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Optimisation of solvent replacement procedures according to economic and environmental criteria in pharmaceutical industry

S. Elgue^a, M. Cabassud^{a,*}, L. Prat^a, J. Cézerac^b

^aLaboratoire de Génie Chimique, UMR 5503, CNRS/INPT(ENSIACET)/UPS,
5 rue Paulin Talabot, BP 1301, 31006 Toulouse Cedex, France

^bSanofi-Synthelabo, 45 Chemin de Météline, BP 15, 04201 Sisteron, France

* Corresponding author

E-mail address : michel.cabassud@ensiacet.fr (M. Cabassud)

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 a batch processes optimisation framework, 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 fact, 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

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 ten or more solvent replacements.

Industrially, in production process, solvent replacements are usually carried out from 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 lab 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 used for the process design [1,5] and can not provide

information with regard to the solvent replacement procedure. Therefore in this way, only the use of optimisation control methodologies applied to solvent replacement procedures 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.

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, distillation columns) and the volatility characteristics of the solvents, different procedures may be considered: loading-evaporation, constant level evaporation, loading-distillation, 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 can not 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.

Loading-evaporation process

Loading-evaporation process represents the standard industrial practice. The replacement is performed by successive steps of evaporations and loadings (figure 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.

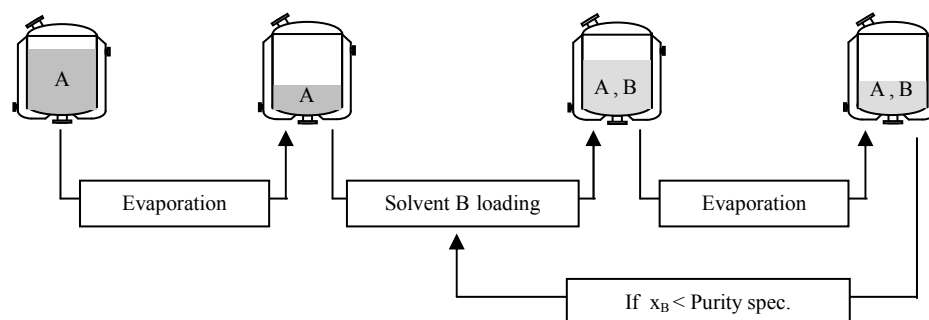


Figure1: Loading evaporation procedure

Constant level evaporation

In a process of evaporation at constant level, the replacement is carried out 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.

Loading-distillation and constant level distillation processes

These processes are based on the same principles as for the previous ones, but the separation of solvents is performed by distillation instead of evaporation. The use of a batch distillation column offers a better separation and then leads to a significant decrease of the solvent consumption. Nevertheless, batch distillation required a specific configuration of solvents volatility to be considered: the replacement solvent has to be less volatile than the original one. Such a constraint restricts the possibilities of application case. Moreover, batch distillation involves longer operating time because of a longer start-up time and of the reflux of distillate. As batch distillation also entails additional investment (purchase of an overhead column) the gain compared to evaporation is not obvious. Consequently, an optimisation study appears necessary to highlight the possible benefits of batch distillation processes.

MODELLING ENVIRONMENT

Optimisation of solvent replacement procedures requires a modelling of the process able at the same time to represent the train of the different occurring steps and to offer significant reliability and accuracy. The model has also to be able to simulate batch reactors and batch distillation overhead columns. To achieve these goals, a dynamic model developed for batch syntheses optimisation has been used [7].

The model is based on a rigorous description of batch equipment (reactor, distillation column, overhead condenser, etc) from a classical equations formulation: mass balances, energy balances, pressure balances, vapour liquid equilibrium relationships, physical properties estimation equations, etc. The resultant differential and algebraic equations system is numerically solved by a general solver based on the Gear method, DISCO [8]. A successive quadratic programming (SQP) method [9] is coupled to the model in order to solve optimisation problems. As this optimisation method requires the knowledge of the objective function and the constraints gradient, a numerical estimation method by finite differentiation is also applied.

The developed model allows from its hybrid feature to simulate the train of loading, evaporation or distillation steps and also to take into account their specific dynamics. The model also appears particularly suitable to represent the start-up of the different steps [10]. Such accuracy is very important from an optimisation viewpoint as start-up time may represent a significant part of the overall operating time.

OPTIMISATION STUDIES

The goal of the present study is to optimise solvent replacement procedures with solvent recovery as main purpose. In this way, three main criteria have to be considered: raw material (amount of replacement solvent), waste treatment and operating time. Evaporation or distillation waste collected at the end of each operation is composed of a mixing of the initial and replacement solvents. Therefore, depending on the composition, the waste treatment consists of recycling or burning. In fact, only quite pure solvents can be recycled.

From an optimisation viewpoint, the standard way to take into account at the same time three main criteria is to consider an economic objective function. Therefore, an objective function representing the replacement

procedure cost has been established (equation 1). Each criterion is then introduced with a specific weight. Depending on the weight associated to each criterion, optimisation will lead to the less wasteful or the faster procedure.

$$C_{\text{procedure}} = t_{\text{operating}} \times C_{\text{operating}} + m_{\text{solvent}} \times C_{\text{solvent}} + m_{\text{waste}} \times C_{\text{waste}} \quad (1)$$

With: $C_{\text{procedure}}$: global cost of the replacement procedure (€)
 $t_{\text{operating}}$: operating time (h)
 $C_{\text{operating}}$: operating cost (230 €·h⁻¹)
 m_{solvent} : amount of replacement solvent used during the procedure (kg)
 C_{solvent} : raw material cost, i.e. replacement solvent cost (€·kg⁻¹)
 m_{waste} : amount of waste (kg)
 C_{waste} : waste treatment cost (€·kg⁻¹)
 $C_{\text{waste}} > 0$ in case of burning
 $C_{\text{waste}} < 0$ in case of recycling

Throughout the optimisation procedure and whatever the considered replacement process is, the heat power delivered to the reactor is assumed to be the same. That means that during evaporation or distillation operations, the batch reactor jacket is supplied by the same heat transfer fluid: same flow-rate and same inlet temperature. Consequently, the heating power indirectly appears in the objective function through the operating cost. In fact, the operating cost gathers at the same time the manpower cost and the energy consumption.

As each replacement process has specific features, the optimisation variables differ according to the process, leading to different optimisation problems (table 1). However, the optimisation constraints are the same: a maximum temperature allowed inside the reactor in order to avoid damage to products, a fixed amount of original solvent left in the reactor at the end of the operation (final purity specification). For a loading-evaporation or a loading-distillation process, the operation is composed of a train of loading and separation steps. The optimisation variables then consist of this number of steps and the associated loading amounts. For a constant level operation, the value of the constant level is optimised in terms of volume or mass. A priori, the optimal constant level will be the minimum level, in order to operate at maximum concentrations of the initial solvent. The optimisation methodology should allow to verify this assumption. In cases where the initial level differs from the constant level, a preliminary step depending on this initial level (separation or loading) has to be carried out. As the aim of this preliminary step is to reach the constant level, its characteristics are not optimised. In cases of distillation operations (loading-distillation or constant level distillation), the reflux policy is studied as an optimisation variable. In this way, various reflux policies have been considered: constant reflux, piecewise constant reflux, specific function-based reflux, controlled reflux.

Optimisation problems are solved by a reliable and accurate SQP method [9]. The SQP method allows solving non linear programming (NLP) problems. Therefore, a specific methodology has been adopted in cases of loading-separation and of loading-distillation optimisations. In fact, as the number of steps constitutes an integer variable, the global optimisation of the process leads to the treatment of a mixed integer non linear programming problem (MINLP). Such a problem involves the use of more complex specific methods that are not easily compatible with a global environment dedicated to batch processes optimisation. For that reason, a simple decoupling methodology has been used: loading-separation or loading distillation processes are optimised for given number of steps, a final comparison then allows to determine the optimal process.

Table 1: optimisation problems

Replacement process	Optimisation variables	Constraints	Objective function
Loading-evaporation	Number of steps Loading amounts	Final purity Maximum temperature Minimum volume	Global cost
Loading-distillation	Number of steps Loading amounts Reflux policy		
Constant level evaporation	Constant level		
Constant level distillation	Constant level Reflux policy		

The present methodology proposes to optimise solvent replacement procedures by mean of an optimisation tool dedicated to overall batch processes. The interest of this methodology lies in the possibility to optimise a given application at different levels. In a first level, it allows to improve the current procedure by providing the optimal operating conditions. In a second level, it allows to determine the optimal conditions of each possible procedure and so to choose the most suitable one. Two application cases within the context of pharmaceutical industry have been studied according to the proposed methodology, in order to highlight its relevant advantages.

TOLUENE-ACETONITRILE REPLACEMENT

During the pharmaceutical synthesis of a Sanofi-Synthelabo's product, a toluene medium has to be replaced by acetonitrile. As toluene is less volatile than acetonitrile, this application constitutes the less favourable replacement case: batch distillation can not be considered. Moreover, the liquid-vapour equilibrium between toluene and acetonitrile presents an azeotropic point (figure 2). Consequently, only two processes will be compared: loading-evaporation and constant level evaporation. This replacement then appears as a simple example to emphasize the proposed methodology.

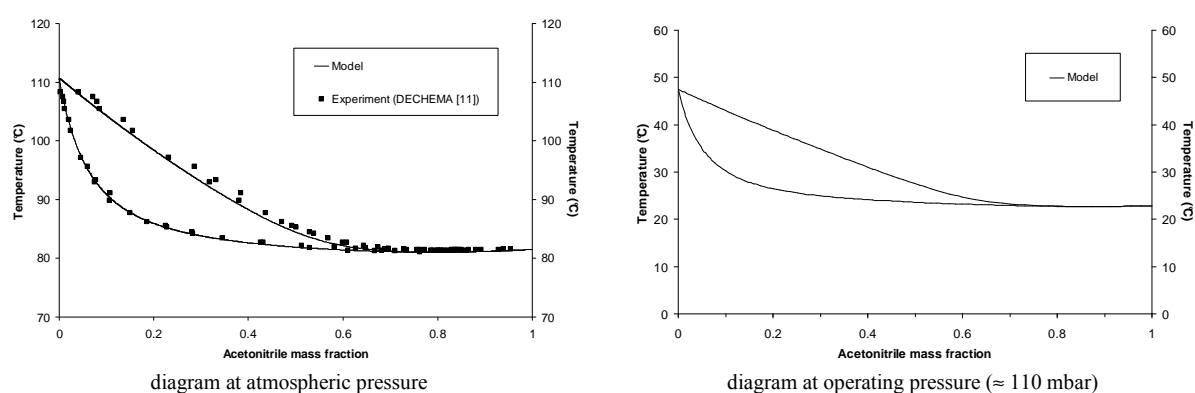


Figure 2: toluene-acetonitrile vapour liquid equilibrium diagrams

Industrial practice

Since the following reaction step is operated in the same reactor, the solvent replacement takes place in the reaction unit, a 100 L De Dietrich glass-lined reactor. As the initial volume is higher than the minimum volume, a loading-evaporation procedure performed in 4 steps, including a preliminary evaporation step, is applied. In fact, the initial volume made up of the reaction products (5 L) and of toluene (14 L) represents 19 L. The minimum volume is 13.5 L. Consequently, a first evaporation step is initially carried out without acetonitrile loading in order to remove the maximum amount of pure toluene. From a process viewpoint, the first loading step is then performed with an amount of acetonitrile equal to zero.

The operation is defined with a temperature constraint of 60°C in order to avoid the thermal degradation of products. Evaporations are then carried out at a reduced pressure of about 110 mbar. The final purity is fixed at 1% weight of toluene in the vapour flow going out of the reactor. The operation also includes another final constraint regarding the final volume which is set to 16 L.

In order to prevent degassing of solvents during loading operations, dead times are enforced before and after loading steps, to make sure that the reaction medium is cold enough. These safety constraints then lead to an important operating time. Therefore, the gain on the separation efficiency related to the addition of new loading-evaporation steps also involves an operating time increase. Optimisation then does not appear obvious. In this way, the developed methodology provides some strategic information.

Validation study

Before optimising the replacement procedure, the accuracy of our model with regard to the toluene-acetonitrile medium has been verified. To achieve this goal, records of the industrial process data are compared

to the simulation results provided by the tool. The comparison has been performed on two different ways: on the toluene-acetonitrile vapour liquid equilibrium (figure 2) and on the overall process (table 2).

During evaporation steps, an operator manually controls the reactor pressure in order to respect the temperature constraint. In table 2, the reactor temperature of the industrial process is then given at the beginning and at the end of any evaporation step. As this control policy is operated manually and does not follow any specific law, it can not be simulated. Therefore, in simulation, the operating pressure is assumed to remain constant during evaporations, that involves slight differences compared to industrial data. Nevertheless, the good agreement observed between industrial data and simulation results, both regarding the vapour liquid equilibrium and the overall process, validates the predictions of our tool with a significant accuracy. Such accuracy appears particularly interesting in the aim of optimisation.

Table 2: validation of the industrial practice of the toluene-acetonitrile replacement

	Industrial data		Simulation results	
	<i>Time</i>	<i>Temperature (°C)</i>	<i>Time</i>	<i>Temperature (°C)</i>
<i>Steps</i>				
Acetonitrile loading: 0 kg	30 min	40.0	31 min	41.0
Evaporation		50.6		
Acetonitrile loading: 23.4 kg	1 h 10 min	27.7	1 h 05 min	29.4
Evaporation		29.4		
Acetonitrile loading: 23.4 kg	45 min	22.3	48 min	22.3
Evaporation		20.1		
Acetonitrile loading: 23.4 kg	48 min	20.2	48 min	24.5
Evaporation		28.9		
<i>Operating time</i>				
Evaporation	3 h 13 min		3 h 12 min	
Total	3 h 33 min		3 h 33 min	

Optimisation study

In this application case, according to purity reasons, the solvents recovered from the reactor can not be recycled for any other application and so are destroyed. The waste treatment cost then corresponds to the solvents burning cost: 0.06 € per waste kilogram. The raw material cost that appears in the global cost definition (see equation 1) corresponds to the toluene cost: 1.23 € per toluene kilogram.

According to these costs, the solvent replacement procedure has been optimised. As previously mentioned, because of the volatilities configuration, only evaporation processes have been studied. That leads to the consideration of two kinds of processes: loading-evaporation and constant volume evaporation. The detailed results of optimisation are given in table 3. From an optimisation viewpoint, 4 processes appear interesting to be compared: the industrial process performed in 4 steps, the 4 steps optimal loading-evaporation process, the optimal loading-evaporation process (performed in 6 steps) and the optimal process of constant volume evaporation.

From a process viewpoint, optimisation leads to strategic conclusions. For a loading-evaporation process and whatever the number of steps may be, optimisation recommends a preliminary evaporation step (first loading amount equal to zero) as performed during the industrial practice. For an evaporation process operated at constant volume, optimisation suggests a constant volume equal to the minimum volume of the batch reactor, as expected.

Table 3: optimisation results of the toluene-acetonitrile replacement

<i>Industrial loading-evaporation process (4 steps)</i>										
Steps	Industrial loading mass (kg)						Waste (kg)	Operating time	Global cost (€)	
number	M 1	M 2	M 3	M 4	Total					
4	0	23.4	23.4	23.4	70.2		74.0	3 h 33 min	910	
<i>4 steps optimal loading-evaporation process</i>										
Steps	Optimal loading mass (kg)						Waste (kg)	Operating time	Global cost (€)	
number	M 1	M 2	M 3	M 4	Total					
4	0	30.6	19.7	16.0	66.3		70.0	3 h 19 min	850	
<i>Optimal loading-evaporation process</i>										
Steps	Optimal loading mass (kg)							Waste (kg)	Operating time	Global cost (€)
number	M 1	M 2	M 3	M 4	M 5	M 6	Total			
6	0	17.7	10.1	8.1	7.7	7.4	51.0	54.7	3 h 11 min	800
<i>Optimal constant volume evaporation</i>										
Steps	Optimal loading mass		Optimal constant volume				Waste (kg)	Operating time	Optimal cost (€)	
number	(kg)		(L)							
1	33.0		13.5				38.0	2 h 31 min	620	

Benefits

According to the optimisation results presented in table 3, the proposed methodology allows to improve the replacement case at different levels (figure 3). In fact, from an adjustment of the loading amounts the cost of the current industrial procedure can be reduced of 7 %. By keeping a loading-evaporation procedure but changing at the same time the number of steps to 6 and the operating conditions (loading amounts), the optimisation leads to a 12 % reduction of the operation cost. Finally, a constant volume evaporation process appears to be the more suitable replacement procedure. In fact, it provides a significant improvement, by reducing the operation cost of about 32%. This reduction is also followed at the same time by a 53 % saving on the toluene consumption (raw material) and a 49 % decrease of the waste amount. Since environmental considerations represent major constraints of today processes, the reduction of about 50 % of the waste amount and so of the waste treatment appears as a main improvement.

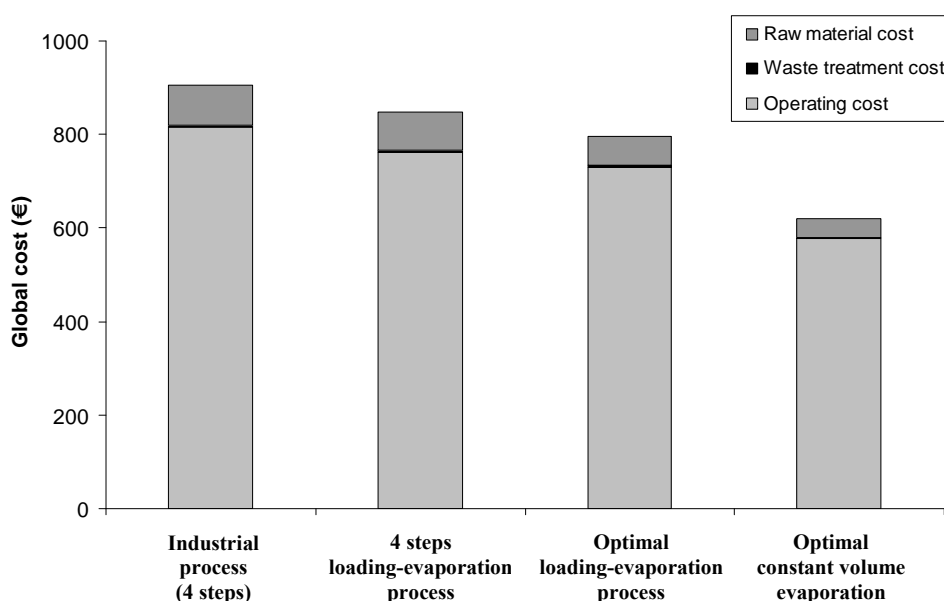


Figure 3: comparison of the replacement cost according to the process

The study of the cost distribution (figure 4) shows that the operating time represents the main part of the global cost, both for the current industrial process and the optimal one. The influence of environmental considerations (raw material and waste treatment) appears very limited. All this different aspects are however linked and go in the same direction: minimising the amount of replacement solvent used will lead to a decrease of the operating time and of the waste amount that has to be treated. The opposite is also true. Consequently, a reduction of the evaporation time by means of a heating power increase or an operating pressure decrease should lead to significant improvements in spite of the additional costs it involves. Once more, the proposed methodology can provide information about such modifications.

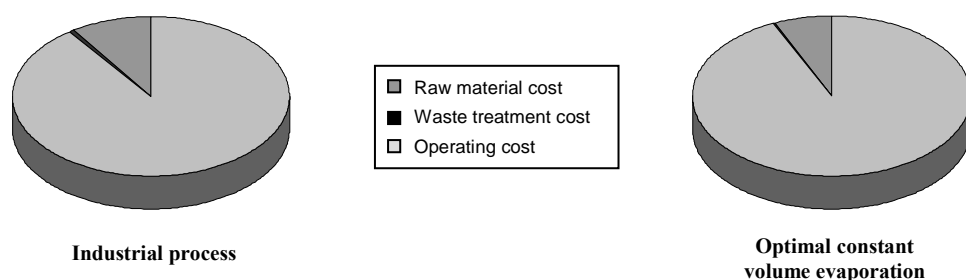


Figure 4: comparison of the costs distribution

METHANOL-PYRIDINE REPLACEMENT

The switching off methanol by pyridine occurs during a Sanofi-Synthelabo's pharmaceutical synthesis. As methanol is more volatile than pyridine (figure 5), this application represents the more favourable case of solvent replacement: all the standard evaporation and distillation procedures can be used. This application case then appears as a good example to emphasize all the advantages provided by the proposed methodology.

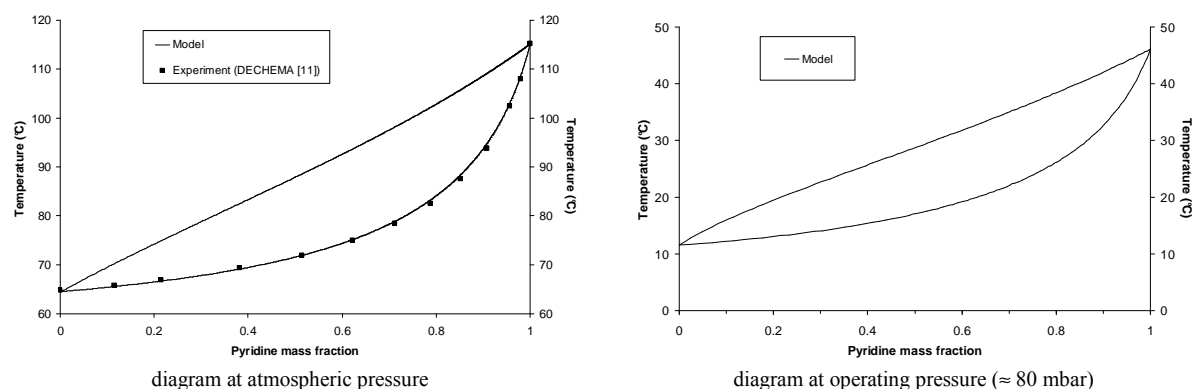


Figure 5: methanol-pyridine vapour liquid equilibrium diagrams

Industrial practice

The reaction steps occurring before and after the solvent replacement are carried out in the same batch reactor, a 2.5 m³ De Dietrich glass-lined reactor. From an industrial viewpoint, it appears more convenient to switch off methanol directly from this batch reactor. A loading-evaporation procedure carried out in 5 steps is then applied. As the initial volume (about 870 L) made up of methanol (744 L) and of the reaction products (128 L) is lower than the minimum volume (1240 L), the initial step consists of a pyridine loading. Moreover, a safety constraint required the loading amount of this initial step to be at minimum equal to 900 kg of pyridine. The operation is also defined with a temperature constraint of 50°C in order to avoid thermal degradation of products. Evaporations are then carried out at a reduced pressure of about 80 mbar and the reactor jacket is provided by hot water. The final purity is fixed at 1% weight of methanol in the vapour flow going out of the reactor. The

operation also includes another final constraint with regard to the final volume which is set to the minimum volume, 1240 L.

In order to prevent degassing of solvents during loading operations, dead times are enforced before and after loading steps (to make sure that the reaction medium is cold enough) leading to significant operating times. Therefore from an optimisation viewpoint, the benefit of additional loading-evaporation steps on the separation efficiency is balanced by an increase of the operating time. Moreover, the enhanced separation provided by distillation also entails an increase of the operating time due to the reflux of distillate. Optimisation of the industrial practice then does not appear obvious. In this way, the developed methodology provides some strategic information.

Validation study

A preliminary step of the optimisation procedure consists of validating the accuracy of our model with regard to the methanol-pyridine medium. This step is performed from a comparison of the industrial process data and the simulation results provided by the tool, on two different ways: on the methanol-pyridine vapour liquid equilibrium (figure 5) and on the overall process (table 4). A good agreement is observed, highlighting the accuracy of our model for the considered application. Such accuracy offers many perspectives from an optimisation viewpoint.

Table 4: validation of the industrial practice of the methanol-pyridine replacement

	Industrial data		Simulation results	
	Time	Temperature (°C)	Time	Temperature (°C)
Steps				
Pyridine loading: 1218 kg	1 h 20 min		1 h 15 min	
Evaporation	7 h 40 min	34.5	7 h 39 min	34.3
Pyridine loading: 490 kg	30 min		30 min	
Evaporation	2 h 40 min	32.0	2 h 40 min	32.3
Pyridine loading: 490 kg	30 min		30 min	
Evaporation	2 h 25 min	36.5	2 h 27 min	35.4
Pyridine loading: 490 kg	30 min		30 min	
Evaporation	2 h 20 min	40.4	2 h 19 min	36.0
Pyridine loading: 490 kg	30 min		30 min	
Evaporation	2 h 30 min	37.9	2 h 31 min	37.4
Operating time				
Pyridine loading	3 h 20 min		3 h 15 min	
Evaporation	17 h 35 min		17 h 35 min	
Total	23 h 55 min		24 h 04 min	

Optimisation study

In this application case, purity reasons involve that any solvents mixing recovered from the reactor can not be recycled for any other application and has to be destroyed. Destruction of solvents by mean of burning costs 0.06 € per kilogram (waste treatment cost). Raw material cost only represents pyridine purchase: 3.90 € per kilogram.

In a first level of the optimisation study, the operating conditions of the industrial procedure have been optimised, leading to the optimal pyridine amounts of a 5 steps loading-evaporation process. In a second level, the number of steps has also been considered as an optimisation variable, leading to the optimal loading-evaporation procedure. Finally, more efficient procedures have been optimised: constant volume evaporation, loading-distillation and constant volume distillation. Table 5 offers a detailed comparison of these different processes.

On a process viewpoint, optimisation leads to strategic conclusions. Thus, for a constant volume operation, as for the previous application and as expected, optimisation recommends a constant volume equal to the minimum volume of the reactor: 1240 L. For distillation operations, optimisation allows to assess the benefits related to specific reflux policy. In this way, different reflux policies have been considered: constant reflux policy,

piecewise constant reflux policy, function-based reflux policy or reflux controlled from the top column temperature. Function-based or controlled policies improve the separation when pyridine concentration increases, leading to a reduction of about 6 to 7 % of the operation cost. Nevertheless, as recycling of the distillate (mainly composed of methanol) is not possible for purity reasons, the benefit of such policies appears low compared to the investment required, in terms of controllers. Consequently, only constant reflux policies are presented in the procedures comparison.

Table 5: optimisation results of the methanol-pyridine replacement

<i>Industrial loading-evaporation process (5 steps)</i>										
Steps number	Industrial loading mass (kg)						Waste (kg)	Operating time	Global cost (€)	
5	M 1	M 2	M 3	M 4	M 5	Total	2690	24 h 04 min	18 040	
	1218	490	490	490	490	3178				
<i>5 steps optimal loading-evaporation process</i>										
Steps number	Optimal loading mass (kg)						Waste (kg)	Operating time	Global cost (€)	
5	M 1	M 2	M 3	M 4	M 5	Total	2443	21 h 37 min	16 470	
	984	482	484	487	486	2923				
<i>Optimal loading-evaporation process</i>										
Steps number	Optimal loading mass (kg)							Waste (kg)	Operating time	Global cost (€)
6	M 1	M 2	M 3	M 4	M 5	M 6	Total	2382	21 h 54 min	16 320
	895	392	394	395	396	395	2867			
<i>Optimal constant volume evaporation</i>										
Steps number	Optimal loading mass (kg)		Optimal constant volume (m ³)				Waste (kg)	Operating time	Optimal cost (€)	
1	2392		1.240				1946	17 h 24 min	13 410	
<i>Optimal loading-distillation process</i>										
Steps number	Optimal loading mass (kg)		Optimal reflux rate R				Waste (kg)	Operating time	Optimal cost (€)	
1	1379		0.624				861	17 h 36 min	9 450	
<i>Optimal constant volume distillation</i>										
Steps number	Optimal loading mass (kg)		Optimal reflux rate R				Waste (kg)	Operating time	Optimal cost (€)	
1	1298		0.621				688	17 h 23 min	9080	

Benefits

By mean of optimisation of the operating conditions, the proposed methodology offers a complete estimation of the gain related to each considered process (see figure 6). With regard to the industrial process carried out in 5 steps, this methodology proposes operating conditions in terms of loading amounts that leads to a significant gain on the replacement cost (about 9%). The methodology also shows that in the case of a loading-evaporation process, operating in 6 steps constitutes the optimal scenario and will provide 10 % reduction of the global cost.

As it appears on the cost distribution (figure 7), the raw material represents the main part of the industrial replacement cost. In fact, pyridine is a very expensive solvent (3.90 €/kg) compared to the other ones (0.15 €/kg < Average solvent cost < 2.5 €/kg). Consequently, enhanced separation processes provide significant benefits (figure 6): constant volume evaporation, loading-distillation and constant volume distillation respectively lead to a 26 %, a 48 % and a 50 % reduction of the replacement cost. This reduction is mainly due to the decrease of the pyridine consumption, as shown on figures 6 and 7.

With regards to this application case, as raw material issues are essential, distillation based processes appear relevant. In fact distillation processes limit solvent consumption and waste amount by an enhanced separation due to reflux. As reflux involves an increase of operating time, the benefit of such processes is mainly dependant on the reflux policy adopted. In this way, the proposed methodology allows to test and compare different policies: constant reflux policy, piecewise constant reflux policy, function-based reflux policy or reflux controlled from the top column temperature.

Constant level distillation combines both the effects of constant level operation and of distillation. Therefore as expected, the constant volume distillation constitutes the best process for the considered application. Nevertheless, its benefit only appears slightly better than the one provided by a loading distillation process. In fact, as the operation required an important initial loading (900 kg) close to the optimal loading-distillation amount (1379 kg), the benefit related to constant level distillation is then limited. However, the proposed methodology offers many solutions to improve the replacement procedure. At this stage, only a complete economic study integrating a return on investment would allow to go beyond and to choose the suitable process: constant level evaporation, loading-distillation or constant level distillation.

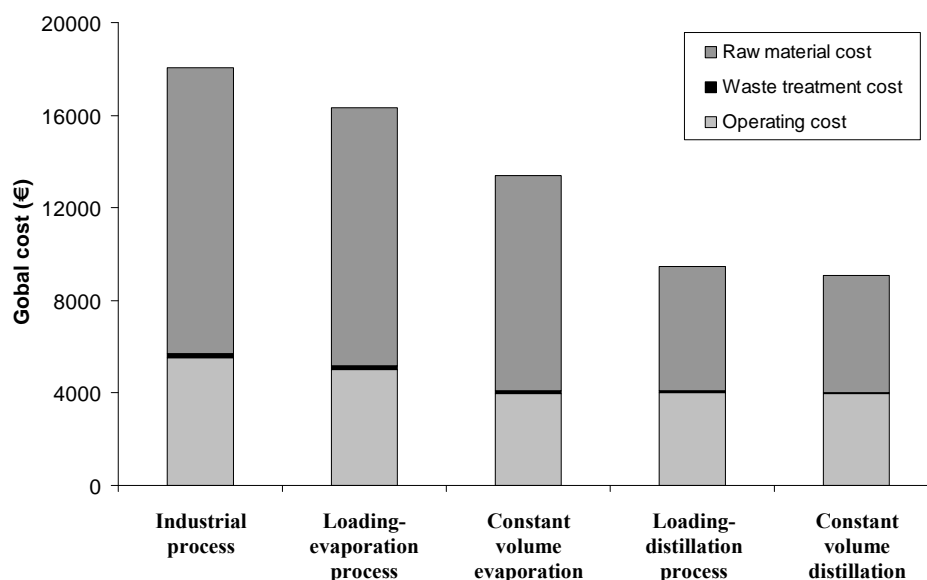


Figure 6: comparison of the replacement cost according to the process

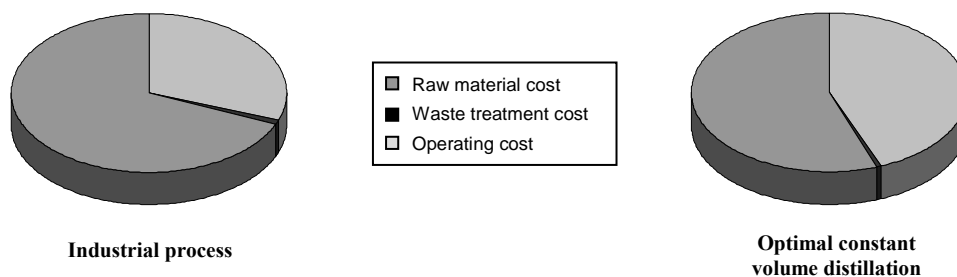


Figure 7: comparison of the costs distribution

CONCLUSION

A new methodology dedicated to solvent replacement optimisation has been presented in this paper. The features of this methodology based on the use of a batch processes optimisation framework, allow to perform optimisation at different levels: optimal design, optimal control and optimal revamping of industrial solvent replacements. Two pharmaceutical applications emphasize the use of the proposed methodology and the related benefits, specially in term of minimisation of the solvent used and of the waste. The industrial validation of the methodology conclusions has then led to the development of a commercial tool in collaboration with Sanofi-Synthelabo. This tool is now systematically used by Sanofi-Synthelabo for the design or revamping of solvent replacement processes.

The interest of the methodology lies not only in the determination of the more suitable process, but also in the valuation of each possible process according to economic and environmental criteria. In fact, the characteristics specific to each process are well-known and the determination of the more efficient procedure does not appear as a very challenging problem for chemical engineers: operations at constant level are always preferable to loading-separation ones and distillation is only advantageous in cases of highly expensive replacement solvents. The main advantages of the proposed methodology then lie in the determination of the optimal operating conditions and of an accurate valuation of each replacement procedure. Such features allow to perform complex economic studies including in particular return on investment, that constitutes the only way to make an accurate choice of the best replacement process.

From a process design viewpoint, the proposed methodology offers relevant perspectives with regard to the choice of the reaction solvent. In fact, the methodology may allow to introduce some separation criteria during the design step of the reaction solvent. The choice of the reaction solvent then results from a compromise between reaction performances and separation facilities. Recent works [12] allow to assess the benefits related to such design in the context of the pharmaceutical industry.

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