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Diastereomeric salt precipitation based resolution of ibuprofen by gas antisolvent method

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ABSTRACT

We investigated the resolution and crystallization of ibuprofen with (*R*)-phenylethylamine based on diastereomeric salt formation using the supercritical gas antisolvent (GAS) method. Our goal was to study the effects of the operational parameters (pressure, temperature and the carbon dioxide–organic solvent ratio) during an antisolvent resolution. The diastereomeric purity of the crystalline diastereomer salt (70–80% in a single step) was not affected by either parameter in the range investigated. However, yields, and thus selectivity (a product of yield and diastereomeric purity) was strongly affected by pressure and the carbon dioxide–organic solvent ratio. Using methanol and ethanol, yield curves as a function of the molar carbon dioxide–organic solvent ratio are the same for both solvents. By selecting appropriate parameters, the crystal habit (average crystal size and crystal size distribution) can be influenced. Some crystals formed thin fibers with diameters in the micrometer range (1–3 μm), but certain parameters yielded shorter and thicker bladed crystals. At the optimal settings (10 MPa, 35 ° C, 12.3 mol/mol carbon dioxide–methanol ratio) the resolvability (0.444) slightly exceeded previously reported values using supercritical carbon dioxide, with a significant reduction in operating time.

1. Introduction

Nowadays, there is a strong demand for the synthesis of chiral compounds in optically active forms, especially in the pharmaceutical industry. Our work focused on the resolution of ibuprofen (IBU) as a pharmaceutical model compound, a widely applied analgesic which is often marketed in racemic form. The racemic form is not harmful due to the biological conversion of inert (*R*)-IBU into useful (*S*)-IBU. However, the bioavailability of pure (*S*)-IBU is 100 times higher than that of the racemic form [1].

The various supercritical antisolvent methods have long been the focus of investigation, there is advanced research into their application in the synthesis of explosives [2], inorganic nanoparticles [3] and formulation of drugs [4–6]. Several authors have prepared review articles on the subject [7–10], in which they describe the wide applicability of antisolvent methods to micro- and nano-size particles. Typically, they conducted detailed investigations of the changes in particle size, particle size distribution and morphology as a function of operational parameters (pressure, temperature and the concentration of the material to be crystallized in the organic solvent). By crystallizing ibuprofen with a carrier polymer, the preparation of micro- and nano-size particles has been successful [11,12], these works focused on increasing the dissolution rate.

Antisolvent methods have been applied to chiral resolutions in relatively few cases [13–15], and the precise effects of operational parameters during resolutions are not well known.

Ibuprofen has been applied as a model compound in all known resolution methods utilizing supercritical fluids: using supercritical extraction after vacuum evaporation, a selectivity of 0.427 has been achieved, while slow *in situ* crystallization yielded a diastereomeric purity of 60.4% and a selectivity of 0.422 [16]. The analytical scale separation of ibuprofen enantiomers can also be realized using supercritical chromatography [17]. The possibility of resolving ibuprofen using a gas antisolvent process was presented by West [18]. In our work, we utilized a batch variant of supercritical antisolvent methods, the gas antisolvent (GAS) technique, for the resolution of ibuprofen with (*R*)-phenylethylamine (PhEA). The aim of our research was a detailed investigation of the GAS method for crystallization and resolution using the IBU–PhEA system, as well as identifying and investigating the effects influencing selectivity.

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2. Materials and methods

2.1. Materials

(*R*)-Phenylethylamine (>99% GC, lot no. S19166-013) was purchased from Merck Ltd. Carbon dioxide (99.5%) was purchased from Linde Ltd. Racemic ibuprofen (≥98% GC) was purchased from Sigma-Aldrich Ltd. Ethanol and methanol (99.98%) were purchased from Molar Ltd.

2.2. Equipment

A schematic of the high pressure crystallization apparatus used for the experiments is shown in Fig. 1. Carbon dioxide is fed to the apparatus by an ISCO 260D (hereafter: ISCO) piston pump, where a needle valve (2) enables it to flow through an inlet tube directly to the bottom of the reactor. This inlet tubing is required to ensure that carbon dioxide can displace most of the reactor volume, so that during the washing phase, no bypass flow can decrease washing efficiency. The ISCO displays the pressure and volume of the carbon dioxide inside its piston, which is tempered so that its temperature is also known. The amount of dispensed carbon dioxide is calculated as the difference between the initial and final volumes, with a precision of 0.01 ml.

The high-pressure reactors were manufactured by the Applied Chemistry Research Institute of the University of Miskolc, supplemented with a porous metal filter (9) to make them suitable for crystallization. Experiments were conducted in 3 reactors with internal volumes between 36.4 and 37.7 ml. The reactors are suitable for investigating carbon dioxide media, up to 25 MPa and 100 °C. The reactor lid is equipped with pressure and temperature transducers (4 and 5, respectively), transmitting their data to a computer for recording. Stirring is accomplished by a stir bar (6) and a magnetic stirrer (7), at 1100 1/min. During depressurization, carbon dioxide flows through the outlet valve (10) into 40 ml methanol (11) in order to collect components dissolved in carbon dioxide. The reactor temperature is held at the desired value by water (8) circulated in the reactor jacket by a thermostat.

2.3. Procedure

For each experiment, the mass of IBU and PhEA required to obtain a 4 mg/ml IBU and 1.17 mg/ml PhEA concentration with respect to the reactor volume was calculated. Solutions were prepared by dissolving the materials in a calculated amount of organic solvent. In experiments studying the effect of the solvent ratio, the amount of organic solvent was varied in order to obtain different ratios. The prepared solutions were allowed to stand for 5–10 min in a sealed vial before being pipetted to the bottom of the pre-tempered reactor. The equipment was then quickly sealed and stirring was started at 1100 1/min. This was followed by slow pressurization, taking approximately 10–15 min depending on the pressure. After the desired pressure was reached, the mixture was stirred for 1 h in order to allow enough time for the diastereomers to precipitate. The reactor was then washed with carbon dioxide at constant pressure. Typically, the volume of carbon dioxide was twice the reactor volume, except in experiments studying the effect of washing duration. The exact volume was calculated from the initial and final volume of the ISCO pump, at a precision of 0.01 ml. After flowing through the reactor, the extract was trapped in methanol. The reactor was then opened and most of the raffinate was recovered in solid form, after which the reactor was rinsed with methanol in order to improve material recovery.

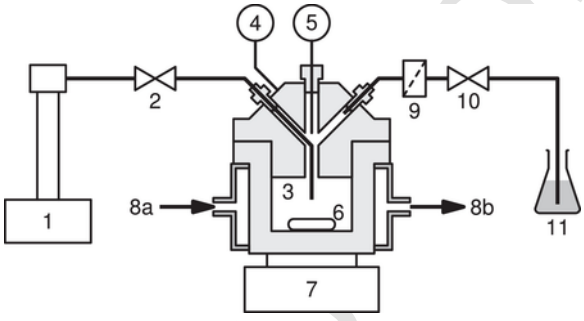


Fig. 1. Apparatus used for the experiments.

2.4. Analysis

2.4.1. Determination of enantiomeric purity using gas chromatography (GC) and capillary electrophoresis

Enantiomeric purity values were determined using chiral gas chromatography and capillary electrophoresis. The gas chromatographic method used was the same as that employed by Bánsághi [16].

Capillary electrophoresis measurements were carried out by Cyclolab Ltd. (Budapest, Hungary) using an Agilent Technologies (Waldbronn, Germany) ^{3D}CE apparatus, equipped with a diode array detector. All measurements were carried out using a silica capillary with untreated surface, with a total length of 58.5 cm, of which 50 cm was before the detector. The internal diameter of the capillary was 50 μm. The capillary was thermostated at 25 °C during measurements, with 20 kV voltage set between the electrodes. Analysis time was 12 min per sample. The separated components were detected at a wavelength of 200 nm. The continuously flowing electrolyte solution was a pH 4.5 Britton–Robinson buffer, with TRIMEB (permethylated-β-cyclodextrin prepared by Cyclolab Ltd.) as a chiral selector in 12.5 mM concentration. During evaluation of the electrophorograms, the percentage ratio of the peaks corresponding to the separated enantiomers compared to the cumulative area of all peaks was calculated.

2.4.2. Crystal structure analysis of raffinates using powder X-ray diffraction (XRD)

X-ray diffractograms were obtained using a PANalytical X'Pert Pro MPD (Almelo, The Netherlands) diffractometer, equipped with an X'celerator detector in Θ–Θ arrangement. The radiation source was an X-ray tube with a Cu anode, analyses were carried out at the Kα wavelength of Cu (1.5408 Å), applying 40 kV voltage and 30 mA current. The Kβ wavelength of Cu was filtered out using a nickel foil. Scattering angles were varied between 4° and 42°. Measurement time was chosen as 10 min in order to improve signal/noise ratio.

2.4.3. Study of raffinates with scanning electron microscopy (SEM)

Analyses were carried out on a JEOL JSM-5500LV tungsten cathode scanning electron microscope. Samples were mounted on a brass stage using double-sided adhesive carbon tape, and were sputter coated with a Pt–Au film using an Ar plasma.

2.4.4. Calculation

Raffinate yields were calculated with the following equation:

$$Y_r = \frac{m_r}{m_{r,\text{theoretical}}} \times 100\%$$

In the above equation, m_r denotes the total mass (g) of diastereomeric salts in the reactor, made up of the following components:

$$m_r = m_{\text{re}} + m_m$$

Here, m_{re} denotes the mass (g) of the diastereomeric salts recovered from the reactor as solids, while m_m denotes the mass (g) diastereomers obtained by rinsing the reactor and evaporating the solution.

The theoretical mass of the raffinate ($m_{r,theoretical}$) is the mass (g) of the calculated mass of diastereomers, i.e. the mass of diastereomeric salt equal in number of moles to the resolving agent.

Values of diastereomeric purity were calculated with the formula below:

$$\text{de} = \text{ee}_{r,\text{IBU}} = \frac{|R - S|}{R + S}$$

S and *R* denote the peak areas of (*S*)-IBU and (*R*)-IBU respectively, on the chromatograms or electrophorograms. Since the diastereomers decompose during analysis, the actual measured value is the enantiomeric excess of ibuprofen. However, since no significant amount of unreacted IBU remains in the reactor after the extraction, this value can be considered to be equal to the diastereomeric excess of the IBU–PhEA salts.

The selectivity with respect to the raffinate was calculated with the following formula:

$$S_r = \text{de} \cdot Y_r$$

In the antisolvent experiments, the ratio between the organic solvent used for preparing the initial solutions and the carbon dioxide used as antisolvent was calculated with the formula as shown below:

$$R = \frac{n_{\text{CO}_2}}{n_{\text{organic}}}$$

In this formula, $n_{organic}$ denotes the amount (mol) of the organic solvent, while n_{CO_2} denotes the amount (mol) of CO_2 measured into the reactor, calculated from the volume change of the ISCO pump as well as the pressure and temperature inside the pump.

3. Results and discussion

In GAS crystallizations, pressure, temperature and concentration are known to have significant effects on average particle size and potentially on morphology [7–9]. However, there is little information available on the effects that these parameters have on the selectivity of reactions based on (diastereomeric) salt formation. We attempted to separate and study the effects of pressure, temperature, solvent ratio and washing duration on the ibuprofen–(*R*)-phenylethylamine system.

3.1. Effect of washing duration on diastereomeric purity and selectivity

All experiments shown in Table 1 yielded dry, crystalline raffinates, indicating that the removal of the organic solvent was effectively accomplished. As the data shows, at a given pressure and temperature, the washing duration has a significant effect on both the diastereomeric excess and yield of the raffinate. This is because during a longer washing phase, relatively more unstable salt can be extracted, which improves raffinate diastereomeric purity, but decreases raffinate yield and extract enantiomeric purity. Although the individual effects on the raffinate yield and diastereomeric purity are strong, they are opposite and roughly equal in magnitude. Thus their aggregate effect on the raffinate selectivity cancels out, and values of S_r are virtually unaffected by the washing duration.

3.2. Effect of pressure and temperature

The combined effects of pressure and temperature were studied at 35, 45 and 55 °C and 10, 15 and 20 MPa, with 5.4 (V/V%) methanol content in the reactor and washing with twice the reactor volume.

Values of diastereomeric purities were between 60 and 70%, however, at 10 MPa and 55 °C, the raffinate was a wet mass/melt instead of the crystalline flakes yielded by other experiments, despite the melting point of the diastereomeric salts being 149–178 °C depending on diastereomeric purity [19]. Experiments at lower temperatures had slightly higher raffinate yields, while diastereomeric purities were not significantly affected.

Plotting the selectivity values against temperature and pressure (Fig. 2), both factors can be seen to have significant effect, with the effect of pressure being more pronounced. The small but definite effect of temperature is caused by increasing yields with decreasing temperature at constant pressure. Higher temperatures may decrease the stability of the salts, as was the case in our earlier work [16] on the *in situ* resolution of IBU with PhEA. Thus, both salts can be extracted in larger amounts during the washing phase, decreasing the raffinate yields, but – as the solubilities of both salts are affected similarly – leaving the diastereomeric purity unaffected.

The best fit for the data points contained only linear terms and no interactions, represented by the equation: $S_r = 0.7622 - 0.01592P - 0.003817T$. Raising both pressure and temperature causes a decrease in S_r, the best parameters in the investigated range were 35 °C and 10 MPa.

Since the effect of pressure is stronger than that of temperature, it was investigated in detail between 9 and 20 MPa at 45 °C, using methanol with a 5.4 (V/V%) concentration in the reaction. The di-

Table 1
Effect of washing on diastereomeric excess, yield and selectivity. 5.4 (V/V%) methanol in the reactor during precipitation.

Pressure and temperature	Washing duration ($V_{\text{CO}_2}/V_{\text{reactor}}$)	*de*	Y_r	S_r
10 MPa, 45 °C	2.0	68.4%	0.670	0.458
10 MPa, 45 °C	4.3	89.5%	0.520	0.465
15 MPa, 45 °C	2.0	67.3%	0.520	0.350
15 MPa, 45 °C	2.8	85.4%	0.384	0.328
15 MPa, 45 °C	3.1	83.6%	0.441	0.369
20 MPa, 45 °C	2.0	61.0%	0.408	0.249
20 MPa, 45 °C	3.0	84.2%	0.278	0.235

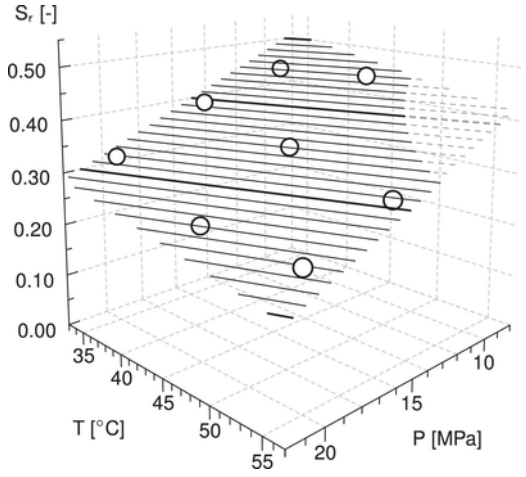
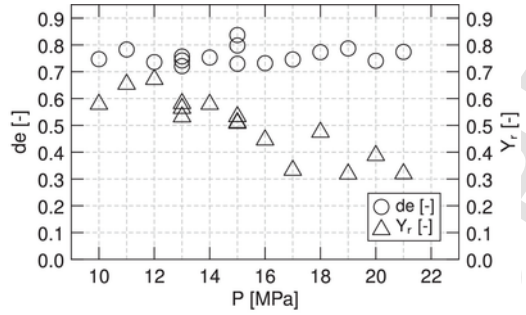


Fig. 2. GAS resolution of IBU with (*R*)-PhEA. Selectivity as a function of pressure and temperature, 5.4 (V/V%) methanol.

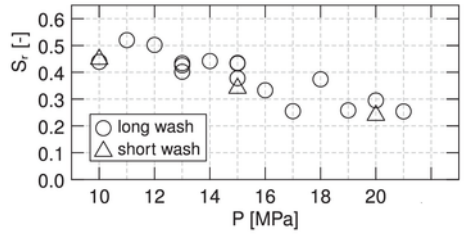
astereomeric purities and yields of the diastereomeric salts are shown in Fig. 3a, selectivities are shown in Fig. 3b. In the investigated range, pressure has no significant effect on the raffinate diastereomeric purity, while the salt yield values continuously decrease as the pressure increases.

As can be seen from Fig. 3b, decreasing the pressure causes a continuous increase in S_r. Although this trend would suggest that 9 MPa would yield the best results, experiments at this pressure suffered from poor reproducibility and non-crystalline diastereomeric salts.

The decreasing yields are probably due to the equilibrium nature of the salt formation. The precipitated salts are in equilibrium with unreacted IBU and PhEA. Increasing the pressure increases the solvent power, thus unreacted IBU and PhEA are washed out in larger quantities, causing more extensive dissociation of the formed salt. This decreases the raffinate yield as well as the extract enantiomeric purity.



(a) Diastereomeric purities and raffinate yield.



(b) Selectivity.

Fig. 3. GAS resolution of IBU with (*R*)-PhEA, at 45 °C, 5.4 (V/V%) methanol.

3.3. Effect of solvent composition

The organic solvent acts as an entrainer, modifying the solvent power of carbon dioxide and increasing solubility. In the experiments investigating the effect of pressure (Section 3.2), the volume fraction of methanol was the same for all experiments, while different pressure values were achieved by varying the mass of carbon dioxide. This caused the carbon dioxide–methanol molar ratio to vary between 10.8 and 13.9, with higher pressures corresponding to higher ratios. The experiments measured the combined effects of pressure and molar ratio, therefore, additional experiments were carried out to study the effect of the carbon dioxide–organic solvent molar ratio (*R*), independent of pressure. These experiments were carried out at 15 MPa and 45 °C using the same amounts of IBU and PhEA (150 mg and 44.2 mg, respectively).

Fig. 4 shows the effect of *R* on raffinate yield in experiments using ethanol, methanol as well as a 1:1 volumetric ratio ethanol–methanol mixture. Both solvents show a similar trend: the yield values increase towards higher values of *R* according to a saturation curve. With ethanol, there are no results above $R = 18.1$, as the solubility of IBU–PhEA in ethanol is lower than that in methanol. The raffinate yield of the experiments conducted with the methanol–ethanol mixture is between those conducted with the pure solvents.

The type of alcohol exerts a slight influence on the diastereomeric purity. Experiments conducted with ethanol had raffinate diastereomeric excess values between 79.6% and 91.0%, while experiments using methanol had diastereomeric excess values between 66.1% and 85.4%. The diastereomeric purity in the experiment with the methanol–ethanol mixture was closer to those obtained in the ethanol experiments.

During the experiments studying the effect of pressure, the effect of the carbon dioxide–methanol molar ratio could not be separated from the effect of pressure. The molar ratio was 10.8 at 10 MPa and 13.4 at 20 MPa. According to Fig. 4, *R* has a significant effect on the raffinate yields in this range and should cause them to increase significantly towards higher molar ratios. However, as Fig. 3a shows, the experiments studying the effect of pressure revealed decreasing raffinate yields as the pressure (and therefore the molar ratio) increased. This appears to indicate that pressure has an independent effect significant enough to mask the trend caused by the molar ratio.

The raffinates obtained in the experiments were studied by powder X-ray diffraction and scanning electron microscopy. Fig. 5 shows the diffractograms of 4 raffinates, exhibiting highly similar peak positions and relative peak intensities, indicating that all raffinates have the same crystalline structure.

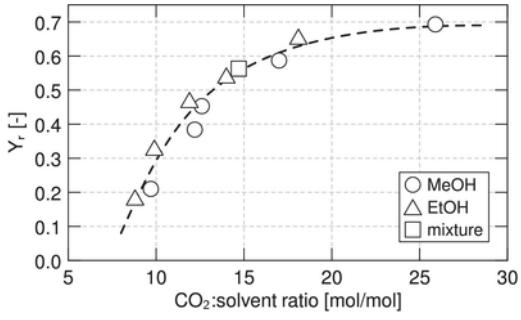


Fig. 4. GAS resolution of IBU with (*R*)-PhEA. Yields in the raffinate at 15 MPa and 45 °C.

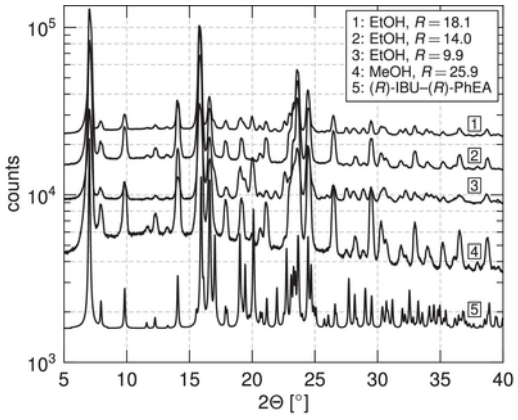


Fig. 5. GAS resolution of IBU with (*R*)-PhEA. Diffractograms of raffinates obtained at 15 MPa and 45 °C.

Fig. 6 shows SEM images from 5 raffinates: one prepared using methanol ($R = 25.9$) and four prepared with various carbon dioxide–ethanol molar ratios (R between 9.9 and 18.1). The methanol and the $R = 18.1$ ethanol experiments (Fig. 6a and c) yielded long interlocking fibrous structures. The diameter of the fibers ranges between 1 and 2 μm, while their length was around several hundred μm, however, is difficult to determine. As the value of R decreases, this fibrous structure begins to change: at $R = 11.9$ (Fig. 6d) crystals become shorter and thicker, while at $R = 9.9$ (Fig. 6e) the fibrous structure disappears and larger, bladed crystals are obtained.

Increasing the amount of ethanol decreases the available oversaturation at the moment of precipitation during the filling phase, changing the crystal structure, yielding shorter and larger crystals.

Similar results were reported by Reverchon [9], while investigating the carbon dioxide–organic solvent ratio in SAS experiments applied to the crystallization of cefonicid at 18 MPa and 40 °C with DMSO as the organic solvent. Decreasing the molar ratio of carbon dioxide from 0.98 to 0.8, the amount of recovered material decreased, the characteristic particle size increased. Further decreasing the molar ratio to 0.5 continued this trend, while yields significantly decreased.

4. Conclusions

We investigated the resolution and crystallization of ibuprofen (IBU) with (*R*)-phenylethylamine using the supercritical gas antisolvent (GAS) method. Studying the effect of pressure in detail between 10 and 20 MPa, we found that increasing the pressure decreases raffinate yields while diastereomeric purities are unaffected. From studying the ratio of carbon dioxide to organic solvent (R), it was revealed that lower values of R lead to significantly lower yields, while diastereomeric purities are once again unchanged. Compared to the effect of pressure, the effect of the carbon dioxide–organic solvent ratio is significant, but in the investigated pressure range the effect of pressure overrides the effect of the solvent ratio.

In terms of diastereomeric purity, there are no significant differences between the application of ethanol or methanol. Plotting the yield values against the carbon dioxide–organic solvent molar ratio, trends for both solvents are very similar, showing no significant effect of the solvent type on either raffinate yields or diastereomeric purities. The XRD analyses of raffinates do not reveal any differences, however, SEM images show significant discrepancies in crystal size and shape. Applying a lower carbon dioxide–ethanol molar ratio causes the structure to change from long and fibrous to short and bladed. This is likely caused by a smaller degree of oversaturation during crystal formation.

Investigating the combined effects of pressure and temperature, pressure was found to have a significant effect, while temperature was seen to have a much smaller but still definite effect. Raising either the pressure or the temperature decreases raffinate selectivity, the best results were obtained at 10 MPa and 35 °C.

Compared to earlier resolution experiments utilizing supercritical carbon dioxide, selectivities were similar [16], operational conditions were more favorable (10 MPa, 35 °C). The reaction time has been reduced from 24 to 120 h which was needed for the earlier *in situ* reaction, to 1–2 h while reaching similar selectivity.

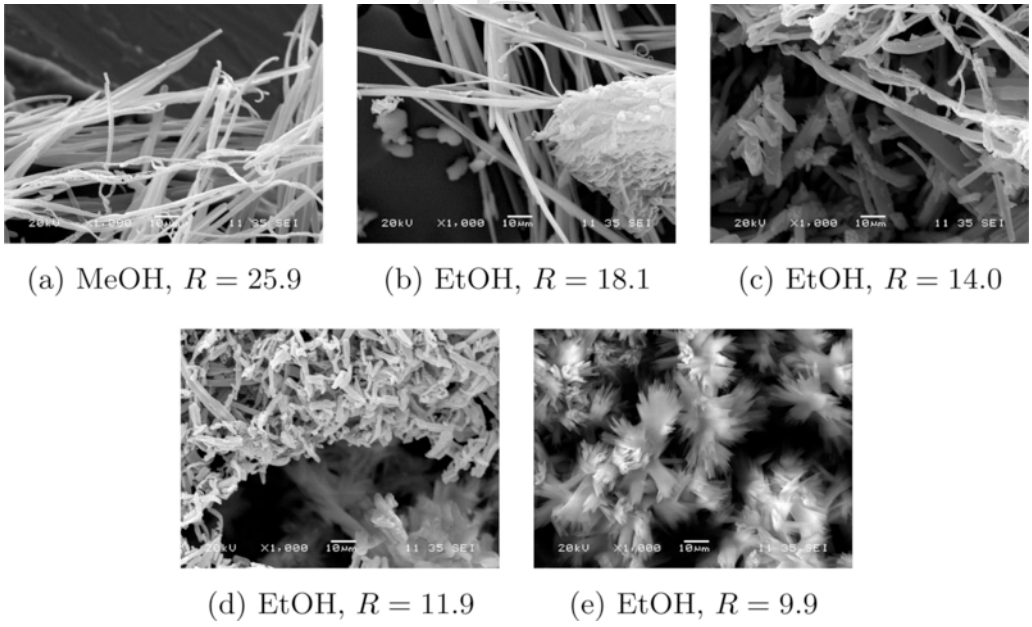


Fig. 6. GAS resolution of IBU with (*R*)-PhEA. SEM images of raffinates obtained from EtOH and MeOH at 15 MPa and 45 °C.

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