MICRONISATION OF VANILLINS BY PGSS^{TM} USING VARIOUS COMPRESSED GASES

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In present work, phase equilibria of vanillin and ethyl-o-vanillin in presence of compressed CO_2, isobutane (R-600a) and some fluorinated hydrocarbons (R23, R134a, R236fa) were determined. The three phase S-L-V lines were determined using modified capillary method and the solubilities of substances in dense gasses were measured by static analytic method. Further, the micronisation of both substances using above gasses were performed by PGSS^{TM} method. In all experiments the pre-expansion pressure was 120 bar and the pre-expansion temperature was 8°C above the S-L transition of substance in dense gas at this pressure.

The results showed that the phase equilibria of vanillins in gases researched are influenced by the position of OH group, bound to aromatic ring of solute and molecular structure of gas, i.e. number of fluoro atoms. For vanillin the highest melting point depression was observed in presence of CO_2 while for ethyl-o-vanillin the melting point depression was the highest in presence of fluorinated hydrocarbons (R134a and R236fa). The solubility of both vanillins in freons researched increases with the number of fluoro atoms of gas.

INTRODUCTION

Particle design using high-pressure techniques for applications mainly in industries such as pharmaceutical, nutraceutical, cosmetic and chemical, is presently a highly interesting field of research. However, there are some problems associated with this processes, which can be avoided with the use of supercritical fluids. The applicability of various high-pressure techniques for particle formation depends mainly on the phase equilibria (solubilities between components in the system and phase transition). Considering the desired parameters a particular method is then chosen.

Generally, the PGSS^{TM} process using supercritical CO_2 gives good results for substances with relatively low melting points at atmospheric conditions and high mutual solubility with CO_2. Problems arise, when the melting point of substance is high and especially if the substance is thermolabile. Therefore, it is highly interesting to search for other alternative solvents, which are very soluble in the substance and thus decrease the melting point even more than CO_2.

In order, to verify the feasibility of PGSS^{TM} process using some fluorinated hydrocarbons instead of CO_2, the S-L phase transitions and equilibrium solubilities of vanillin and ethyl-o-vanillin in binary systems with compressed gases (CO_2, R23, R134a and R236fa) were determined and analysed in the present work. Furthermore, the equilibrium data obtained were used for development of PGSS^{TM} experiments.

MATERIALS AND METHODS

Materials

Vanillin (99 %, Cat. No. V-110-4) and ethyl-o-vanillin (97 %, cat. No. 16,098-9) were obtained from Aldrich (Seelze, D). CO_2 (4.5) was obtained from Messer (MG-Ruše, SI), trifluoromethane (R23, 2.8), 1,1,1,2-tetrafluoroethane (R134a, 2.0), 1,1,1,3,3,3-hexafluoropropane (R236fa, 2.0) and isobutane (R-600a, 2.5) were obtained from Linde (Linde plin d.o.o., Celje, SI).

Determination of melting point under pressure

The three phase S-L-V lines for vanillins under the pressure of compressed CO_2, isobutane (R-600a) and some fluorinated hydrocarbons (R23, R134a, R236fa) were determined using modified capillary method. A detailed description of the method can be found in the literature [1, 2]. The apparatus consists of 74 mL optical cell (SITEC, Zurich, CH), designed for maximum pressure 500 bar and temperature 450 °C. The cell has two sapphire windows and three openings for introducing and emptying the gas and introducing the thermocouple. The thermocouple was calibrated using pure substances with known melting points. The substance was filled in the glass capillary and put together with the thermocouple into the high-pressure cell. The gas was introduced by high-pressure pump and heated. Pressure was measured with electronic pressure gauge (Digibar PE 500 Hotting-Baldwin to ±0.1 %) and the cell was electrically thermostated by a heating jacket to ±0.5 °C. The melting of the substance in the capillary was observed by camera, connected to the computer. Temperature and pressure were registered at the beginning and at the end of melting. In screening experiments it was checked whether the observed melting temperature range depend on the mode of operation (pressure/temperature increase: "upward strategy" or pressure/temperature decrease: "downward strategy"). No hysteresis was found within experimental accuracy (±0.2 °C/±0.5 bar).

Determination of the equilibrium solubilities

A static analytical method was used for the measurements of the solubility of vanillins in different gases. A detailed description can be found in literature [3, 4]. Approximately 10 g of substance was introduced into 120 mL cell, designed for maximum pressure 350 bar and temperature 100 °C. The gas from the supply tank was cooled to a liquid state and compressed into the cell by a high-pressure pump. The content of the autoclave was mixed with a magnetic stirrer under constant operating conditions until the equilibrium was reached. After of phase separation, a sample (approximately 0.2 mL) was taken through the sampling valve into a solvent trap (ethanol), where the substances were solubilized. The expanding valve and lines were purged with 5-7 mL of solvent. Since the quantity of the sample was sufficiently small compared to the volume of the equilibrium cell, further experiments could have been done.

The concentration of the solute in ethanol was determined by UV spectrophotometer. The absorbance was measured (accurate to ±0.001) at the absorption maximum of 232 nm for vanillin and 270 nm for ethyl-o-vanillin.

**Micronisation of vanillins by PGSS^{TM} using various compressed gases**

PGSS method was used for micronisation of vanillin and ethyl-o-vanillin, using the following gases: CO_2, R23, R134a and R236fa. A detailed description of the experimental procedure can be found in literature [5]. The substance (app. 8 g) was placed into 130 mL autoclave, which was built for maximum pressure 500 bar and temperature 150 °C. The autoclave was then heated up to the operating temperature, which was 8 °C above melting point of the substance at operating pressure. The gas was introduced using high-pressure pump until the desired operating pressure was reached. The content of autoclave was mixed under constant operating conditions until the equilibrium was reached. After reaching the equilibrium the gas saturated solution was expanded through the nozzle and the gas evaporated in the expanding chamber, what caused the micronisation of dry particles of the substance [6].

CONCLUSION

Determination of melting point under pressure

The S-L phase transition of vanillin and ethyl-o-vanillin under pressure of gases (CO_2, isobutane, R23, R134a, R236fa) are presented on Figures 1 and 2. The melting point of vanillin under pressure of CO_2 decreases from 82.3 °C at atmospheric conditions to 72.5 °C at 94 bar. With further increase of pressure very small decrease in melting point could be observed (65.7 °C at 331 bar). The increase of pressure to 483.5 bar increases the melting point to 68.1 °C. From Figure 1 similar behaviour of melting point of vanillin under pressure of R23 and R134a can be observed. The S-L-V phase line for system vanillin/R23 shows temperature minimum at 74.2 °C and 152.5 bar. With further increase of pressure the transition temperature increases to 75.9 °C at 306.7 bar. The melting point of vanillin under pressure of R134a is slowly decreasing until reaching temperature minimum 73.9 °C at 92 bar. Further increase of pressure leads to increase of melting point to 76.9 °C at 304.5 bar. The S-L-V lines of vanillin under pressure of R236fa and isobutane also show temperature minimum, but the decrease of temperature is not so high. The temperature minimum of S-L-V line for phase transition of vanillin under pressure of R236fa is 77.7 °C at 13 bar and with increase of pressure to 283 bar also temperature increases to 82.7 °C. The S-L-V line for phase transition of vanillin under pressure of isobutane reaches temperature minimum at 77.3 °C and 12 bar, further increase of pressure to 306.7 bar increases the temperature to 83.0 °C.

On Figure 2 similar behaviour for S-L-V phase line of ethyl-o-vanillin under pressure of CO_2 and R23 is observed. With increase of pressure of CO_2 the melting point of ethyl-o-vanillin decreases from 67 °C at 1 bar to 42.8 °C at 109.8 bar. Above this point very small decrease of melting point is observed (to 38.6 °C at 343.5 bar). The melting point of ethyl-o-vanillin under pressure of R23 is significantly decreasing to 45.8 °C at 97 bar and further to 42.6 °C with increase of pressure to 247.5 bar. The three phases S-L-V line of ethyl-o-vanillin under pressure of isobutane shows a temperature minimum at 57.9 °C and 25.3 bar, increase of pressure to 308.5 bar increases the temperature to 62.9 °C.
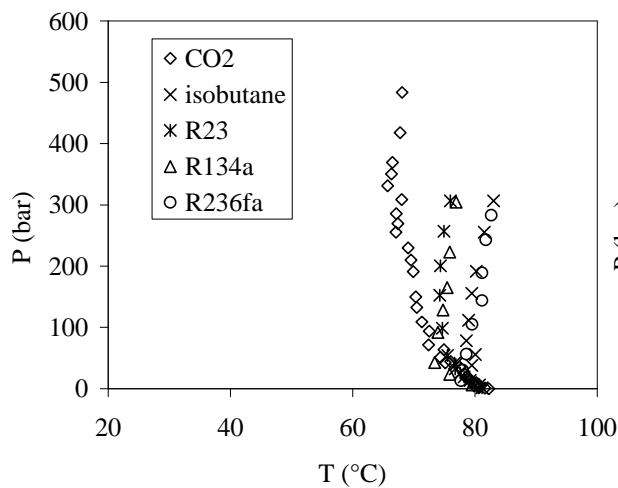
**Figure 1:** S-L phase transition of vanillin under pressure of gas.
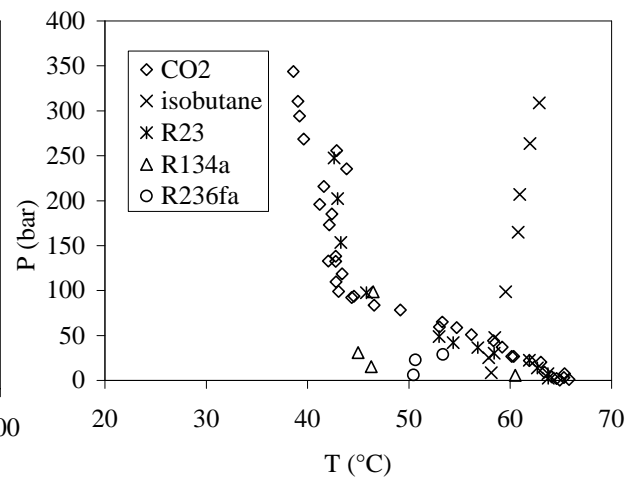
Figure 2: S-L phase transition of ethyl-o-vanillin under pressure of gas.

Determination of the equilibrium solubilities

The solubilities of vanillin and ethyl-o-vanillin at 40 °C are presented on Figure 3. The solubilities at 60 °C on Figure 4 show similar behaviour like those presented on Figure 3. From Figure 3 it can be seen that solubilities of vanillin in CO_2 and R23 are in the same order of magnitude and are higher in R134a and R236fa. The solubilities of vanillin in CO_2 are in the range from $0.014*10^{-2}$ mole fraction at 60 °C and 84.3 bar to $0.507*10^{-2}$ mole fraction at 60 °C and 276.5 bar. The solubilities of vanillin in R23 are in the range from $0.005*10^{-2}$ mole fraction at 60 °C and 42.5 bar to $0.416*10^{-2}$ mole fraction at 40 °C and 159.75 bar. The solubilities of vanillin in R134a are in the range from $0.027*10^{-2}$ mole fraction at 40 °C and 11 bar to $4.03*10^{-2}$ mole fraction at 60 °C and 200.3 bar. The solubilities of vanillin in R236fa are in the range from $1.490*10^{-2}$ mole fraction at 40 °C and 13.3 bar to $5.509*10^{-2}$ mole fraction at 60 °C and 65 bar.
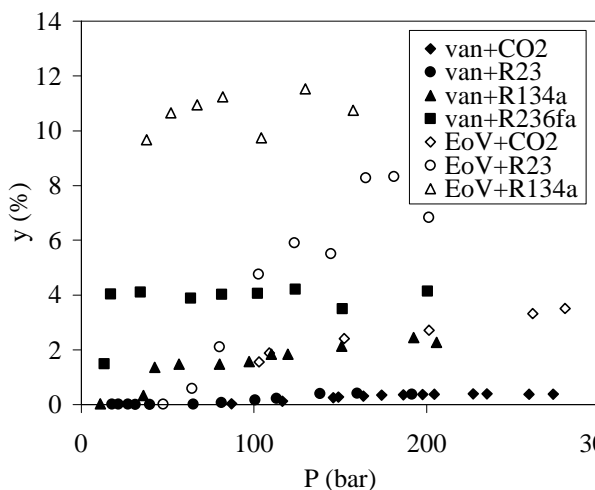
Figure 3: Solubility of vanillin (van) and ethyl-o-vanillin (EoV) at 40 °C.
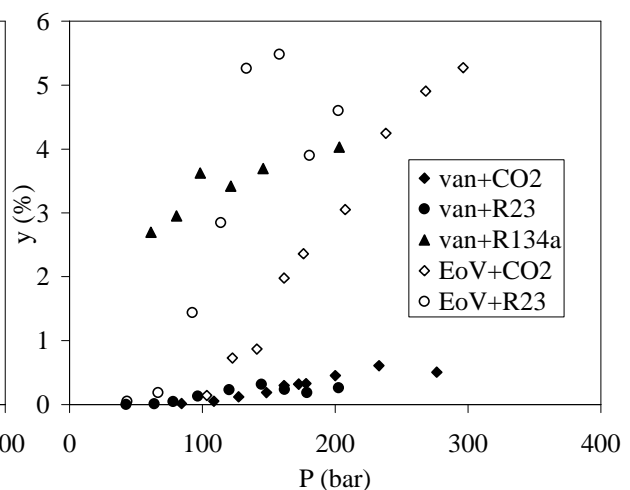
**Figure 4:** Solubility of vanillin (van) and ethyl-o-vanillin (EoV) at 60 °C.

Generally, the solubilities of ethyl-o-vanillin are higher than those for vanillin. The solubilities of ethyl-o-vanillin in CO_2 are in the range from $0.1415*10^{-2}$ mole fraction at 60 °C and 103.3 bar to $5.27*10^{-2}$ mole fraction at 60 °C and 296.3 bar. The solubilities of ethyl-o-vanillin in R23 are higher than in CO_2 and are in the range from $0.02*10^{-2}$ mole fraction at 40 °C and 47.5 bar to $8.32*10^{-2}$ mole fraction at 40 °C and 181 bar. The solubilities of ethyl-o-vanillin in R134a are even higher than those for R23 and are in the range from $9.67*10^{-2}$ mole fraction at 40 °C and 37.8 bar to $11.53*10^{-2}$ mole fraction at 40 °C and 129,8 bar.

The results of the present work show that the para position of hydroxyl group in aromatic ring reduces the solubility due to the stronger solute-solute interactions [7]. Furthermore, the intramolecular H-bonding weakens the solute-solute interactions and consequently higher solubility is observed. The solubilities of both vanillins in dense fluorinated hydrocarbons increase with the number of fluoro atoms in solvent molecule.

Micronisation of vanillins by PGSS^{TM} using various compressed gases

Figure 5 presents the SEM images of vanillin before and after micronisation. The PGSS^{TM} process changed the appearance of the particles, which are no longer regularly shaped. The original particles of vanillin are round and fibrous shaped and have wide size distribution between 190 and 310 nm. The particles resulting from PGSS^{TM} are smaller (between 60 and 120 nm) and their size distribution is narrower. Their size increase in following sequence: R134a, CO_2, R236fa and R23. The particles obtained by PGSS with CO_2 and R236fa are round shape, the particle obtained with other gases have more irregular surface. It was found out that solubility of vanillin in the gas is not directly related to the size of the particles obtained by PGSS^{TM}. It was expected that higher is the solubility of substance in gas, smaller would be the size of particle obtained. In fact, when R23 was used for micronisation of vanillin (low solubilities), the obtained particles are the biggest. However, the use of R236fa (highest solubilities) does not lead to the smallest particle size.

The original particles of ethyl-o-vanillin have conical and prolonged form with length of approximately 110 nm. The PGSS^{TM} process changed the appearance of the particles of ethyl-o-vanillin, which are no longer regularly shaped, but their size decreased to 35-50 nm. Depending on the gas, the size of the particles increases in following sequence: R236fa, R134a, R23 and CO_2. When CO_2 was used for micronisation of ethyl-o-vanillin (low solubilities), the obtained particles are the biggest. The use of R236fa leads to the smallest particle size.
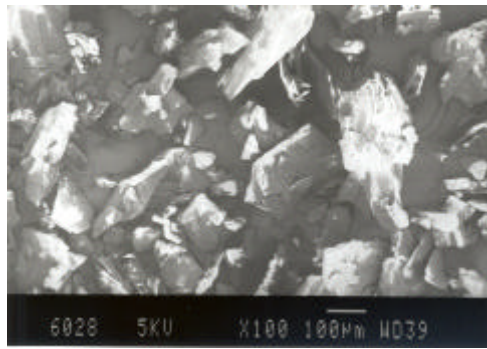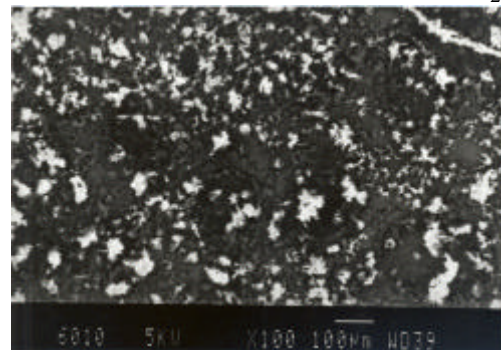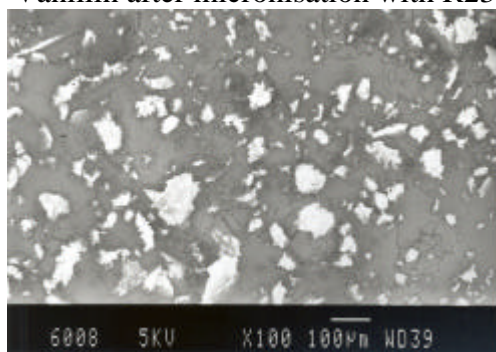
Vanillin before micronisation
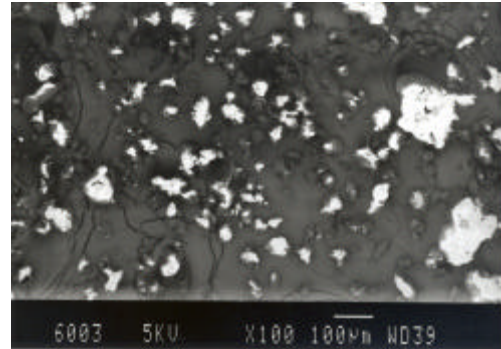
Vanillin after micronisation with CO_2
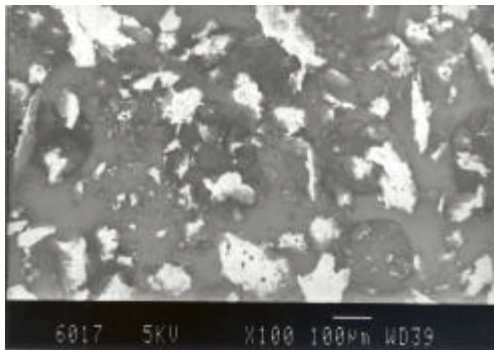
Vanillin after micronisation with R23

Vanillin after micronisation with R134a

Vanillin after micronisation with R236fa

Figure 5: SEM images of vanillin before and after micronisation with different gases. Amplification of 100 times.

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