SEPARATION OF IBUPROFEN ENANTIOMERS BY DIASTEREOMIC SALT FORMATION AND PRECIPITATION IN SUPERCRITICAL CARBON DIOXIDE

S. Santarossa, A. Martín*, M.J. Cocero
High Pressure Process Group.
Department of Chemical Engineering and Environmental Technology,
University of Valladolid, Prado de la Magdalena, 47001 Valladolid, Spain
e-mail: mamaan@iq.uva.es (A. Martín)

ABSTRACT

The aim of the investigation is to study the potential of SAS crystallization process to resolve racemic ibuprofen. The resolution is performed via diastereomic salt formation and subsequent salt precipitation in a supercritical CO_2 environment. Chiral agent chosen was (S)-methylbenzylamine ((S)-MBA) and the reaction was performed in a Et-AC, DMSO or in a Et-OH, DMSO mixture. Depending on the experiment Ibuprofen and (S)-MBA are added in stoichiometric or half of the stoichiometric proportions and the reaction was performed in the vessel, in a supercritical environment or out of the vessel and the mixture injected when it was clean. Two different plants were used, in the first one two types of experiments were performed: a discontinuous process with expansion of the reacted mixture; a semi-continuous one with injection of the solution reacted or not reacted when the vessel is under pressure. In the second plant the reaction was performed in the vessel and CO_2 was saturated with Ibuprofen before been putted inside the vessel to reduce the use of organic solvents. Semi-continuos process was demonstrated to be better technology to precipitate the (S)-Ibuprofen/(S)-methylbenzylamine salt at the condition of the experiments even if the amount of precipitate is quite low. Mixture of ethyl acetate and DMSO was found to be better solvent than ethanol/DMSO to precipitate the salt because supersaturation is achieved more easily. Better results were achieved using the second plant.

INTRODUCTION

Ibuprofen is a type of NSAID (Non-Steroidal Anti-Inflammatory Drug), it contains a single chiral centre at an asymmetric substituted carbon atom and therefore exists in two enantiomeric forms. It is known that (S)-Ibuprofen is the active form while (R)-Ibuprofen is accumulated in fatty issue but nowadays it is still sold as racemate [1]. FDA, since 1992, doesn't allow new medicine to be sold as a mixture of enantiomers and in the last years the research has been focus to resolve the racemate still present in the market.
Ibuprofen is classically resolved by crystallization or liquid chromatography. One of the crystallization methods is based on the formation of diastereomic salt formed by the reaction between the isomers and a chiral agent, several patents describe this kind of cristallization (optical active compound) [2].
$ScCO_2$ is known to be an excellent media for separation avoiding use of organic solvent and giving the possibility to work at mild temperature. $ScCO_2$ cromatography was successfully applied to the resolution of several enantiomers [3, 4].

Ibuprofen was also resolved via partial diastereomic salt formation with (R)-phenylethylamine and subsequent supercritical fluid extraction of the unreacted enantiomer [5].
In a previous work, we studied the resolution of mandelic acid as a model drug by diastereomeric salt formation with (S)-methylbenzylamine ((S)-MBA) in a Sc-CO_2 environment. Different separation mechanisms were investigated, and a separation yielding a resolution efficiency with an enantiomeric excess e.e. = 63% with high recovery yields was achieved with the best process conditions [6].
In this work, resolution of Ibuprofen was investigated via diastereomic salt formation with (S)-methylbenzylamine ((S)-MBA) in a Sc-CO_2 environment. Enantiomers compound have identical chemical and physical properties in an achiral environment, while diastereoisomers have different chemical and physical properties due to the presence of more than one asymmetric centre. The two diastereomic salts formed have different melting temperature and enthalpy of fusion which result in large difference in solubility in CO_2.
(S)-MBA was selected as chiral agent because there are plenty of information about the diastereomic salt formation and the diastereomic salts. Organic solvents used were ethanol, ethyl acetate and dimethylsulfoxide. Ethanol and ethyl acetate were used for their volatile, which improves the performance of the precipitation, DMSO was used too high the solvent power because the solubility of the salt in Et-OH and Et-AC was too low.

MATERIALS AND METHODS

Materials

Racemic ibuprofen was purchased by Sigma with purity higher than 98%. (S)-Methylbenzylamine was given by Sigma-Aldrich. CO_2 was 99.95% pure, supplied by Carburos Metalicos. Organic solvents ethyl acetate, ethanol and dimethylsulfoxide (DMSO) were given by Panreac Quimica with 99% purity.

Equipments and procedure: First Plant

The precipitator is a cilindric steel vessel with a inner volume of 75 ml, pressure inside the vessel is controlled by a micrometering valve heated to prevent freezing. Two diaphragm pump are used to pump CO_2 and the solution inside the precipitator. In GAS process CO_2 is bubbled in the solution while in ASES process is charged from the top. Solution is always charged from the top (Figure 1).
Reaction between ibuprofen and (S)-methylbenzylamine was performed in a Et-AC, DMSO or in a Et-OH, DMSO mixture with a volume relation of 5:2. Depending of the experiment, Ibuprofen and (S)-MBA are added in stoichiometric or half of the stoichiometric proportions. In the case the reaction was performed out of the vessel the mixture was injected when it was clean.
Two types of experiments were performed: a discontinuous process with expansion of the reacted mixture (expansion) and a semi-continuous one with injection of the sample when the vessel is under pressure (sprayed). In the first type of experiments the solution is charged into the vessel and then the CO_2 is added to expand the solution till working pressure. When it is reached the micrometering valve is opened to drain the solution to the separation flask. In the second type of experiments compressed CO_2 is preheated at the desired temperature and then charged to the vessel, when pressure condition are reached and the CO_2 flow is stable, the

solution is sprayed into the precipitator. In the second type of experiments the reaction was performed out of the vessel or inside. In all the experiments, before depressurization, the precipitator is flushed with pure CO_2 at constant pressure in order to remove the solvent and dry the particles.

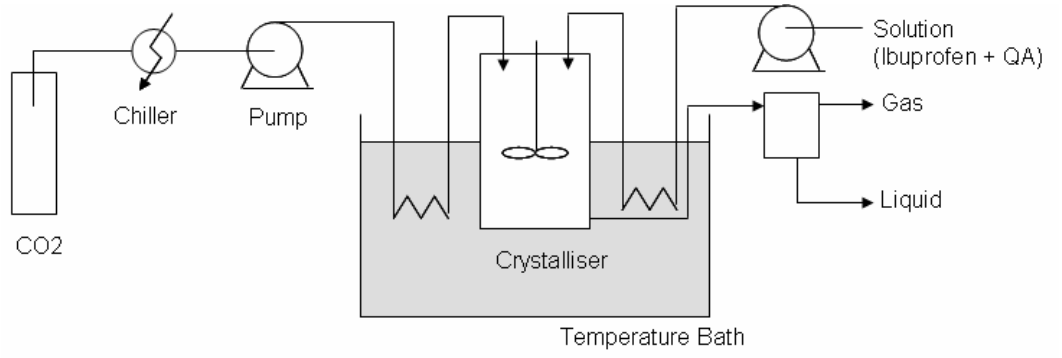

Figure 1: Flow diagram of the first plant

Equipments and procedure: Second Plant

To avoid that precipitate was wet some changes were made on the plant. Before entering in the vessel CO_2 is saturated with Ibuprofen. An extractor containing Ibuprofen supported on glass beads of 800-1200 μm of diameter was added in CO_2 line. (S)-MBA was added in Et-AC solution to avoid reaction with CO_2. A coriolis meter (Sensor MICRO Elite CMF010 NB, Transmitter MICRO Motion Elite RFT91) was used to measure CO_2 flow rate (Figure 2). Using this plant is possible to reduce the use of organic solvent because the quantity of solvent used is just the quantity necessary to dissolve the chiral agent.

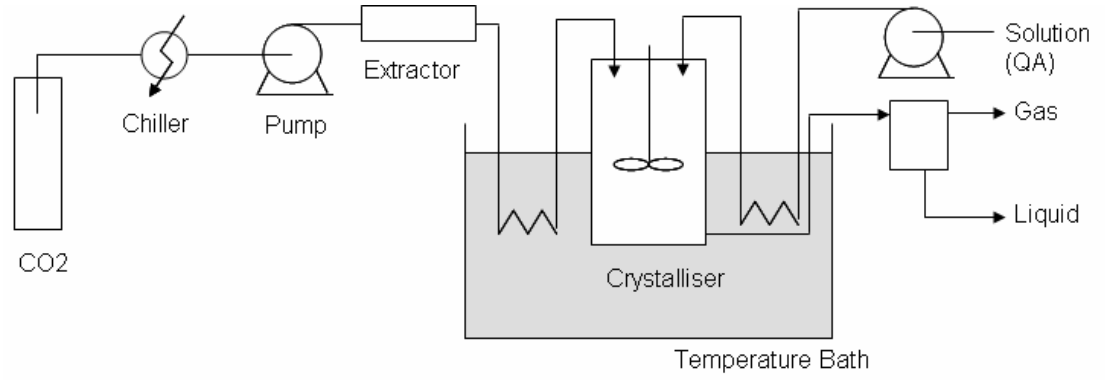

Figure 2: Flow diagram of the second plant

In all the experiments, before depressurization, the precipitator is flushed with pure CO_2 at constant pressure in order to remove the solvent and dry the particles.

Analysis

Samples of the powder collected from the precipitator were analyzed by polarimetry. Polarimeter used was a Sucromat® (digital automatic saccharimeter) with a resolution of 0.001 angular degrees and a wave length of 589.44 nn (sodium D spectral line)

RESULTS AND DISCUSSION

Fisrt Plant

Using mixture of Et-OH/DMSO there was not precipitation neither with GAS process nor with ASES process performing the reaction out or in the vessel.
Using mixture of Et-AC/DMSO there was precipitation only with ASES process performing the reaction in the vessel. Results are reported in table 1, experiments were performed with Ibuprofen's concentration of 40g/l and molar ratio of 0.5.
The results of the separation are presented in terms of enantiomeric excess and the yield of precipitation. Enantiomeric excess is defined as

$$e.e.(\%)=|(R-S)/(R+S)| \quad (1)$$

Yield of precipitation is defined as

$$Y(\%)= \text{(S)-Ibupofen in the particles / (S)-Ibuprofen in feed} \quad (2)$$

T (°C)	P (bar)	Yield (%)	e/e (%)
40	100	14.6	
40	120	4.9	22.37
40	120	9.99	35
50	120	32.97	12.76

Table 1: ASES process, reaction in the vessel, Et-AC/DMSO as solvent.

Using this plant there were some problems to dry the particles, yields were quite low and there were some problems of reproducibility, so second plant was used to continue the experiments.
The difference in precipitation between the two solvent mixture is due to the difference of diastereomic salt's solubility in the two mixture. Diastereomic salt is more soluble in Et-OH/DMSO mixture, this means that supersaturation and then precipitation is more difficult to achieve.

Second Plant

In table 2 are reported the results of experiments done, CO_2 flux was 0.36-0.42 g/s, (S)-MBA concentration in Et-AC was 25 g/l, molar ratio was 0.5. Also in this case the results are presented in terms of ee% and yield%.

T (°C)	P prec (bar)	Yield (%)	e/e (%)
35	95	12.02	27.34
35	110	18.34	34.02
35	125	21.46	37
40	95	24.20	21.96
40	110	19.02	33.46
40	125	13.03	28.1
50	95	22.44	23.9
50	110	9.56	34.24
50	125	11.49	35.76

Table 2: Experiments done using second plant, CO_2 flux 0.36-0.42 g/s, (S)-MBA concentration in Et-AC 25 g/l, molar ratio 0.5

For this kind of experiments the reproducibility was good. As expected increasing pressure there is an increasing in ee%, while temperature does not have a strong influence, the behaviour is shown in Figure 3 in terms of (S)-Ibuprofen % towards temperature and pressure.

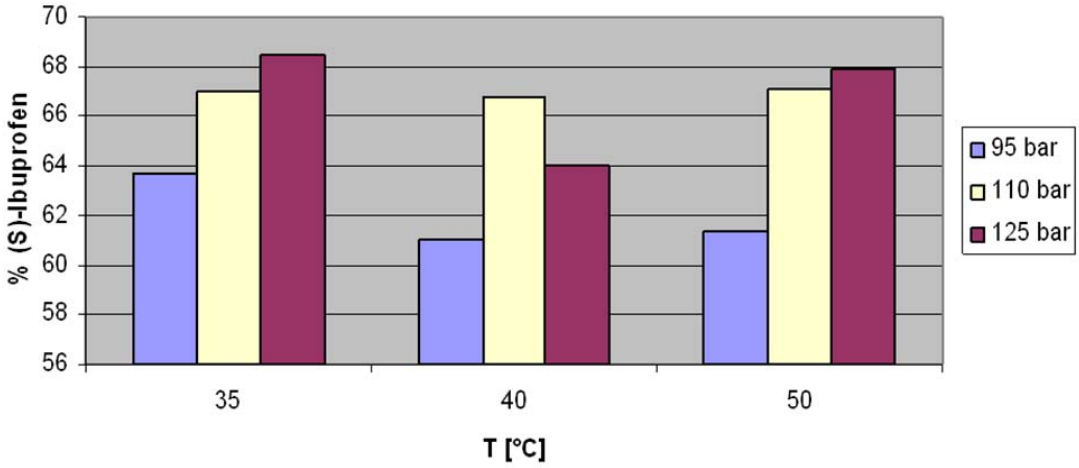

Figure 3: %(S)-Ibuprofen towards T at different pressure

These results show that there is a separation of the two enantiomers, in one step the percentage of (S)-Ibuprofen pass from 50% to 69%.

CONCLUSIONS

The separation of Ibuprofen by diastereomic salt formation and precipitation in supercritical CO2 has been successfully performed. Different process configurations and operating conditions have been analyzed. Two different plants were used, the second one was demonstrated to be better plant for the separation process. In order to enhance ee it is suggested to try to use different solvent.

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