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Optimisation of solvent replacement procedures according to economic and environmental criteria

Sébastien Elgue [a], Laurent Prat [a], Michel Cabassud [a,*], Jérôme Cézerac [b]

[a] *Laboratoire de Génie Chimique, UMR 5503, CNRS/INPT/UPS, 5 rue Paulin Talabot, BP 1301, 31006 Toulouse Cedex, France*
[b] *Sanofi-Synthelabo, 45 Chemin de Météline, BP 15, 04201 Sisteron, France*

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Abstract

During pharmaceutical syntheses, the reaction solvent has often to be switched off from one reaction step to the following one. Because of the standard industrial practices, solvent replacement generally constitutes a slow and high solvent-consuming operation. In this paper, a specific methodology, based on an optimisation framework dedicated to batch processes, is proposed for the optimisation of solvent replacement procedures. Optimisation may be performed at different levels according to economic and environmental criteria and satisfying safety and waste treatment constraints. In this way, the proposed methodology allows both to design new procedures of solvent replacement and to improve existing industrial processes. Two industrial applications are detailed to emphasize the benefits related to this methodology. In each case, the proposed methodology leads to the suitable recipe from comparison of traditional and empirical replacement procedures generally used in the pharmaceutical industry.

Keywords: Solvent replacement; Dynamic optimisation; Batch processes; Environment; Pharmaceutical application

1. Introduction

The syntheses of fine chemicals or pharmaceuticals, widely carried out in batch processes, imply many successive steps: reaction and separation. For various considerations such as selectivity, solubility, restricted heat dissipation, etc., reaction steps are carried out with solvent in diluted media. The solvent is chosen according to the reactants and the reaction characteristics. Each reaction has then a given optimal solvent that satisfies at the same time objectives of selectivity and solubility, safety constraints and economic and environmental criteria. Therefore, the solvent generally differs from one reaction step to the following. Consequently, the solvent has often to be switched off before the beginning of a new reaction step. Solvent replacements are particularly frequent in pharmaceutical chemistry. For instance, some Sanofi-Synthelabo's synthesis can include 10 or more solvent replacements.

Industrially, in production process, solvent replacements are usually carried out by evaporation or distillation operations, in the batch reactor used during the reaction. The detailed procedure depends on the reactor equipment in terms of overhead distillation column and control loops but generally imitates the laboratory methodology developed by the chemist who perfected the process. Consequently, robust and reliable but also slow and high solvent-consuming procedures are applied in industry. Such procedures are all the more wasteful because basically they are hard to tune in terms of operating conditions, reflux policies, ... In the recent years, environmental considerations hold a more and more important place in the chemical industry. Thus, from environmental and also economic viewpoints, restriction of the solvents consumption appears very interesting. Recent issues in dynamic simulation and optimisation may be exploited to solve this challenging problem.

In recent years, simulation and optimisation issues have mainly turned towards two directions: the development of computer aided methodologies for the substitution of reaction solvents by environment-friendly solvents and the optimisation of the industrial batch processes with solvent usage reduction as main purpose. Computer aided methodologies for the selection of the optimal solvent are based on the group contribution concept. However, these methodologies are generally only used for the process design [1–5] and not to obtain information with regard to the solvent replacement procedure. In this way, the use of optimisation control methodologies applied to solvent

* Corresponding author. Tel.: +33 5 34 61 52 59; fax: +33 5 34 61 52 53.
E-mail address: michel.cabassud@ensiacet.fr (M. Cabassud).

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replacement procedures also appears relevant. Nevertheless, as solvent replacements involved complex dynamic procedures, such methodologies are difficult to set up. In fact, from a modelling viewpoint, the train of the different steps and the complex dynamics occurring are difficult to represent and to take into account. Thus, only studies based on simple models are reported in literature [6].

The purpose of this article is to present an optimisation methodology applied to solvent replacement, able on one hand to optimise current industrial processes and on the other hand to compare their performances with other standard processes. The methodology is based on the use of an accurate and reliable optimisation framework dedicated to global batch processes, that allows in particular to represent the complex dynamics found during solvent replacements. Such methodology then allows to optimise solvent replacements at different levels: design and choice of procedure for new solvent replacements, optimisation of the current procedure for existing processes, improvement or choice of a new process. Two pharmaceutical applications are detailed to emphasize the related benefits in an economic and environmental context.

2. Industrial processes of solvent replacement

The standard procedures applied to switch off solvents are mainly based on evaporation or distillation operations. In fact, purity considerations do not allow liquid–liquid extraction. The procedures are usually operated in the reaction units to be ready for the next reaction step and to avoid additional problems of storage and of units management. According to the equipment associated to the reactor (control loops and distillation columns) and the volatility characteristics of the solvents, different procedures may be considered: loading–evaporation, constant level evaporation, loading–distillation and constant level distillation. All these processes are detailed in the following sections.

As pharmaceutical products are very sensitive, solvent replacement processes involve a lot of constraints. As products cannot withstand to be dried up, a minimum volume of solvent is then required all through the process. This minimum volume is defined from the products solubility or sometimes by the stirring device of the reactor. Moreover, as products are very sensitive to heat, temperature constraints are generally adopted, that leads to operations carried out at reduced pressure. A constraint is also fixed on the amount of original solvent left in the reactor. This constraint then defined the end of the replacement procedure.

2.1. Loading–evaporation process

Loading–evaporation process represents the standard industrial practice. The replacement is performed by successive steps of evaporations and loadings (Fig. 1). First, the batch reactor is boiled down to the minimum volume to remove much of the original solvent. Next, the replacement solvent is loaded. Then, the batch is boiled down again to the minimum volume to remove the remainder of the original solvent. The last two steps are repeated until the desired amount of original solvent left is obtained (final purity specification).

This process is traditionally used because of its simplicity and polyvalence. In fact, the replacement can be carried out directly in the reaction unit, without additional equipment required. Moreover, such a procedure may be adopted whatever the volatility of solvents is. The main drawbacks of this procedure lie in a high solvent consumption and in dead times following upon the train of the different occurring steps.

2.2. Constant level evaporation

In an evaporation process at constant level, the replacement is carried out by maintaining a constant level inside the reactor during the operation. The level is kept constant by a continuous feeding of the replacement solvent. Such a procedure requires a control loop to continuously adjust the feed of solvent to the reactor level. Therefore, according to the kind of level sensors, the constant level may be defined in terms of volume or mass. Depending on the initial level inside the reactor, a constant level operation may begin by a loading step (initial level < constant level) or by an evaporation step (initial level > constant level).

If the constant level is set to the minimum volume, the principle of the process guarantees to operate all through the replacement at the maximal concentrations of the initial solvent. This procedure is then less solvent consuming compared to the previous one. Moreover, the continuous feeding of the replacement solvent allows to avoid the dead times involved by loading steps. Furthermore, as for a loading–evaporation procedure, this process can be considered whatever the volatility of solvents is. The main drawback of this procedure then lies in the set-up of a control loop to control the reactor level.

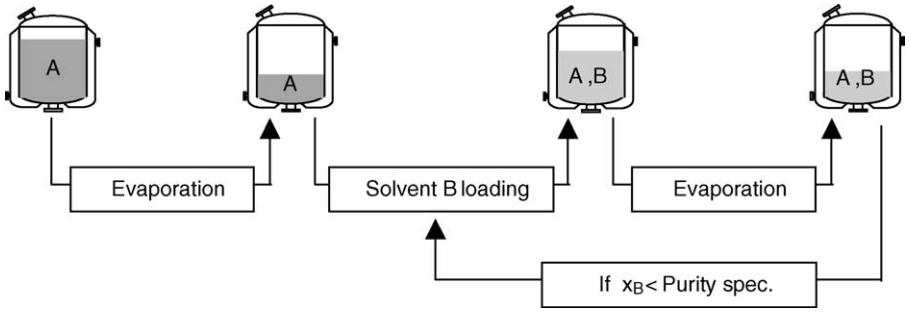

Fig. 1. Loading–evaporation procedure.