Contents lists available at ScienceDirect

Chemical Engineering Research and Design

journal homepage: www.elsevier.com/locate/cherd

Chiral purification of S-ibuprofen from ibuprofen enantiomers by stripping crystallization

Lie-Ding Shiau[a,b,*], *Keng-Fu Liu*[a], *Yu-Chao Hsu*[b]

[a] *Department of Chemical and Materials Engineering, Chang Gung University, Taoyuan, Taiwan, ROC*
[b] *Department of Urology, Chang Gung Memorial Hospital, Linko, Taiwan, ROC*

ARTICLE INFO

Article history:
Received 4 January 2016
Received in revised form 20 June 2016
Accepted 9 October 2016
Available online 20 October 2016

Keywords:
Crystallization
Vaporization
Purification
Thermodynamics process
Ibuprofen

ABSTRACT

A new technology, stripping crystallization (SC), is introduced in this work for chiral purification of S-ibuprofen from ibuprofen enantiomers. Basically, SC combines distillation and crystallization operated at reduced temperature and pressure for the liquid mixture feed to produce pure S-ibuprofen crystals and mixture vapors by maintaining a series of the three-phase equilibrium conditions based on the variations of the liquid composition. SC is continued until liquid is nearly eliminated. The final product only consists of S-ibuprofen crystals as all the vapors produced are removed from the system. A thermodynamic model is developed to simulate the three-phase equilibrium during the SC operation and to direct the batch SC experiments. The experiments show that, when SC is operated from 50 °C and 290 Pa to 37 °C and 148 Pa, seeding with ultrasound mixing or magnetic stirring can be efficiently employed to purify S-ibuprofen from ibuprofen enantiomers. The experimental results, including the final enantiomeric purity and recovery ratio of S-ibuprofen, are consistent with the simulation results predicted by the model.

1. Introduction

Stripping crystallization (SC) is a new technology which combines distillation and crystallization to separate the mixtures with close boiling temperatures (Shiau et al., 2005, 2006, 2008; Shiau and Yu, 2009; Shiau and Liu, 2013). No solvent is added when SC is applied to produce crystals from the liquid mixture. As opposed to the solid–liquid equilibrium involved in melt crystallization (Ulrich, 2003; Jiang et al., 2012; Micovic et al., 2013; Beierling et al., 2014), SC is operated at a triple-point condition, in which the liquid mixture is simultaneously vaporized and crystallized due to the three-phase equilibrium. By lowering temperature and reducing pressure during the operation, SC results in the formation of pure crystals, and liquid phase and vapor phase of mixtures. In essence, SC is continued until the liquid phase is nearly eliminated and only pure crystals remain in the feed.

Ibuprofen, also called 2-(isobutylphenyl)-propionic acid, is a non-steroidal anti-inflammatory drug widely used to treat headaches and minor pains (Adams et al., 1976). Although it is known that S-ibuprofen is responsible for the anti-inflammatory effects while R-ibuprofen might cause some long-term side effects (Sheldon, 1993), ibuprofen is still sold as a racemic mixture in the market due to the complexity involved in the separation of enantiomers. Various separation methods to obtain enantiopure ibuprofen have been proposed in the literature, including chromatographic separation (Peper et al., 2002; Park et al., 2008), crystallization method (Zey et al., 1992; Trung et al., 2006), enzymatic separation (Huh et al., 2006; Kim et al., 2010), and membrane separation (Cauwenberg et al., 1999; Long et al., 2005; Wang et al., 2007).

The objective of this research is to study the feasibility of SC in purification of S-ibuprofen from ibuprofen enantiomers. The effect of seeding on the enantiomeric purity and recovery ratio of final S-ibuprofen crystals is investigated. The results should provide important information in the pharmaceutical industry.

1.1. *Principle of SC*

The basic principles of the SC process can be explained by referring to the phase diagrams. In Fig. 1(a), the upper part illustrates the ideal vapor–liquid equilibrium (VLE) phase diagram for R-ibuprofen

* *Corresponding author at*: Department of Chemical and Materials Engineering, Chang Gung University, Taoyuan, Taiwan, ROC. Fax: +886 3 2118700.
E-mail address: shiau@mail.cgu.edu.tw (L.-D. Shiau).
http://dx.doi.org/10.1016/j.cherd.2016.10.019

Nomenclature

$\Delta H_{m,j}$	Heat of melting for j-component (>0), J/mol
$\Delta H_{m,R}$	Heat of melting for rac-buprofen (>0), J/mol
$\Delta H_{V,j}$	Heat of vaporization for j-component (>0), J/mol
L_n	Mass of the liquid phase out of stage n, g
P	Pressure, Pa
P_j^{sat}	Saturated pressure of the liquid of j-component, Pa
R	Ideal gas constant, 8.314 J/mol-K
$R_{B,E}$	Experimental recovery ratio, dimensionless
$R_{B,S}$	Simulated recovery ratio, dimensionless
S_n	Mass of the solid phase out of stage n, g
T	Temperature, K
$T_{b,j}$	Boiling temperature of j-component, K
$T_{m,j}$	Melting temperature of j-component, K
$T_{m,R}$	Melting temperature of rac-ibuprofen, K
t	Time, min
V_n	Mass of the vapor phase out of stage, g
W_0	Initial weight of the liquid mixture feed, g
W_f	Final weight of the liquid mixture feed, g
X_j	Mole fraction of j-component in liquid phase, dimensionless
$X_{B,0}$	Mole fraction of B-component in the liquid mixture feed, dimensionless
$X_{B,f}$	Experimental purity of B-component in the final product, dimensionless
$X_{B,S}$	Simulated purity of B-component in the final product predicted by simulation, dimensionless
Y_j	Mole fraction of j-component in vapor phase, dimensionless

Greek letters

$[\alpha]_D^{20}$	Specific optical rotation at 20 °C for the sodium light (589 nm)
γ_j	Activity coefficient of j-component in liquid phase, dimensionless

Subscript

0	In the feed
f	In the final product
j	Component j (j = A or B)
n	In stage n

(A-component) and S-ibuprofen (B-component) while the lower part illustrates the experimental solid–liquid equilibrium (SLE) phase diagram obtained by Dwivedi et al. (1992). Thus, ibuprofen can form a racemic compound, which is characterized by a crystal form in which the two enantiomers coexist in the same unit cell (Jacques et al., 1981). In VLE phase diagram, the equilibrium liquid line coincides with the equilibrium vapor line due to the same saturated vapor pressure for R-ibuprofen and S-ibuprofen. In SLE phase diagram, two eutectic points exist at T = 44.3 °C, one at $X_B = 0.18$ and the other at $X_B = 0.82$.

As pressure is reduced, SLE usually remains almost the same while VLE will be moved downward. Fig. 1(b) illustrates the solid–liquid–vapor equilibrium (SLVE) phase diagram at P = 289 Pa, which is the triple-point pressure of pure S-ibuprofen or pure R-ibuprofen. It shows the existence of two three-phase states at T = 50 °C. One is a three-phase state of pure S-ibuprofen (point b) on the right-hand side of the figure. The other is a three-phase state of pure R-ibuprofen (point a) on the left-hand side of the figure.

As pressure is further reduced, Fig. 1(c) illustrates the SLVE phase diagram at P = 252 Pa, which is lower than the triple-point pressure of pure S-ibuprofen or pure R-ibuprofen. It shows the existence of two three-phase states at T = 47.4 °C. One is a three-phase state (points b and b′) having pure S-ibuprofen crystal (point b), and liquid phase and vapor phase of mixtures at $X_B = 0.90$ (point b′) on the right-hand side of the figure. Note that the liquid composition is the same as the vapor composition at point b′. The other is a three-phase state (points a and a′) having pure R-ibuprofen crystal (point a), and liquid phase and vapor phase of mixtures at $X_B = 0.12$ (point a′) on the left-hand side of the figure. Note that the liquid composition is the same as the vapor composition at point a′. Thus, SC provides a potential method not only to purify S-ibuprofen in the range $0.82 < X_B < 1$ but also to purify R-ibuprofen in the range $0 < X_B < 0.18$. Note that cocrystallization occurs at T_{eu}.

1.2. Simulation of SC process

The SC process is simulated in a series of stage operations shown in Fig. 2, which can also be an abstract representation of a batch process in a single vessel. Each stage corresponds to a three-phase equilibrium at a given time, t_n. During the temperature-decreasing operation in a batch process, the temperature of each stage is chosen to meet $T_{n-1} - T_n = \Delta T$ for $n = 1, 2, \ldots, N$. Note that T_0 is the triple-point temperature of the mixture feed. The vapor formed in each stage is condensed to the liquid and removed while the solid and the liquid formed in each stage enter the next stage. The whole process starts from the liquid mixture feed and is usually stopped at T_{eu} when no vaporization occurs.

When SC is applied to purify S-ibuprofen from the liquid mixture feed in the range $0.82 < X_B < 1$, each stage is maintained at a three-phase equilibrium state having pure S-ibuprofen crystals, and liquid phase and vapor phase of mixtures. Due to the formation of S-ibuprofen crystals in each stage, the liquid composition of S-ibuprofen decreases during the batch process. The corresponding three-phase equilibrium condition in each stage can be determined as follows.

The SLE of S-ibuprofen in stage n is generally described by the Schroder–Van Laar equation as (Jacques et al., 1981)

$$\ln (X_B)_n = \frac{\Delta H_{m,B}}{R}\left(\frac{1}{T_{m,B}} - \frac{1}{T_n}\right) \quad (1)$$

The physical properties of S-ibuprofen and R-ibuprofen needed in the simulation are taken from Table 1. However, as there are great deviations between the calculated SLE data from Eq. (1) and the experimental SLE data obtained by Dwivedi et al. (1992), the SLE of S-ibuprofen in stage n is described by the following experimentally fitted equation as

$$T_n = -150.2(X_B)_n^2 + 302.2(X_B)_n - 102.3 \quad (2)$$

Note that the operable range for crystallization is from 50 °C to 44 °C for $0.82 < X_B < 1$ in Fig. 1(a).

As SC is operated at low pressures (<0.101 MPa), the VLE in stage n can be described by (Smith et al., 2001; Sandler, 2006)

$$(Y_A)_n P_n = (X_A)_n (\gamma_A)_n (P_A^{sat})_n \quad (3)$$

$$(Y_B)_n P_n = (X_B)_n (\gamma_B)_n (P_B^{sat})_n \quad (4)$$

As the temperature-dependent saturated vapor pressure data for S-ibuprofen and R-ibuprofen are not available, the Clausius–Clapeyron equation is adopted to describe the dependence of the saturated vapor pressure on temperature (Smith et al., 2001; Sandler, 2006), Thus,

$$\ln\left[\frac{P_j^{sat}(T)}{P_j^{sat}(T_{b,j})}\right] = \frac{\Delta H_{V,j}}{R}\left(\frac{1}{T_{b,j}} - \frac{1}{T}\right) \quad (j = \text{A or B}) \quad (5)$$

As $P_j^{sat}(T_{b,j}) = 0.101$ MPa (j = A or B), $P_j^{sat}(T)$ can be subsequently determined. Due to the structure similarity between S-ibuprofen and R-ibuprofen, it is assumed that $\gamma_A = 1$ and $\gamma_B = 1$. Besides, we have

$$(X_A)_n + (X_B)_n = 1 \quad (6)$$