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Process modelling issues in the design of a continuous flow route for the production of pharmaceuticals in multiphase processes: the case of Ibuprofen

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1. Introduction

Continuous Pharmaceutical Manufacturing (CPM) of Active Pharmaceutical Ingredient (API) may offer many advantages over batch practice: lower costs, reduced wastes, decreased time-to-market for new drugs. Continuous flow reactors can deliver significantly higher yields and lower solvent and energy waste.

Ibuprofen (2-[4-(2methylpropyl)phenyl)]propanoic acid) is one the most sold Non Steroidal Anti Inflammatory Drug in the world and it is considered suitable for continuous manufacturing on the basis of technical and economic considerations [1]. While the continuous synthesis of the API has lately been established at the lab-scale level [2], the purification and crystallization section are still treated with batch procedures. Also, the reviewed simulation attempts are quite general [1,3,4]. Hence, we investigated the process in detail to evidence the lacking information for process optimization and intensification: detailed reaction kinetics is often missing, preventing reactor modelling, sizing and cost evaluation. Furthermore, the product separation is as important as the continuous flow synthesis, but its conversion from a batch to a continuous protocol is usually missing. Finally, the molecules taken into account are often very complex, undergo very specific transformations, whose thermodynamic description is mostly unavailable. This can lead to unreliable heat consumption/release predictions and to misleading prevision of products separation.

2. Methods

The flowsheet is based, for the reactive part, on the work of Bogdan et al. [5] as already rescaled by Jolliffe et al. [3], while the separation and crystallization part is originally derived from the experimental protocol of the former article and of similar patented procedures [6]. Since the API has to be separated from organic (*e.g.* unreacted isobutylbenzene), but also polar (*e.g.* acetic acid) residues, the adopted process design (yielding the soluble potassium salt in presence of methanol) imposes two purification stages in series. The material and heat balances of the process were calculated using Aspen Plus V9®. The molecular structures and properties for all the involved chemicals were retrieved from the APV9-PURE35, APV9-AQUEOUS and NIST-TRC databanks. Due to the strongly polar or even ionic character of liquid phase, the ENRTL model (**E**lec-**N**on-**R**andom **T**wo **L**iquids). The UNIFAC (**Unif**ied **A**ctivity **C**oefficients) system was much more reliable when dealing with the crucial methanol-water-solvent phase split and thus it was applied to the extraction section, due to its good prevision of liquid-liquid equilibria. The gas-phase behavior was described via the RK (**R**edlich-**K**wong) equation of state.

3. Results and discussion

The Elec-NRTL thermodynamic model was found adequate to describe the mass balances of the reaction section, while mixing and heat exchangers were modeled based on literature data. Despite its importance in this process, triflic acid is not already fully parametrized in the archives available. The presence of electrolytes, prevents a safe estimation of the properties of the mixture by the predictive UNIFAC method, that was instead used for the separation section, involving accurate description of liquid-liquid equilibria with a definitely non-polar solvent, which cannot be safely accounted for by using the NRTL model.

A preliminary study of the recovery of Ibuprofen allowed the selection of the most appropriate extraction solvent that is also used for the crystallization stage. However, due to the very high complexity of the mixture, an experimental validation of the results was needed, together with a review of the pertinent literature. The experimental tests evidenced indeed the formation of co-products (KCl), unpredicted during the simulation, that can give problems during the extraction due to the formation of a considerable amount of precipitate and also imposes an unpredicted separation of the solid in the scaled-up flowsheet.

Furthermore, NMR analysis showed that the amount of Ibuprofen split in the aqueous and organic phases was different form the predictions of Aspen Plus®, due to a very complex solvent mixture, but the results showed a sufficient level of agreement and, moreover, their difference can be fully explained by the well identified criticisms of the selected reaction solvent.

According to this study, heptane can be considered as the best solvent for Ibuprofen recovery and a convenient recrystallization medium. If this last stage is performed continuously, with a surnatant recycle, its recovery fraction approaches the 100% at least in a preliminary design, confining the API losses to the washing stages.

Any possible scale-up of the reactive section will have to consider acid-base solvation heats, as high as the endothermal duties of the microreactors, and even more critical for the equipment because they are developed under higher temperature gradients. Also the non-negligible solubility of triflic acid in many alcohols and ethers cannot be neglected, so we regard the organic solvent chemical nature as a key point, because (together with its flowrate) it determines the ibuprofen recovery in the final crystallization.

4. Conclusions

The study of a continuous flow process for the production of Ibuprofen was carried out using Aspen Plus as process simulation tool using literature data. The latter focus mainly on the reactions leading to the ibuprofen salt, but do not specify in detail the separation section. Many variables need to be accounted for and few reference data are available, especially those needed for a reliable estimation of the separation and extraction sections of the continuous plant.

References

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