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Racemic resolution of propranolol in membrane contactors: Modelling and process optimisation

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Abstract

This work reports the study of the chiral resolution of propranolol, an amino-alcohol with proven efficacy in the treatment of hypertension, ischemic heart disease and arrhythmia. Among all β-blockers, propranolol was selected also due to the distinct properties of its enantiomers.

Extraction and stripping kinetic studies were performed using a tubular module contactor, with ceramic ultrafiltration supporting membranes. Three different configurations were evaluated in terms of enantio-selectivity and enantiomeric excess of the desired enantiomer: (1) single extraction; (2) simultaneous extraction, where each enantiomer is preferentially recovered to a different extraction phase; (3) simultaneous selective extraction and stripping of a target enantiomer.

The kinetic model developed, comprising an equilibrium modelling of the extraction process and differential mass balances in pseudo steady-state, fully describes the overall process. Moreover, the model allowed the optimisation of the operating conditions and enables to predict the optimum combination of module configurations in order to maximise the enantiomeric excess.

Keywords: Chiral separation; Racemic resolution; Enantio-selective extraction; Propranolol; Membrane contactors; Modelling

1. Introduction

The synthesis industry is frequently challenged by difficulties to perform racemic resolutions, an issue of major importance as in many cases just one of the enantiomers of the mixture presents activity, whereas the other is inactive or presents adverse secondary effects. The most well known case occurred in the 60's with thalidomide, whose (*R*)-enantiomer possesses excellent analgesic properties while its (*S*)-enantiomer is teratogenic.

This issue has been receiving increasing attention from authorities, such as the Food and Drug Administration (FDA). In 1987, the FDA [1] published guidelines regulating the submission of new drugs, imposing pre-clinical and clinical studies to both enantiomers of a racemate. In 1989, a FDA commission published the *Stereoisomer Drug Policy* [2]. This policy imposes that the pharmaceutical companies must provide clear justification for the approval of racemates. The Japanese authorities also approved similar regulations [3].

From the scientific point of view, this issue is also of most relevance, as is demonstrated by the award of the Nobel Prize in Chemistry to K. Barry Sharpless, William S. Knowles and Ryoji Noyori in 2001, for the development of catalytic asymmetric synthesis.

For resolution of racemic mixtures the most used method is diasteriomeric crystallisation [4]. However, this technique usually requires many steps, increasing the complexity of the process and leading to a considerable loss of product. To avoid these problems asymmetric synthesis and kinetic resolution are usually considered as viable alternatives [5]. However, these processes require the development of an appropriate path for each product, leading to considerable costs and long development periods. Analytical resolution methods, although available for practically all the racemates, are usually not adequate for large-scale production. Liquid–liquid extraction, usually preformed by dispersion of one immiscible phase in the other, may constitute a good alternative. This dispersion creates a high interfacial area thus considerably increasing the rate of extraction.

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More recently, membrane processes have been pointed as promising alternatives to conventional resolution methods [6,7]. The first attempts recurred to liquid membranes' configurations [8] and since then other studies have been reported, using bulk liquid membranes [9,10], supported liquid membranes [11,12], emulsion liquid membranes [13], liquid membrane contactors [12,14–16] and carrier membranes [17–22]. Most of the studies performed are focused on the racemic resolution of amino acids and their derivatives.

Liquid membrane extraction has received considerable attention due to the advantages of combining liquid–liquid extraction with membranes in one single process. Some of the potential advantages of these processes are [23]:

(1) The possibility of performing simultaneous extraction and stripping, with a single equipment, allowing the reduction of investment costs.
(2) Highly selective separations can be achieved, by using an excess of complexing agent, which is very valuable for low solute concentrations.
(3) It is only required a small amount of extracting agent because, as the reaction is reversible, it is continuously regenerated.

Among the liquid membrane processes, membrane contactors have gained ground to supported liquid membranes (SLM) as they allow overcoming some of the problems of the SLM related with their instability, due to loss of solvent from the membrane pores, keeping their advantages. Thorough descriptions of the applications of membrane contactors can be found in the literature [24–27].

This work discusses the racemic resolution of propranolol, an amino-alcohol β-adrenergic receptor antagonist drug efficient in the treatment of hypertension, ischemic heart disease and arrhythmia. Among all β-blockers, propranolol was selected also due to the distinct properties of its enantiomers: (*S*)-propranolol is much more potent than (*R*)-propranolol and mediates the antiarrhythmic and antihypertensive activity of the racemic mixture, whereas only (*R*)-propranolol appears to be beneficial in treating angina pectoris [28].

Previous work [29] has shown that di-alkyltartrates exhibit chiral discrimination towards the corresponding chiral β-amino-alcohol in the presence of boric acid, by the formation of a non-polar tetrahedral complex, soluble in organic phase, between the enantiomer of the amino-alcohol, boric acid and the corresponding tartrate enantiomer.

Given the highly promising results obtained by Abe et al. [29,30], in our previous work [31] we evaluated the impact of the most relevant physico-chemical variables, such as the character of the extraction solvent, the concentration of reagents propranolol, boric acid and tartrate, and the pH of the aqueous phase. The two-phase equilibrium studies performed allowed modelling of the extraction process and optimising the chemical conditions that maximise the enantiomeric excess (ee). It was concluded [31] that for organic/aqueous volume ratios (V_{org}/V_{aq}) higher than 0.075 the enantiomeric excess was maximum for a tartrate concentration of 50 mmol/dm^3, a boric acid concentration of 100 mmol/dm^3 and for a pH of 5.2. These conditions will be used during the kinetic experiments discussed in this work.

Two tubular contactors will be used, allowing the study of three different configurations: (1) single extraction; (2) simultaneous extraction, where each enantiomer is preferentially recovered to a different extraction phase; (3) simultaneous selective extraction and stripping of a target enantiomer.

These three configurations will be evaluated considering two parameters: (1) the enantio-selectivity (α), a measure of the separation efficiency of the process and (2) the enantiomeric excess (ee), a measure of the purity of the product. The product recovery ratio (rec, defined as the ratio of the quantity of enantiomer recovered over its initial quantity) will be also referred as an indicator of the productivity of the process.

2. Experimental

2.1. Materials

The feed solutions, containing 100 mM of boric acid (Riedel-de Haën AG, Germany) were prepared from propranolol hydrochloride racemates (Aldrich Chemical Co., USA), with concentrations up to 10 mM, buffered at pH 5.2 with acetic acid (Merck, Germany), 29.5 mM, and sodium acetate (Merck, Germany), 111 mM.

The extractants (*R*)- and (*S*)-di-*n*-dodecyltartrate, were prepared as described in Abe et al. [29], from tartaric acid (Aldrich Chemical Co., USA) and dissolved in chloroform. For the re-extraction step, a formic acid (Merck, Germany) solution 0.1 M was used.

For the three set-up configurations tested, the tubular ceramic membranes used (reference M2 CAR02040) were supplied by Carbosep (Orelis, France). The active layer of these membranes consists of a thin ZrO_2–TiO_2 layer deposited on the internal surface of a carbon support. The membranes have internal and external diameters of 6 and 10 mm, respectively, 600 mm of length and a molecular weight cut-off of 15 kDa.

Ceramic membranes were chosen in order to avoid compatibility problems with the organic solvent used. Tubular membranes were selected as to provide good hydrodynamic conditions of the flowing phases.

For the single extraction experiments, the membrane housing used was supplied by Orelis (France), with 11 mm of inner diameter and 600 mm of length. For the simultaneous extraction and simultaneous extraction and stripping a second housing was built in stainless steel, with 25 mm of inner diameter and 600 mm of length.

2.2. Kinetic experiments

For the kinetic experiments, two different module configurations were used: one with a single membrane and another where the module contained two tubular membranes. While the first configuration only allows to circulate two streams simultaneously, one aqueous and the other organic, the second configuration allows to combine three streams, one inside each membrane and a third one in the shell side of the module. This