L-Menthol crystal micronized by rapid expansion of supercritical carbon dioxide

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ABSTRACT

Rapid expansion of supercritical solutions (RESS) is a promising alternative for micronizing various materials including L-menthol of which dissolution would be mainly controlled by its particle size and morphology. The aim of this work is to study the effect of ethanol co-solvent, pre-expansion temperature and pre-expansion pressure on the size and morphology of L-menthol crystals micronized by rapid expansion of supercritical CO2 in prior to their microencapsulation. Calculation of L-menthol dissolution in supercritical CO2 (SC-CO2) was conducted, suggesting that the appropriate pre-expansion temperature would be below 50 °C. Verification based on FT-IR analysis suggested that the fine particles of L-menthol crystals with controlled size and morphology could be prepared by rapid expansion of supercritical CO2 without any structural change.

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1. Introduction

The dissolution of drugs has been a major concern for controllable drug delivery application, especially drugs of which dosage requirement is close to their toxicity limits [1–3]. The dissolution rate of drug can be enhanced or controlled by adjusting particle size and morphology of the drug crystals. Generally, drug particles with small size and narrow distribution are desirable for manipulating their delivering rate. However, various kinds of drugs have been subject to size reduction processes with a concern of their degradation due to the thermal stability problems [4]. So far, mechanical methods have been used for particle size reduction, resulting in very broad particle size distribution and inevitable thermal degradation [5,6]. Therefore, other alternative processes for drug particle size reduction or micronization have become an attractive issue for many research teams.

L-Menthol (C10H16OHCH3C3H7) is herbal extract which is basically composed of cyclic terpene alcohol. It has been widely used in various medication, food and esthetic applications for over a few centuries [1,7]. Normally, L-menthol is available in crystal form with the melting point in a range of 41–43 °C, depending on its size and crystallinity. It is well recognized that its high volatility and transformation to amorphous whisker are very important problems for its practical application in drug delivery system. As a result, there are requirements of other methods for micronizing L-menthol crystal without its degradation.

For a few decades, supercritical fluid (SCF) technique has been developed for a variety of particulate material treatment. Such technique could provide ultrafine particles without usage of any toxic solvents. The simplistic supercritical fluid application with sudden change of pressure is the so-called rapid expansion of supercritical solution (RESS) [8]. With the RESS process, desired solute is dissolved in SCF and then resulting solution is expanded through a nozzle to cause a sudden decrease in the solubility and hence particle formation by precipitation [4–8]. Among various fluid media, supercritical carbon dioxide (SC-CO2) shows its greatest advantages of being environmental friendly because of its low critical temperature (31 °C) and pressure (7.38 MPa). Thereby, it can be used as a clean medium which could potentially replace other traditional solvents. The key advantage of the RESS with SC-CO2 is formulation of various particulate products, which can be adjusted by tuning pressure and temperature in an autoclave before the expansion to control nucleation and growth rate of the products [8,9]. As a further development, adding co-solvent would help enhance the dissolution of solute in SC-CO2 significantly. Ethanol is an attractive solvent to use as co-solvent in the RESS process because it is inexpensive and edible. Though there would be some previous works reporting the applications of RESS
to design and control of fine particles [8–12], no clear investigation of micronization of L-menthol crystal using RESS with SC-CO$_2$ has been conducted.

The aim of this work is to study the effects of ethanol on size and morphology of the micronized L-menthol crystal under different treating temperature and pressure. It could be emphasized that the prime importance of our finding is the usage of the RESS with SC-CO$_2$ could provide L-menthol microcrystal without any change in its chemical structure. The morphological and size characteristics of the micronized L-menthol crystal which could be verified by microscopic and FT-IR analyses were discussed.

2. Experimental

L-Menthol purchased from Sigma–Aldrich was pre-ground by a mortar in prior to its classification by a screen with a standardized size ranged below 100 μ.m. CO$_2$ with a purity of 99% was received from PRAXAIR (Thailand) while ethanol with a purity of 99% for HPLC grade was procured from Carlo Erba.

With the batch RESS apparatus shown in Fig. 1, menthol and ethanol were loaded into an autoclave and then the temperature of the autoclave was increased until reaching a designated temperature then feeding of CO$_2$ was conducted until achieving a designated pressure by high pressure pump (PU-1580-CO$_2$; JASCO, Japan). The autoclave chamber was kept quiescently for 2 h in prior to spraying of the supercritical solution through a nozzle with an inner diameter of 0.3 mm. The spraying nozzle was covered with a heating coil to control the isothermal expansion condition at around 40 °C [10]. Particulate products were collected in a collecting chamber (I.D. = 6 cm.) equipped with HEPA filter to ensure the total collection of the micronized products. Those collected particulate products were characterized by an optical microscopy (CX31, Olympus), particle size analyzer (Mastersizer2000, Malvern) and Fourier-Transform Infrared spectroscopy (FT-IR, Prestige21, Shimadzu).

3. Results and discussion

3.1. Solubility of L-menthol in supercritical CO$_2$

In order to estimate the limitation of the amount of L-menthol which can be dissolved in SC-CO$_2$, a selected thermodynamic model has been applied. Sovova et al. [7] proposed the thermodynamic model for menthol solubility in CO$_2$ using Soave–Redlich–Kwong (SRK) cubic equation of state (EoS).

$$P = \frac{RT}{v - \bar{b}_{mix}} - \frac{a_{mix}}{v(v + \bar{b}_{mix})}$$

(1)

Meanwhile, the one fluid van der Waal mixing rule [11] is essentially employed for determining $a_{mix}$ and $b_{mix}$ as follows,

$$a_{mix} = \sum_{i} \sum_{j} x_i x_j a_{ij}$$

(2)

and

$$b_{mix} = \sum_{i} \sum_{j} x_i x_j b_{ij}$$

(3)

whereas,

$$a_{ij} = (a_{i} a_{jj})^{0.5} (1 - k_{ij})$$

(4)

and

$$b_{mix} = \sum_{i=1}^{N_c} x_i b_{ji}$$

(5)

According to all aforementioned equations, Fig. 2 illustrates a simulating result of amount of L-menthol dissolved in SC-CO$_2$. It is found that at a near critical temperature of 30 °C the energy binary interaction parameter, $k_{ij} = 0.127$, would attribute to the dissolved amount of L-menthol which was gradually increased with the

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**Nomenclature**

- $a_{ij}$: cross-energy parameter in SRK EoS
- $a_{mix}$: mixture energy parameter in SRK EoS
- $b_{ij}$: cross-co-volume parameter in SRK EoS
- $b_{mix}$: co-volume parameter in SRK EoS
- $k_{ij}$: energy binary interaction parameter in SRK EoS
- $P$: pressure
- $R$: universal gas constant
- $T$: temperature
- $v$: molar volume
- $x$: mole fraction in the liquid phase
- $y$: mole fraction in the vapor phase

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**Fig. 1.** Schematic diagram of RESS apparatus.
increased pressure. However, with a further increase in temperature above the critical temperature of CO₂ to 40 and 50 °C, a further increase in \( k_{ij} \) to 0.130 and 0.145 would result in the significant increase in the dissolved amount of \( \alpha \)-menthol with respect to the increase in pressure. It should be further noted that with the increased temperature a higher pressure would be necessary for achieving the homogenous dissolution stage, attributed to the increased vapor pressure of \( \alpha \)-menthol [11]. In comparison among all cases, it could be observed that almost 20% of \( \alpha \)-menthol could be dissolved in SC-CO₂ under the condition which temperature of 50 °C and pressure of 20 MPa, suggesting that there is high possibility to employ RESS-CO₂ for preparation of micronized \( \alpha \)-menthol crystal. However, because the melting point of \( \alpha \)-menthol is lower than 50 °C it is necessary to select the operating temperature of 40 °C to avoid the loss of \( \alpha \)-menthol due to its vaporization.

3.2. Batch micronization of \( \alpha \)-menthol

Pre-expansion temperature \((T_{\text{pre}})\) in range of 30–50 °C and pre-expansion pressure \((P_{\text{pre}})\) in range of 10–20 MPa were examined in a batch operation manner. A typical optical micrograph in Fig. 3(a) reveals that unprocessed \( \alpha \)-menthol crystal exhibits a smooth surface appearance with a size of larger than 10 mm. When the \( \alpha \)-menthol crystal was treated in the apparatus with SC-CO₂ without ethanol at the pre-expansion temperature of 30 °C, which is below the melting point of \( \alpha \)-menthol, the RESS process would provide needle-shaped clear crystal of \( \alpha \)-menthol as could be observed in Fig. 3(b). However, under the same treatment condition but with ethanol introduced into the apparatus, a distinctively small needle-shaped crystal of \( \alpha \)-menthol was detected as shown in Fig. 3(c). A further increase in the pre-expansion temperature to 40 °C could provide product of micronized \( \alpha \)-menthol with a similar appearance (Fig. 3(d)). These results would suggest that ethanol and pre-expansion temperature would play important roles in controlling the formation of micronized \( \alpha \)-menthol, attributed to the change in \( \alpha \)-menthol solubility in CO₂ [7,9].

Kongsombut et al. [10] reported that with introduction of ethanol, PLGA solubility in SC-CO₂ would be increased remarkably by the enhancement of solution polarity due to the engagement of ethanol molecule and PLGA. The non-polar part of ethanol could conjugate with the non-polar hydrocarbon while its hydroxyl group could interact with carbon dioxide due to the hydrogen attracting force. The increase in temperature would also increment the diffusion coefficient of both carbon dioxide and ethanol into the hydrocarbon matrix, resulting in the enhanced solubility of hydrocarbon in supercritical solution [11].

Regarding to morphology of micronized \( \alpha \)-menthol, an increase in the ethanol concentration exerts a traceable effect. The
micronized menthol changed from needle-like to quasi-spherical morphology. With the ethanol concentration higher than 10 wt%, the needle shape was hardly found but the quasi-spherical product is obtained. These results are also consistent with that of previous works [1,7]. This result would be attributed to the change of rheological property of L-menthol and ethanol mixture in SC-CO2 before its rapid expansion [12]. Though not shown here, it was found that with the higher ethanol content, L-menthol dissociation due to polarity of ethanol would hinder the formation of solidifies menthol particles after being sprayed.

As shown in Fig. 4(a), typical particle size analysis reveals that the unprocessed L-menthol has an average particle size of 16.5 μm attributed to existence of fragile portions due to its handling. After the RESs process, L-menthol samples which were subject to SC-CO2 with the absence of ethanol at the pre-expansion temperature of 30 °C exhibit a significantly smaller average size of 1.0 μm with a variance of 0.9 as illustrated in Fig. 4(b). Furthermore, when L-menthol was processed by SC-CO2 with the presence of 10 wt% ethanol at the same temperature of 30 °C, its average size was further declined to 0.4 μm with a smaller variance of 0.2 (Fig. 4(c)). However, a further increase in the pre-expansion temperature to 40 °C, Fig. 4(d) reveals that there is no significant change in both the average and variance of L-menthol crystal size. These results would be attributed to the effect of change of supersaturation of L-menthol dissolved in SC-CO2. With the presence of ethanol, higher level of supersaturation of L-menthol would be achieved, resulting in a faster formation of much smaller nuclei [1,8]. However, the increased temperature would slightly affect the dissolution of L-menthol in SC-CO2 due to the limited loading of L-menthol in the autoclave. Additional examination on the significance of temperature on processed L-menthol would be an issue to pursue further.

In order to examine the stability of L-menthol, the micronized L-menthol samples were analyzed by FT-IR (not shown here). The unprocessed L-menthol exhibits characteristic IR spectrum at wave number of 3310, 2950, 2870, 1290 and 960 cm⁻¹, which represents OH stretching, C–H stretching, CH₃ and C–H(ring), respectively [7]. Almost identical spectra could be observed from the analyses of L-menthol crystal micronized by RESs with and without ethanol incorporation. These results suggested that their chemical characteristics are not affected by the RESs treatment whether ethanol would be incorporated or not. Regarding to the designated conditions on pre-expansion temperature and pressure employed in this work which was still in a narrow range, it would be implied that the processing condition was mild enough for maintaining the internal structure of L-menthol. Nevertheless, these results would be a good evidence to support that RESs of L-menthol dispersed in SC-CO2 with or without ethanol would be a good alternative process for preparing micronized L-menthol which would be applicable to controlled drug delivering system. Based on all of our experimental results, it is clear that employing rapid expansion of SC-CO2 with the presence of ethanol could provide L-menthol crystals with a narrow size and no significant change of its composition.

4. Conclusion

This work investigates the micronization of L-menthol by using RESs process of SC-CO2 with the presence of ethanol as co-solvent. Our experimental results show that rapid expansion of L-menthol with SC-CO2 could provide micronized L-menthol with/without using ethanol co-solvent. The obtained L-menthol crystals were in a range of micro-scaled with acceptably narrow size distribution. Adding ethanol to increase L-menthol solubility in SC-CO2 could significantly affect morphology but slightly influence particle size distribution. With higher ethanol concentration, the micronized L-menthol changes from needle-like to quasi-spherical morphology with smaller particle size. Anyway, based on our FT-IR analyses, no significant change in chemical composition of the micronized L-menthol crystals was detected.

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References