Aqueous biphasic systems based on chiral ionic liquids as platforms for chiral resolution

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The production of enantiopure drugs is a major challenge for the pharmaceutical industry [1]. Considering the increased difficulty in the production of pure enantiomers by direct synthesis, the synthesis of racemates followed by their chiral resolution is a simpler, more flexible and cheaper alternative. This approach is commonly achieved by chromatography and crystallization, yet other methods, such as enantioselective liquid-liquid extraction can provide a better balance between costs, operational versatility and scale-up opportunities. Aqueous biphasic systems (ABS) are good candidates to turn enantioseparations not only into more biocompatible but also more versatile approaches [2]. Ionic liquids are alternative solvents with an enormous degree of structural diversity, allowing the design of task-specific solvents and, by their introduction in ABS, of highly performant extraction/separation approaches. Being made up of ions, if one can select/develop chiral structures to function as cations, anions or both, the opportunity of creating chiral ionic liquids (CILs) emerges [3,4].

This work proposes the development of a versatile enantioseparation platform for the chiral resolution of racemic mandelic acid. ABS using CILs simultaneously as chiral selectors and phase forming agents is proposed. Five different ABS were studied to determine the CIL structure and salt role on the ABS aptitude to separate mandelic acid enantiomers. Optimization studies were further pursued, as representative CIL-based ABS were employed in optimization studies, where the mandelic acid content, temperature, tie-line length, salt and phases weight ratio were studied. The influence of these parameters is shown to be highly dependent on the CIL-based ABS, nevertheless the results attained suggest that the key driving the enantioseparation in these ABS is a combination of the enantiorecognition ability of a given CIL with the solubility of mandelic acid in the corresponding CIL-rich phase. By closely manipulating the two conditions of the purification process, good enantioselective separations can be achieved.

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