety of solubilization methods has been developed, reaching from changes of the physicochemical parameters of the solution, including pH adjustment and temperature variation, up to the application of cosolvents and excipients, like complexing agents or surfactants (Jinno et al., 2000; Kallinteri and Antimisiaris, 2001; Verheyen et al., 2002; Viernstein et al., 2003).

Silymarin is an antihepatotoxic polyphenolic substance isolated from the milk thistle plant, *Silybum marianum*. Derivatives of milk thistle have been used as herbal remedies for almost 200 years. Silymarin was considered as a pure compound with the structure of 7-chromanol-3-methyl-taxifolin, but after the introduction of more accurate methods of analysis and separation, it was shown that silybmarin consists of a large number of flavonolignans, including silybin, isosilybin, silydianin and silychristin. Among them, silybin is the main component, and has been separated commercially as a pure substance. The molecular structure of silybin, isosilybin, silydianin and silychristin are shown in Fig. 1. Currently, the most important medicinal application of milk thistle is its use as a hepatoprotectant and as supportive treatment of chronic inflammatory liver disorders, such as cirrhosis, hepatitis and fatty infiltration due to alcohol and toxic chemicals (Kvasnicka et al., 2003). Its use has been widespread since preparations became officially available for clinical use. A major problem in the development of an oral solid dosage form of this drug is the extremely poor aqueous solubility, possibly resulting in dissolution-limited oral absorption (Li et al., 2003).

The solubility enhancement of poorly soluble compounds can be induced by changes of temperature and solvation properties using different cosolvent compositions (Viernstein et al., 2003). Among the techniques to increase aqueous solubility/dissolution rate, the formulation of solid dispersions is one of the most popular ones, although few marketed products rely on this concept. Polymers, such as poly(ethylene glycol) (PEG) (Verheyen et al., 2002; Damian et al., 2000) and poly(vinylpyrrolidone) (PVP) (Van den Mooter et al., 2001), have frequently been used as a

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doi:10.1016/j.ijpharm.2005.10.032

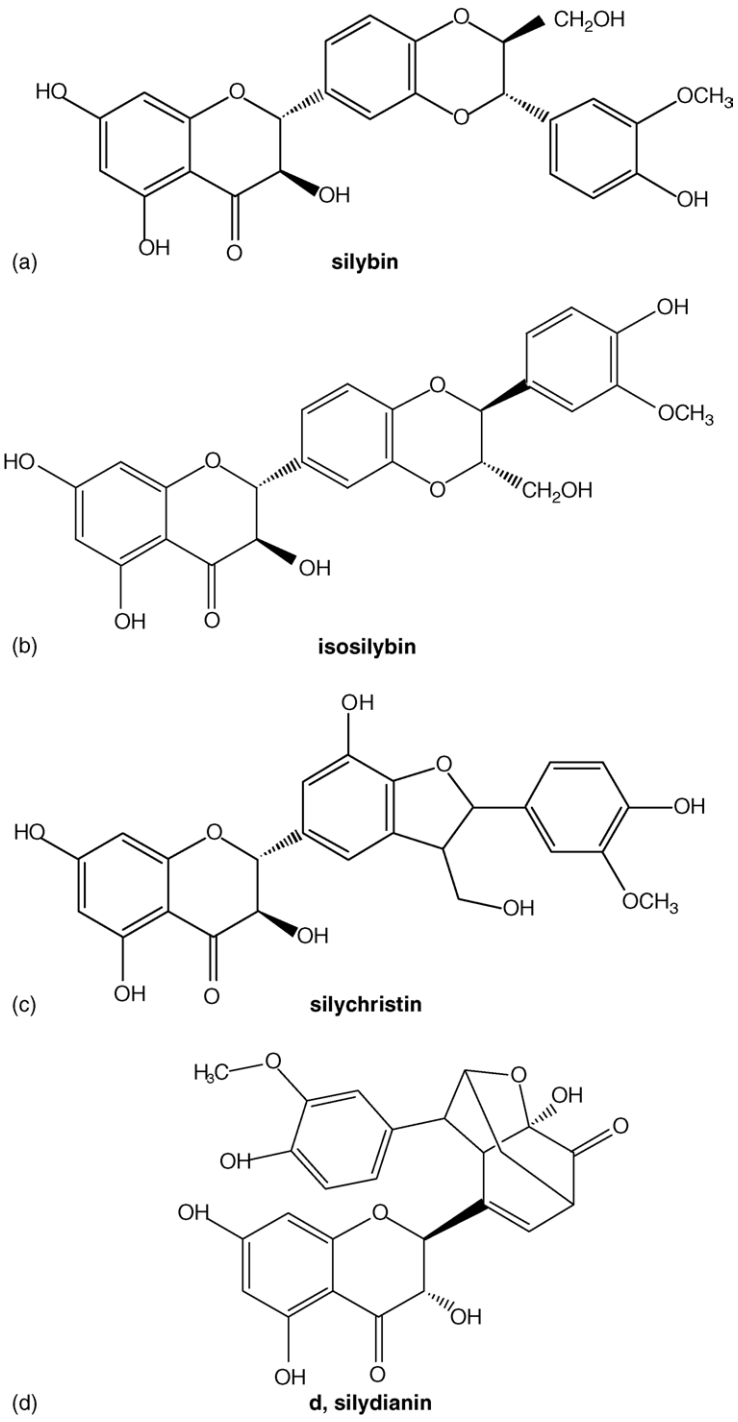

Fig. 1. Molecular structures of (a) 3,5,7-trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-2,3-dihydrobenzo[1,4]dioxin-6-yl]-chroman-4-one, silybin; (b) 3,5,7-trihydroxy-2-[2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzo[l,4]dioxin-6-yl]-chroman-4-one, isosilybin; (c) 3,5,7-trihydroxy-2-[7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-2,3-dihydrobenzofuran-5-yl]-chroman-4-one, silychristin; (d) 8-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4-(3,5,7-trihydroxy-4-oxo-chroman-2-yl)-9-oxa-tricyclo[4.3.1.$0^{3,8}$]dec-4-en-7-one, silydianin.

carrier in solid dispersion formulations. Numerous attempts to understand the physico-chemical principle behind the improvement of the dissolution of drugs by solid dispersion formulation with polymers have been reported (Verheyen et al., 2002). Equilibrium solubilities of the drug in aqueous polymer solutions of different polymer concentrations reveal the solubilization capacity of a polymer for the drug. Several approaches have been used to explain the solubility of organic compounds as well as its temperature dependence (Jouyban-Gharamaleki and Acree, 1998). Enthalpy of solution values can be measured directly from the temperature dependence of the saturation concentration (Viernstein et al., 2003; Verheyen et al., 2002; Reinwald and Zimmermann, 1998). In this work, we focus our attention on the solubilization capacity of PEG in dilute concentration region.