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Gas antisolvent fractionation based optical resolution of ibuprofen with enantiopure phenylglycinol

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ABSTRACT

Optical resolution is still the dominant route to obtaining enantiopure active ingredients. The traditional methods require large organic solvent quantities and long processing times. Antisolvent fractionation with supercritical carbon dioxide offers intensified processing by drastically reducing the time requirement of the diastereomeric salt precipitation. A novel optical resolution of ibuprofen was developed and optimized with phenylglycinol as a resolving agent and gas antisolvent fractionation as the separation method. Above the critical values of certain operational parameters (carbon dioxide to methanol ratio, apparent diastereomeric salt concentration, equilibration time, the relative volume of the extracting fluid) the selectivity was roughly constant, the optical resolution is robust. The scalemic mixtures were purified by repeated resolution and enantiomeric purities above 99% were reached in three consecutive steps.

1. Introduction

There is a growing demand for technologies with low environmental impact in several areas of the chemical industry [1]. There is an urgent need, especially in the pharmaceutical industry, for innovative and productive processes in contrast with traditional batch processes [2]. Supercritical carbon dioxide [3] based methods are good candidates for replacing slower, organic solvent consuming technologies. Carbon dioxide is a non-expensive, non-toxic, eco-friendly nonpolar solvent, which can be recovered and reused by condensation and compression. One of the major advantages from the viewpoint of the pharmaceutical industry, besides the possibility of continuous precipitation, is that after depressurization a solvent free solid crystalline or amorphous powder is typically obtained. The solubility, supersaturation and diffusion controlled phenomena can be fine-tuned by pressure and temperature.

Various supercritical carbon dioxide technologies have been developed over the past decades, and many of them are applied at industrial scales. Extraction of biologically active or edible component from plants [4] is the most widely applied supercritical carbon dioxide process, but its reverse process, the impregnation of wood [5,6] or polymers [7] and textile dying has also been upscaled. The enhanced diffusion coefficients of supercritical fluids are especially useful for drug formulations [8] and chemical [9] or enzyme [10] catalyzed reactions. The first study on using supercritical fluid extraction for optical resolution was published in the mid 90's by Simándi and Fogassy [11].

Optical resolution is a process in which enantiomers are separated from their one-to-one mixture, referred to as racemate. Separating enantiomers became the focus of attention in the 1960's when the Contergan scandal highlighted that different enantiomers of pharmaceutical ingredients can have different, sometimes dangerous effects. Nowadays chiral drugs can be only marketed in their enantiopure forms unless a one-to-one mixture of the enantiomers, has the same efficiency. Racemates are obtained by non-chiral synthesis, and the isolation of single enantiomers is required as they typically have different biological effects and activities.

Since the first publication of Simándi and his group, several supercritical extraction based optical resolutions have been investigated [12–14]. The *in situ* process [15] employs carbon dioxide as the only solvent to produce optically active salts, while a two-step carbon dioxide extraction process subsequent to the melt crystallization of the diastereomers [13] is also possible.

Small, relatively non-polar molecules typically dissolve readily in supercritical carbon-dioxide. When processing an active pharmaceutical ingredient that has a larger molecular weight or a more polar character [16], it is recommended to use supercritical antisolvent technologies. With these antisolvent methods, heat-sensitive substances can be micronized to obtain large specific surface areas and thus increased dissolution rates. Antisolvent technologies, especially

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Nomenclature

Materials

CO_2	carbon dioxide

Methods

GAS	gas antisolvent
CE	capillary electrophoresis
XRD	powder X-ray diffraction
SEM	Scanning Electron Microscope

Quantities

n [mol]	molar quantity
m [g]	mass
M [g/mol]	molecular weight
R [mol/mol]	carbon dioxide-methanol molar ratio
C [mg/ml]	diastereomeric salt concentration relative to the reactor volume
t [h]	reaction time
T [°C]	experiment temperature
P [MPa]	experiment pressure
Y [-]	yield
ee [-]	enantiomeric excess
de [-]	diastereomeric excess
S [-]	selectivity
V [ml]	reactor volume

Indices

r	raffinate
th	theoretical
initial	initial optical purity
product	product optical purity

antisolvent precipitation, were first mentioned in connection with micronizing explosives [17], later the techniques were applied for inorganic salts [18] and active pharmaceutical ingredients [19]. Changes in crystal structures and morphological variations [20–23] caused by varying the process parameters were extensively studied. Multiple review articles are available in the antisolvent precipitation field [24–27].

When gas antisolvent precipitation is combined with an extraction, it is referred to as supercritical antisolvent extraction [28], or supercritical antisolvent fractionation [29]. We prefer to use the latter term.

So far, antisolvent techniques have been used for optical resolutions only in a few cases [30–37] and even less so for the enrichment of scalemic mixtures (i.e. nonracemic enantiomeric mixture, a mixture having non-zero enantiomeric excess value) [34,35].

This study presents a novel optical resolution of ibuprofen (IBU) with optically active (*S*)-2-phenylglycinol (PhG).

Ibuprofen is a non-steroidal analgesic and a widely used pharmaceutical model compound used for research purposes. Ibuprofen's (*S*) enantiomer is approximately 3 times more effective than its racemic form [38]. Optical resolution of ibuprofen has already been demonstrated with multiple technologies, such as crystallization from organic solution [39], making it a good basis of comparison when developing a resolution system. The resolution of ibuprofen was investigated and recommended with several different resolving agents, for example ephedrine [39], phenylethylamine [40] or lysine [41]. Resolution of ibuprofen with (*S*)-phenylglycinol was previously investigated by the *in situ* method, without any success [42]. However, structural similarities [43] and differential scanning calorimetry (DSC) analysis results [44] suggest that (*S*)-phenylglycinol could be a suitable resolving agent. The efficiency of an optical resolution in general is strongly influenced by the properties of the solvent and the conditions under which the solid phase is formed. Taking the DSC results and the typical sensitivity of optical resolutions into account, we were motivated to develop a suitable optical resolution method for ibuprofen with phenylglycinol, applying an antisolvent approach.

2. Materials and methods

2.1. Materials

Racemic ibuprofen (2-(4-isobutylphenyl)propanoic acid) (≥98%), (*S*)-ibuprofen (≥98%) and (*S*)-2-phenylglycinol (≥97%) were purchased from Tokyo Chemical Industry Ltd. Carbon dioxide (≥99.5%) was purchased from Linde Gas Hungary Co. Cltd and was used freshly distilled. Methanol (≥99.5%) was purchased from Merck Ltd.

2.2. Gas antisolvent fractionation procedure

The optical resolution was performed by the half-molar-equivalent method (Fig. 1.). According to the DSC thermograms, (*S*)-PhG forms a more stable salt with (*S*)-IBU than with (*R*)-IBU [44], because the

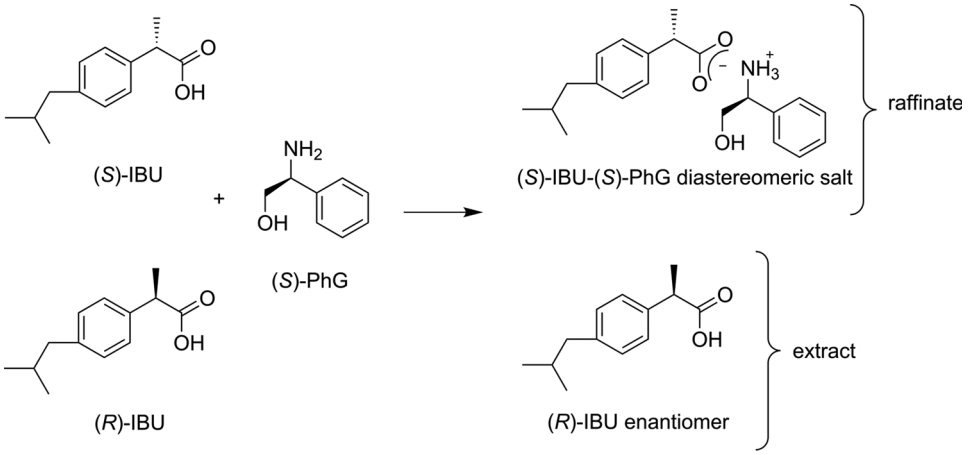

Fig. 1. Reaction scheme of the optical resolution of ibuprofen with (*S*)-phenylglycinol.