Influence of solvent choice on the optimisation of a reaction–separation operation: application to a Beckmann rearrangement reaction

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Abstract

In pharmaceutical syntheses, the solvent choice generally represents a complex design step. Traditionally, this choice is operated according to criteria connected with the reaction step and without any consideration on the following separation steps. The purpose of this study is to highlight the benefits of a global approach of optimisation for the solvent determination. In this way, an optimisation framework dedicated to global synthesis is applied to a simple reaction–separation operation integrating a Beckmann rearrangement reaction, leading to interesting solvent choices.

Keywords: Optimisation; Solvent choice; Batch process; Reaction–separation operation; Dynamic simulation

1. Introduction

The synthesis of fine chemicals or pharmaceuticals, widely carried out in batch processes, implies many successive reaction steps. For selectivity and solubility reasons, reaction solvent often differs from one step to another. Thus, in addition to concentration and purifying product steps, synthesis progress is made up of many solvent substitution steps. Solvent substitutions are particularly frequent in pharmaceutical chemistry. Thus, some syntheses can include about 10 or more solvent changing. Traditionally, in cases where different reaction solvents are potentially fit for use, separation steps are not considered for the determination of suitable solvent. In fact, solvent selection is made according to criteria defined in order to improve the reaction, in terms of spent time or reaction yields. In this way, the solvent design leading to a maximal conversion of the reaction is generally privileged. Nevertheless, considering the global synthesis, such an approach can be proved prejudicial. For instance, a solvent cannot only lead to faster kinetics or better selectivity, but also involve further difficulties in the following separation operations.

During the last 15 years, techniques of computer-aided molecular design have been proposed for optimal solvent selection. Based on the use of the group contribution concept in order to estimate physicochemical properties, these works lead to optimal solvent selection satisfying economical and

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environmental criteria. Nevertheless, majority of these applications is restricted to the study of a particular step of processes: reaction or separation. Optimal solvent selection is then achieved according to criteria only connected with the considered step. Thus, applications have been reported for the solvent design of separation processes [1–5] and for the solvent selection of reaction operations [6,7]. The purpose of this work breaks free from previous applications by a global approach taking into account the overall synthesis, in which the reaction solvent simultaneously influences the optimisation of the reaction and the separation steps.

2. Formulation of the problem

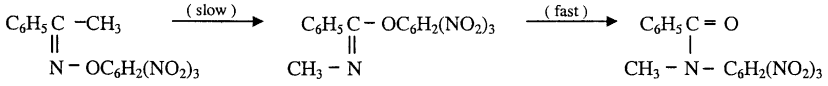
As part of this study, a simple synthesis composed of a single reaction with a consecutive separation step has been considered. A Beckmann rearrangement reaction composes the reaction step followed by a solvent substitution process (separation step). The operation is carried out in an industrial reaction–separation device composed of a 2.5-m^3 standard industrial reactor and able to integrate an overhead distillation column and a condenser. The main characteristics of this device are given in Table 1.

Table 1
Main characteristics of the process

Reactor		
Vessel	Volume (m^3)	2.5
	Diameter (m)	1.6
Jacket	Volume (l)	382
	Heat transfer area (m^2)	8.70
Stirring	Stirring device (m)	0.96
	Rate ($tr\,min^{-1}$)	110
Distillation column		
Column	Diameter (m)	0.2
	Height (m)	2
	NET	7
Condenser	Volume (l)	50
Heat-transfer fluid		
	Type	Water–ethylene glycol 50%
	Temperature (°C)	10–140
	Flow rate ($m^3\,h^{-1}$)	24

2.1. Reaction step

Beckmann rearrangement reactions are principally carried out in polymers industry. The reaction mechanism of Beckmann rearrangements is very complex. A simple representation of this mechanism consists of two consecutive reactions. The following equation (1) summarises this scheme for the considered Beckmann rearrangement:



(1)

In a kinetic study, Chapman and Howis [8] show that this synthesis can be performed with different reaction solvents. Only three have been retained: chloroform, dichloroethane and acetonitrile. Each solvent involves peculiar kinetic characteristics for the associated reaction. Table 2 gives Arrhenius parameters of a global representation of Beckmann rearrangement for each solvent. The study highlights a fast reaction rate linked to the use of acetonitrile and in some degree of dichloroethane and a slow reaction rate with regard to the use of chloroform (Fig. 1).

The reaction is operated at atmospheric pressure. The initial volume of the reaction mixture is about 750 l with a concentration of reactant set to 0.043 mol l^{-1} in order to respect the kinetic study conditions. During the reaction step, a constant policy of 80 °C has been adopted for the temperature control of the reaction mixture.

2.2. Separation step

The separation step consecutive to the Beckmann rearrangement consists of a substitution of the reaction solvent. This substitution is carried out for the benefit of a new solvent called substitution solvent, parameter of this study. Bubble-point temperature and cost constitute the specific characteristics of this substitution solvent. Therefore, in order to avoid the consideration of any other characteristics, substitution solvents are represented by ideal thermodynamic models. As

Table 2
Kinetic parameters of Beckmann rearrangement according to the reaction solvent

Solvent	Formula	Activation energy, E_a (kJ mol^{-1})	Pre-exponential factor, k (s^{-1})	Reaction order (Or)
Chloroform	$CHCl_3$	6.41	4.46×10^{-12}	1
Dichloroethane	$C_2H_2Cl_2$	6.17	3.19×10^{-12}	1
Acetonitrile	CH_3CN	6.45	5.27×10^{-13}	1

Arrhenius law, $r = k\exp\left(\frac{-E_a}{RT}\right)[A]^{Or}$, where T in K and R in kcal mol^{-1} K^{-1}.

shown in Table 3, the considered substitution solvents have been chosen in order to represent the whole of the possible thermodynamic configurations. To simplify the substitution simulations, a pure solvents assumption has been adopted, i.e. the reactant and product only constitute a dead volume in the reactor and do not take part in the vapour phase or in vapour–liquid equilibrium. The low volatility of the reactant and product, and the strong dilution of the reaction mixture justify this assumption (Table 4).

Three industrial batch processes have been considered for the solvent substitution: a loading evaporation process, a process of evaporation at constant volume and a process of distillation at constant volume. These processes are detailed in the following sections. It has to be noted that in pharmaceutical syntheses, products resulting from reaction steps are generally very

Table 3
Comparison of bubble points between different reactions and substitution solvents

Solvent	Bubble point (°C)
Reaction solvent	
Cholroform	61
Acetonitrile	82
Dichloroethane	83
Substitution solvent	
1	40
2	56
3	65
4	78
5	97
6	110

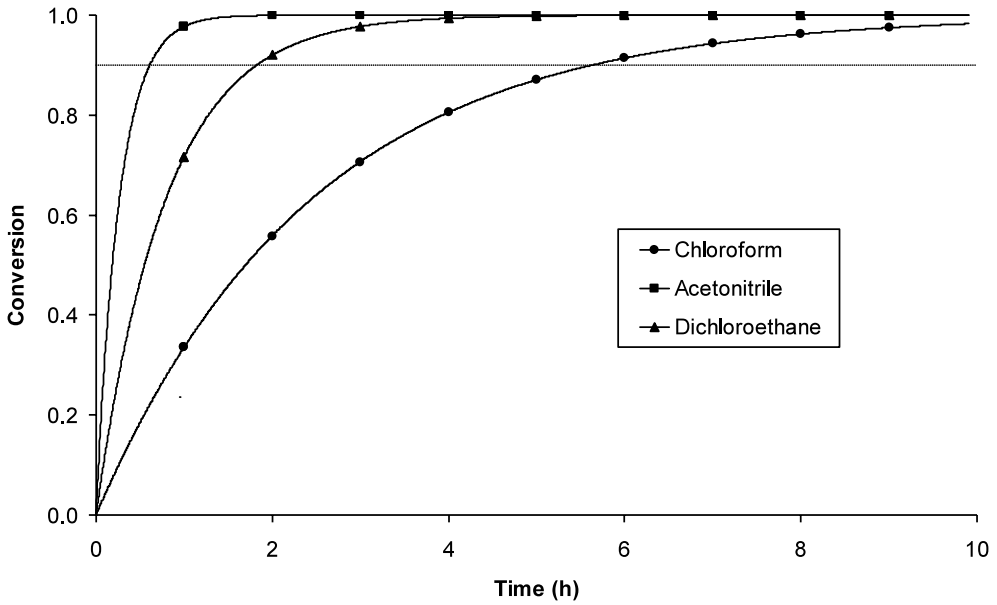


Fig. 1. Variations of conversion with time according to the reaction solvent.

Table 4
Composition of the medium at the end of reaction step

Weight fraction (%)	Reactant	Product	Reaction solvent
Chloroform	0.24	2.19	97.57
Dichloroethane	0.12	1.10	98.77
Acetonitrile	0.20	1.78	98.02

heat-sensitive and cannot afford to be dried up easily. Thus, whatever the solvent-changing process may be, a minimum volume of solvent is required all through the process. This minimum volume is defined by the product solubility and sometimes by the vessel stirring system. Solvent changing is supposed to end when the concentration of the substitution solvent reaches the purity specification.

2.2.1. Loading evaporation process

Loading evaporation process represents the standard industrial practice. Solvent changing is performed by successive evaporations and successive steps of substitution solvent loading (Fig. 2). During the process, evaporations end at the minimum reactor volume. This process is traditionally used because of its polyvalence. In fact, substitution can be carried out directly in the reactor, without additional equipment and whatever the solvents' thermodynamic configuration may be. The main drawbacks lie in high solvent consumption and in dead-times involved by the train of different steps.

2.2.2. Evaporation at constant volume process

In a process of evaporation at constant volume, changing is operated at a constant volume. During evaporation, volume is kept constant by continuously adjusting the feed of substitution solvent, by means of a PID controller. In the case of an initial volume greater than the constant volume, a concentration step is initially performed. Evaporation at constant volume allows operating at maximum reaction solvent concentrations, and hence less solvent is consumed compared with previous process. The continuous feeding of substitution solvent also avoids dead-times linked to loading steps. As for loading evaporation, this process can be performed whatever the solvents' thermodynamic configuration may be. Evaporation at constant volume only needs installation of a control valve in order to regulate substitution solvent feeding.

2.2.3. Distillation at constant volume process

Based on the principle of the previous process, distillation at constant volume, because of the outstanding solvent separation due to the column, is poor in solvent consumption. Nevertheless, batch distillation can only be performed with a substitution solvent more volatile than the reaction one and involves a longer operating time during startup operations. Compared with the previous ones, process of distillation at constant volume needs additional investment (overhead column) and depends on solvents' thermodynamic configuration. Thus, an optimisation study appears necessary to determine the possible benefits.

2.2.4. Separation protocol

Solvent substitutions are carried out at atmospheric pressure and with a 750-l minimum volume. The final purity specification is 0.5% of molar reaction solvent in the reaction mixture. In the cases of distillation at constant volume processes, substitutions are performed in a 0.2-m diameter and 2-m length overhead batch distillation column with seven theoretical plates including condenser.

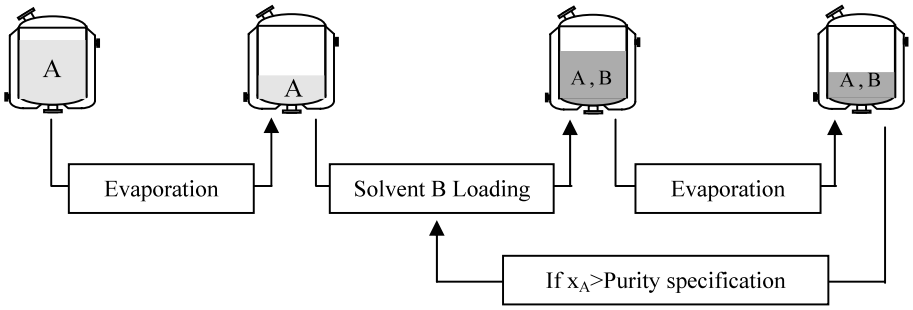


Fig. 2. Loading evaporation procedure.

3. Synthesis optimisation

The goal of this study is to determine, for the present synthesis, the optimal operating conditions satisfying economical and environmental criteria. In this way, an objective function representing the operating global cost and based on the estimation of the operating time, the solvent consumption and the treatment of waste solvents have been defined (Eq. (2)). Because of purity reasons and economical considerations, waste solvents collected during the substitution operation are not recycled, but destroyed by burning. According to environmental constraints about atmospheric waste, the presence of chlorinated solvents (mass chlorine fraction >2%) leads to an increased treatment cost.

$$C = C_{\mathrm{Mo}} t_{\mathrm{op}} + C_{\mathrm{sol}} M_{\mathrm{sol}} + C_{\mathrm{tre}} M_{\mathrm{tre}} \tag{2}$$

where C is the operation cost, t_{op} the operating time, M_{sol} the amount of solvent used, M_{tre} the amount of solvent treated, C_{Mo} the manpower cost (230 € h^{-1}), C_{sol} the solvent cost, and C_{tre} the solvent treatment cost (non-chlorinated solvents 60 € t^{-1} and chlorinated solvents 300 € t^{-1}).

According to the objective function definition, the synthesis optimisation leads to an operating time reduction associated to a restriction of solvent consumption and treatment. Because of the synthesis dynamic and according to the assumptions adopted, the global synthesis optimisation amounts, from a mathematical point of view, to the dissociated optimisation of the reaction and substitution steps. Consequently, different optimisation problems associated to each step are separately solved by means of a successive quadratic programming (SQP) method [9]. The objective function evaluation is performed by the resolution of the hybrid and differential–algebraic equation (DAE) system [10], representing the global synthesis (reaction and separation steps). This task is performed by a general solver of DAE systems based on the Gear method, DISCo [11]. Thanks to the use of operator sparse and automatic initialisation procedure, DISCo allows an accurate and fast determination of the mathematical model solution. The gradients of objective function and constraints required for SQP method are obtained by the use of a finite difference method.

Table 5
Optimisation results of the reaction step according to the reaction solvent

Reaction solvent	Operating time	Solvent consumption (kg)	Reaction cost (&0x20AC;)
Chloroform	5 h 38 min	1065	3240
Dichloroethane	1 h 49 min	900	734
Acetonitrile	0 h 37 min	561	833

3.1. Reaction optimisation

Optimisation of the reaction step is performed according to the previously defined cost criteria (Eq. (2)), but without solvent wastes. Optimal operating conditions have been determined for the three possible reaction solvents. In this way, the different solvent costs used are the following:

- chloroform: 1.83 € kg^{-1}
- dichloroethane: 0.35 € kg^{-1}
- acetonitrile: 1.23 € kg^{-1}

Operating time represents the single optimisation variable taking into account. Moreover, a 90% constraint on the final reactant conversion is introduced in the optimisation problem formulation. Thus, optimisation problem leads to the determination of the minimal time required in order to obtain 90% conversion.

The optimisation results for the reaction step (Table 5) show that the choice of the solvent leading to the fastest kinetics (acetonitrile) is not the most interesting one with regards to the reaction cost. In fact, the use of dichloroethane allows a better compromise between the reaction rate and the solvent cost. From the reaction point of view, chloroform does not have any advantage because it combines the effects of a slow kinetics and a high price. These results associated to the choice of dichloroethane represent the conclusions of a standard approach to determine the suitable reaction solvent.

3.2. Solvent substitution optimisation

As previously said, three different solvent-changing processes have been considered: a loading evaporation process, an evaporation process operated at constant volume and a distillation process operated at constant

Table 6
Heat of vaporisation of different solvents

Solvent	Bubble point (°C)	Heat of vaporisation	
		($kJ\,mol^{-1}$)	($kJ\,kg^{-1}$)
Reaction solvent			
Chloroform	61	34.2	249
Acetonitrile	82	33.0	795
Dichloroethane	83	37.5	290
Substitution solvent			
1	40	28.0	329
2	56	29.1	501
3	65	35.2	1100
4	78	38.7	841
5	97	41.7	695
6	110	33.2	360

volume. Even though the first two processes can be realised whatever the thermodynamic configuration of solvents is, distillation process requires a substitution solvent more volatile than the reaction one. Therefore, the possible processes are defined by the substitution solvent volatility according to the reaction solvent. The thermal environment of the reactor is assumed to be the same, whatever the solvent-changing process is. Thus, in each case, temperature and flow rate of the heat-transfer fluid circulating into the jacket are, respectively, 24 $m^3\ h^{-1}$ and 140 °C. This assumption involves that operating time only depends on the heat of vaporisation of the solvents. Each substitution solvent has a specific heat of vaporisation related to actual components supplied by the associated database (see Table 6).

For a given substitution solvent, optimisation of the solvent-changing step is carried out according to the reaction solvent and the substitution process. In this way, the variation of substitution solvent price is discretised in four values, representative of the price range of solvents frequently used in industry: 0.36, 0.72, 1.08 and 1.44 &0x20AC; kg^{-1}. For each process, the optimal operating conditions of the control variables (Table 7) are then determined satisfying the separation cost criterion previously defined (Eq. (2)).

The optimisation results of the solvent-changing step show that independent of the process and the substitution solvent considered, the minimal cost is consistently directed to the use of chloroform as reaction solvent. Nevertheless, conditions improving separation (high bubble-point temperature of the substitution solvent, process of evaporation or distillation at constant volume) appear to reduce the gap between the optimal costs related to the use of chloroform and other reaction solvents because of the high price of chloroform compared with other solvents.

Schematically, a process of evaporation at constant volume represents continuous adaptation of a loading evaporation process: infinite number of loading mass and elimination of dead-times. Moreover, its installation only requires a volume controller, and so involves a light additional investment. Thus, in the case of a substitution solvent more volatile than the reaction one, the choice of the suitable substitution process amounts to an evaporation or a distillation at constant volume process. Then, the determination of the optimal operating conditions allows choosing the suitable process.

Compared with a process of evaporation at constant volume, distillation at constant volume allows reducing the substitution solvent consumption by an enhanced separation. Nevertheless, this reduction also involves an increase of operating time due to the column reflux. Solvent consumption and operating time are opposed in the definition of the global cost. Thus, a distillation process appears interesting in cases where the benefit from the reduction of the substitution solvent consumption is greater than the resultant operating time increase, i.e. in cases where substitution solvent cost is important and where separation is easy (important gap of volatility between solvents).

Table 7
Characteristics of the substitution step optimisation problems

Substitution process	Steps	Objective function	Control variables	Constraint
Loading evaporation	N	Substitution cost	Loading amounts	Final purity
Evaporation at constant volume	1	Substitution cost	Constant volume	Final purity
Distillation at constant volume	1	Substitution cost	Constant volume, reflux ratio	Final purity

Table 8
Reaction solvent choice according to the considered step

Reaction optimisation	Separation optimisation
1. Dichloroethane	1. Chloroform
2. Acetonitrile	2. Acetonitrile
3. Chloroform	3. Dichloroethane

4. Reaction solvent choice

The contradictory results obtained at the end of the reaction and separation steps optimisation (Table 8) clearly show that the reaction solvent choice necessarily involves taking into account of the whole synthesis by means of a global approach. The global synthesis cost is then evaluated through the optimal solutions related to each step (reaction and separation). Afterwards, the comparison of different global costs directly leads to suitable reaction solvent choice. Moreover, the optimisation studies carried out provide the optimal operating conditions connected with this solvent choice. Thus, optimal costs and the associated reaction solvent are given according to the volatility and price of the substitution solvent and for each solvent changing process, in Figs. 3–5.

Fig. 6 shows that independent of the substitution process, optimal solutions almost exclusively lead to

Bubble	**Solvent cost (€/kg)**					
point (°C)	0.38	0.76	1.14	1.52		
40	13771 (C)	19774 (C)	25776 (C)	31779 (C)		
56	9246 (C)	11303 (C)	13360 (C)	15417 (C)	(C)	Chloroform
65	8181 (C)	9491 (C)	10802 (C)	12112 (C)		
78	**6902 (A)**	7996 (C)	8887 (C)	9779 (C)	*(D)*	Dichloroethane
97	**5793 (A)**	**6777 (A)**	7670 (C)	8252 (C)		
110	*4971 (D)*	*6393 (D)*	*7214 (D)*	7775 (C)	**(A)**	Acetonitrile

Fig. 3. Synthesis optimal cost for a loading evaporation substitution process.

Bubble	**Solvent cost (€/kg)**					
Point (°C)	0.38	0.76	1.14	1.52		
40	11159 (C)	14796 (C)	18432 (C)	22069 (C)		
56	**5743 (A)**	8131 (C)	9443 (C)	10755 (C)	(C)	Chloroform
65	*6495 (D)*	7435 (C)	8369 (C)	9304 (C)		
78	**4570 (A)**	**5822 (A)**	**7073 (A)**	8055 (C)	*(D)*	Dichloroethane
97	**4088 (A)**	**4910 (A)**	**5733 (A)**	**6555 (A)**		
110	**3896 (A)**	**4615 (A)**	**5334 (A)**	**6054 (A)**	**(A)**	Acetonitrile

Fig. 4. Synthesis optimal cost for an evaporation at constant volume substitution process.

Bubble	**Solvent cost (€/kg)**					
Point (°C)	0.38	0.76	1.14	1.52		
40						
56					(C)	Chloroform
65	6554 (C)	7462 (C)	8370 (C)	9279 (C)		
78	5871 (C)	6565 (C)	7178 (C)	7680 (C)	*(D)*	Dichloroethane
97	**4150 (A)**	**4941 (A)**	**5731 (A)**	**6515 (A)**		
110	**3904 (A)**	**4558 (A)**	**5098 (A)**	**5591 (A)**	**(A)**	Acetonitrile

Fig. 5. Synthesis optimal cost for a distillation at constant volume substitution process.

Bubble point (°C)	Solvent cost (€/kg) 0.38	0.76	1.14	1.52
40	11159 (C)	14796 (C)	18432 (C)	22069 (C)
56	**5743 (A)**	8131 (C)	9443 (C)	10755 (C)
65	*6495 (D)*	7435 (C)	8369 (C)	9279 (C)
78	**4570 (A)**	**5822 (A)**	**7073 (A)**	7680 (C)
97	**4088 (A)**	**4910 (A)**	**5731 (A)**	**6515 (A)**
110	**3896 (A)**	**4558 (A)**	**5098 (A)**	**5591 (A)**

(C) Chloroform
(D) Dichloroethane
(A) Acetonitrile
Loading evaporation
Cst V Evaporation
Cst V Distillation

Fig. 6. Synthesis optimal cost according to the solvent characteristics and the process of the substitution step.

the use of chloroform or acetonitrile. The choice of one solvent instead of the other depends on the process and the solvent characteristics of the substitution step. Thus, conditions improving separation (high bubble-point temperature of the substitution solvent, process of evaporation or distillation at constant volume) appear to favour the use of acetonitrile. In fact, separation improvement involves a reduction of the gap between the substitution costs related to different solvents, which favour the use of fast kinetics reaction solvents. The similar characteristics of dichloroethane and acetonitrile then lead to the choice of acetonitrile that is slightly more volatile and kinetically faster.

Compared with the results of an optimisation only based on the reaction step, Fig. 6 highlights the benefits of a global approach. In fact, a classical methodology favours the use of dichloroethane. When taking into account the overall synthesis, the use of dichloroethane rarely appears advantageous, only one case in of 24. Chloroform is more adapted when the volatility of the substitution solvent is low or its cost is high (12 cases out of 24) and acetonitrile in other cases (11 out of 24).

A comparison between different processes (Fig. 6) allows the determination of the reaction solvent and the substitution process, leading to an optimal synthesis for a given substitution solvent. In the case of this study, this comparison shows a privileged choice for a process of evaporation at constant volume. In fact, advantages related to the distillation process (reduction of solvent consumption and treatment) compensate its drawbacks (increased operating time) only for high bubble-point temperatures and high prices of substitution solvent.

5. Conclusion

A global approach for the reaction solvent choice, based on the whole synthesis optimisation, has been successfully used. In the case of a reaction–separation operation, integrating a Beckmann rearrangement reaction, this approach allows determining the reaction solvent leading to the lowest operating costs. Moreover, the global approach framework has been extended to the determination of the optimal operating conditions and hence the suitable separation process choice. As part of this study, a classical methodology based only on the reaction step has also been studied. For the considered reaction–separation operation, the comparison of the two different approaches highlights the benefits linked to the use of global approach.

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