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Separating closely resembling steroids with ionic liquids in liquid–liquid extraction systems

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ABSTRACT

Separation of steroids by liquid–liquid extraction with ionic liquids (ILs) as solvent was studied both experimentally and by simulation using a model mixture of progesterone and pregnenolone. The studies involved a solvent screening using COSMO-RS software for estimation of progesterone solubility. An experimental compatibility study of several solvents with reasonable progesterone solubility with several ILs. The results showed *tert*-butyl methyl ether (TBME)–butyl methyl imidazolium tetrafluoroborate (BMIM BF_4) as the most promising solvent combination. Next, equilibrium partitioning of both progesterone and pregnenolone in this solvent combination was determined experimentally. Fixed bed studies using solvent impregnated resin (SIR) obtained by impregnation of BMIM BF_4 in silica showed that it is feasible to obtain highly pure progesterone in such a process. However, the yield was far from quantitative and thus a fractional extraction process was studied by simulation of a counter current extraction process. The simulation study showed that with fractional extraction highly pure progesterone (excess >0.99) can be obtained at a yield of >0.95 when a minimum of 24 equilibrium stages are applied.

1. Introduction

Steroids are an important class of drugs due to their biological activity [1]. The characteristic of the molecular structure of steroids is the rigid four ring backbone [1], and due to their structure, steroids are hardly soluble in water. Also for most other solvents, the solubility is rather low [2]. The low solubility is challenging for any process, and makes the choice of solvent an important task in the process development. Productions often include intermediates with similar structures, and purification of the desired steroid can be a difficult task. Typically, crystallization is the method of choice in the pharmaceutical industry [3,4]. Not all species do crystallize, and alternative separation technologies are desired. Simulated Moving Bed chromatography (SMB) is one approach [5–8], but although the technique is highly sophisticated, solvent use is very large compared to liquid–liquid contacting methods. Furthermore, the stationary state can be highly expensive. Liquid–liquid contacting methods are scalable, and well-developed chemical engineering design rules may be applied, resulting in relatively easy scaling as compared to more complicated SMB technology. Therefore, we suggest to use methods based on liquid–liquid contacting for the separation of closely resembling steroids. In this work the use of solvent impregnated resins (SIRs) and fractional multistage extraction was studied as methods for fractionation of a model mixture consisting of 90% progesterone and 10% pregnenolone (see Fig. 1). This mixture reflects a real industrial case, as progesterone is industrially produced through the intermediate pregnenolone.

For both SIRs and fractional extraction, the choice of the solvent combination is important, and since both components have a negligible water solubility, traditional aqueous-organic biphasic systems are not optional. Therefore, first the solubility of progesterone in organic solvents will be considered, after which for solvents with reasonable solubility the solvent combinations with ionic liquids will be studied. Room temperature ionic liquids, salts that are liquid at room temperature, could be highly interesting for this specific task, as they can be hydrophobic but still show a large miscibility gap with many organic solvents. The organic solvent of choice should not have a too high boiling point, as the most logical recovery of the extracted steroid is through back-extraction with the same solvent followed by solvent evaporation.

In this study, selection of a solvent system is followed by equilibrium distribution measurements of the steroids in competitive fashion, i.e. the distribution of both pregnenolone and progesterone was measured in mutual presence. After the equilibrium

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Nomenclature

Symbols and abbreviations

c	concentration [mM]
D	diffusion [m^2/s]
d_p	pore diameter
ε	porosity
F	feed flow [L/s]
FREX	fractional extraction
K_D	distribution factor
k_L	mass transfer coefficient
ND	not determined
Preg	pregnenolone
Prog	progesterone
q	loading in IL phase [mmol/L]
q^*	loading in IL phase that would be in equilibrium [mmol/L]
S	solvent flow [L/s]
SMB	Simulated Moving Bed
u	interstitial velocity [m/s]
W	wash flow [L/s]
y	yield [–]
z	position in the bed

Superscripts and subscripts

ax	axial
b	bed
eff	effective
Extr	extract phase
IL	ionic liquid phase
LDF	linear driving force
Prog	progesterone
TBME	*tert*-butyl methyl ether phase

measurements, two processes are considered as options to scale up the separation of the steroids. Because of the closely resembling structures, it was not likely that a high selectivity would be observed in the separation, and for that reason fixed bed operation using SIRs was also considered. SIRs may be interesting as a hybrid between adsorption and liquid–liquid extraction [9–14], and may allow many equilibrium stages, where in traditional liquid–liquid extraction the number of stages is limited [15,16]. Furthermore, in situations where foaming or emulsification is an issue, the use of SIRs could be applied to avoid these problems [15,16]. The use of such a SIR-based process was compared with a multistage fractional extraction process in traditional liquid–liquid fashion. In multistage fractional extraction, the mixture of species that needs to be separated is fed as a solution to the feed stage, which typically is not the first stage, and in symmetrical operations located close to the middle of the cascade of stages (see also Fig. 5). On the feed stage, the feed joins the wash stream, which is fed to the first stage in the operation. The stages before the feed stage are called the wash section, and the stages after the feed stage are called the strip section. Having a wash section is beneficial in the case of low selectivities, because in this section co-extracted material that is undesired can be washed out of the extract phase, increasing the purity of the extracted material. This operation can be compared with the reflux in a distillation column.

2. Experimental

2.1. Chemicals

Pregnenolone (99%) was purchased from Acros Organics, Belgium. Progesterone (99%), TBME (99.8%), acetonitrile (99.9%), acetone (99.9%), and silica gel Davisil Grade 636 (pore size 60 Å, 35–60 mesh) were obtained from Sigma–Aldrich, Germany. Ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate (99%) was received from Iolitec, Germany, whereas ethanol (99.9%) was bought from Merck Chemicals, Germany. All chemicals were used as received. MiliQ water was used for preparing mobile phase for HPLC analysis.

2.2. Experimental methods

2.2.1. Experiments determining IL solubility in the feed solvent

In these experiments 1.2 g IL and 1.2 g organic solvent were stirred in a closed vessel. After 5 h the stirring was stopped and the mixture allowed to settle for 12 h. The phases were separated, and from the organic solvent phase, the solvent was removed by evaporation, and the amount of IL determined gravimetrically. The residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR to verify the absence of organic solvent material.

2.2.2. Screening of steroids-partitioning into the ILs

The relative partitioning of the steroids into the ILs was studied by contacting 0.5 mL IL with 0.5 mL of a 10 mg/mL organic steroids solutions, where the progesterone:pregnenolone ratio was 9:1 (28.62 mM progesterone and 3.16 mM pregnenolone) for 3 h. After separation of the equilibrated phases, the organic solvent was evaporated and the ratio of the steroids determined by ^1H NMR.

2.2.3. Quantification of the liquid–liquid equilibrium partitioning of the steroids

The competitive liquid–liquid equilibrium partitioning was determined by liquid–liquid extraction experiments. Extraction

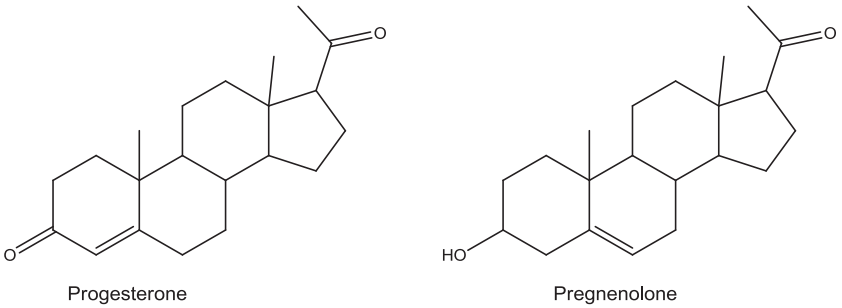

Fig. 1. Structures of the steroids progesterone and pregnenolone.