Development of systematic procedures for the evaluation of solvent selection at an early stage in pharmaceutical process.
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Development of systematic procedures for the evaluation of solvent selection at an early stage in pharmaceutical processes

S. Perez-Vega[a], P. Sharratt[a] and A. Nieva-de la Hidalga[b]

[a] *School of Chemical Engineering and Analytical Science, The University of Manchester, PO Box 88, Sackville St, Manchester, M60 1QD, UK*

[b] *Information Systems Group, School of Informatics, University of Manchester Manchester, PO Box 88, Sackville St, Manchester, M60 1QD, UK*

Abstract

Three levels of evaluation for the selection of solvents have been developed, taking account the lack of information as one of the main characteristics of the problem. Tools to aided the evaluations and able to be applied early in design were identified. The first level is based on system properties analysis. A second level considers the impact of the potential streams to be formed on the system. A third level exploits process simulation in order to evaluate industrial scale issues of the solvents on the system. A case study based on the synthesis of P*ropranolol* is presented, where in a typical manufacturing process solvents such as water, isopropylamine, diethyl ether and cyclohexane are used for different operations. The evaluations revealed that solvents such as isopropylamine and diethyl ether gave high costs as implications of their management and containment. On the other hand, some of their characteristics are necessary for the successful performance of operations such as reaction and extraction. Through the analysis future implications related with the use of a group of solvents are explored with the aim of providing decision-support information. By this means, the efforts at early stage can be aimed towars a more sustainable process.

Keywords: evaluations, system, solvents, early stage, cost implications

1. Introduction

Solvent are one of the main raw materials in a pharmaceutical process. This is because many operations commonly applied at this industry need the application of a solvent. It is considered that solvents represent between 80% and 90% of the total mass utilization in a pharmaceutical industry (Constable, Jimenez-Gonzales et al. 2007). This reflects the great importance that solvents have in the complete process. Moreover, the issues arising from the use of solvents are reflected in high costs for the industry.

Over many years the use of solvents has brought severe consequence to the industries, and as a result, the regulations regarding the use of such chemicals has become severe. Emissions to the environment, great amounts of waste for disposal and difficulty in handling solvents at the plant are some of the common issues present in the pharmaceutical industry.

In contrast with the chemist who has to discover and provide a synthetic route for the synthesis of the drug at laboratory scale, the chemical engineer needs to analyse the recipe and take it to an industrial scale. Since many of the conditions in the laboratory are hard to replicate at industrial scale (time and cost constrains), many issues arise during scale-up. Solvents that had a very good performance in the laboratory might present lots of complications when the synthesis it is scaled up. One of the reasons of this common issues it that the chemist and chemical engineer, due to their different backgrounds work with different views. Another aspect it is that both work under completely different conditions, and delivering different outcomes. Whereas the chemist it is trying to deliver a synthetic route for producing few grams of drug in the lab, the chemical engineer it is trying to produce tones with equipment available at industrial scale.

1.2 Current approaches to solvent selection and evaluation

Solvent selection is an issue that has been studied for a long time. One common approach is to look for desired solvent properties for certain task (Modi, Aumond et al. 1996; Li, Harten et al. 2002). Solvent design is another approach that has been applied to select solvents. Methodologies such as CAMD (computer aided molecular design) are applied for the design of solvents with desired "ideal" properties. Examples of this approach have been presented in the academic field (Sinha, Achiene et al. 1999; Kim and Diwekar 2002). Other approaches (Hostrup, Harper et al. 1999) have included environmental criteria for the design of solvents, optimisation techniques such as MINLP (Mixed Integer Non Linear Programming) and Simulation (PROII) in order to design and detect good solvents for separation tasks and provide separation flow sheets.

Physical properties have had a big influence in the selection of solvents; as a result, much work has been published (Jaksland, Gani et al. 1995; Zhao and Cabezas 1998; Wypych 2006). Solubility has been one of the most important characteristics in some approaches to aid the selection of solvents(Kolar, Shen et al. 2002), where the selection it is based in the prediction of solubility mainly based on thermodynamic models (Frank, Downey et al. 1999; Chen and Crafts 2006).

Other industrially originated methodologies are based on scoring the weighting that solvent properties and characteristics have on SHE (Saftey Health and Environment) implications (Jimenez-Gonzales, Curzons et al. 2005). These methodologies aim to advise to the chemist about potential SHE and life-cycle issues associated with paticular solvents.

Recently, there has been work published (Gani, Jimenez-Gonzalez et al. 2006) about the latest approaches applied for the selection of solvents, where criteria such as desired properties, database screening, reactivity, properties simulation and software tools have been proposed.

Even with the great number of solvent selection methodologies available there is a great number of gaps that need to be covered, especially for the selection of solvents for the pharmaceutical industry. The academic community has been slow in considering solvent selection as a part of broader considerations, hence, approaches are still in their infancy (Constable, Jimenez-Gonzales et al. 2007). Because of the complexity of the molecules produced by the pharmaceutical industry modelling of solubility and other properties is not a common practise. Solvent design methodologies sometimes suggest unavailable or costly solvents. Other methodologies suggest the use of mixtures when process engineer might rather single solvents in order to avoid complexity in handling mixtures. In the case of optimisation models there is a need to extend these models and explore what are the real constraints to evaluate. Because of this, it is necessary to explore more about the process behaviour. Each process will have different key variables. Also, it is necessary to have a more realistic representation of the real problem. For example, many of this approaches tend to optimise the use of solvent for certain operations such as reaction, distillation, extraction, or cleaning, without looking into the implications for the whole process. It is clear that all the operations are related in some way; so solvent selection should be extended towards the study of solvent performance in the complete system.

2 Methodology

2.1 System evaluation

One of the important aspects that needs to be covered to succeed in the selection of solvents it is that the evaluation of their performance should consider the whole process. Implications that arise from the use of solvents can aid the appreciation of potential issues very early in design. Figure 1 displays some of the principal activities where solvent selection has potential impacts.

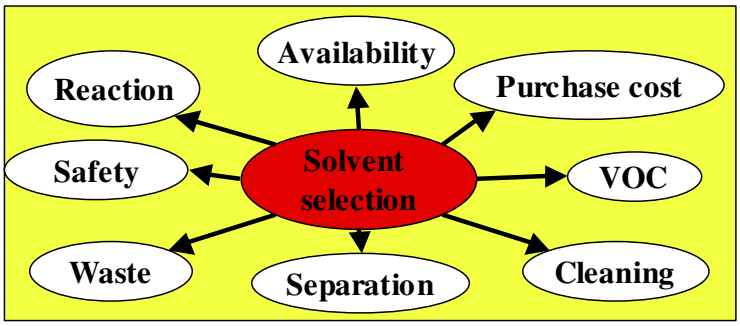

Figure 1. Activities related with solvents

A methodology based on the application of a variety of tools is proposed. The individual tools were selected considering their applicability at an early stage. The integration of the tools into a user-friendly framework has been discussed elsewhere (Perez-Vega and Sharratt 2007). There, three levels of evaluation where introduced (Table 1) of the issues presented in Figure 1. Each level starts with a question to be answered by the chemist; this answer is the starting point of the evaluation.

Level	Starting point	Type of analysis
1	*What solvents are you planning to employ?*	Property-Based analysis to identify most suitable solvents
2	*What are the potential conditions?*	Phase analysis to support design of processing operations
3	*What is the Laboratory recipe?*	Industrial Scale analysis to deliver manufacturing process

Table 1. Levels of analysis.

The evaluation steps were integrated into systematic evaluation procedures, with different algorithms for the evaluation of each level. An interactive tool containing such algorithms was created in order to guide the chemist through the evaluations. As a result, the approach can interact with the chemist in a user-friendly environment.

2.2 Tools employed in the methodology

Some of the type tools employed for the evaluation of solvents at the different levels and some examples of are displayed in Figure 2. As well as being suitable for use with limited information at an early stage, a tool should be easy to apply and provide understandable outcomes for the user.

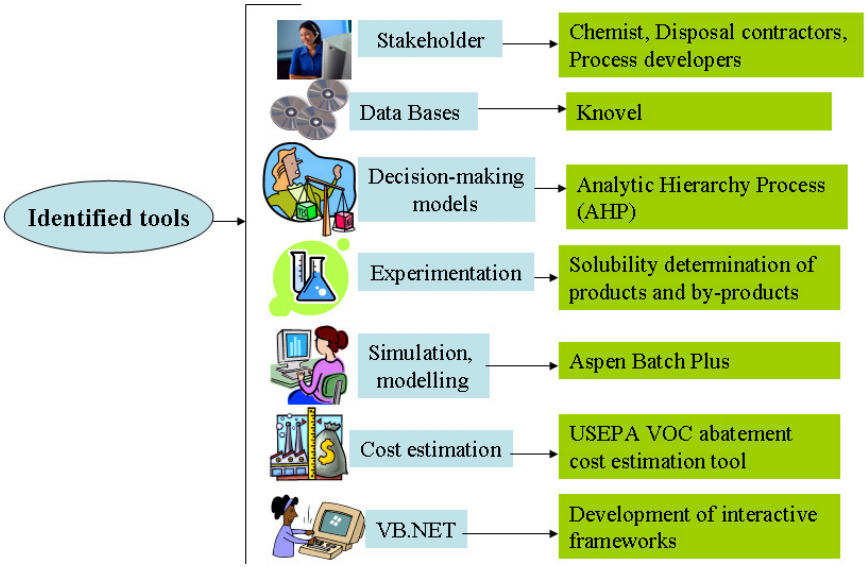

Figure 2. Tools identified to include in the methodology

2.2.1 Stakeholders interaction

An important aspect to consider in this methodology is to identify the most important stakeholders involved in the synthesis of pharmaceuticals. The aim is to detect what kind of information can be obtained from each stakeholder in order to develop an effective evaluation. For example, disposal contractors are frequently considered only when solvent disposal is the only option (and not at an early stage). As a result the cost for solvent disposal increases. Solvent contractors need to be considered with the aim of evaluating potential mixtures at an early stage and provide better alternatives for the process.

2.2.2 Solvent databases

Solvent databases are used in order to obtain solvent properties for a given duty and the evaluation of potential solvents for a synthesis. These databases have been identified in other work (Gani, Jimenez-Gonzalez et al. 2006). However, it is important to developed procedures for the effective management of such information and developed especial procedures for the use of properties exclusively for the evaluation of solvents in the pharmaceutical industry. This work explores the development of tools for the querying and analysis of solvent properties coming from databases. To achieve such goal, VB.NET tools where developed in order to developed a user-friendly framework

2.2.3 Decision making models

A mathematical method for multi-criteria desicion making was integrated into the framework with the aim of producing ranked groups of available solvents with desired characteristics. To achieve this, the well known Analytic Hierachy Process methodology (AHP) was used. The complete methodology has been explained by Saaty (1977) and examples of its used have been presented (Amna, Ludmil et al. 2004). The methodology consists of five steps:

- Problem statement,
- Assesment of criteria weights,
- Construction of a normalized performance matrix,
- Construction of a weight -normalized performance matrix, and
- Calculation of the relative Euclidean distances.

As a result, the solvent with the smallest Euclidean distance from the ideal would be the solvent requested by the user. For convenient application the tool was implemented within the tools developed in the VB.NET framework.

2.2.4 Experimentation

Experiments, which can provide important data for the evaluation of solvents in the system, are considered. Experiments developed by the chemist such as solubility of

the products and by-products and mixture behaviour help when exploring the behaviour of the process. The aim of this methodology is to determine which experiments might be useful for the evaluations.

2.2.5 Simulation

A simulation package such as ASPEN Batch Plus (ASPEN 2004) is used for the simulation of a pharmaceutical synthesis provided in a recipe as well as with information obtained from the last level of evaluation. The goal is to obtain reliable mass balances of the principal solvent streams in order to evaluate their performance in the process from an industrial scale.

2.2.6 Cost estimation

Tools for developing cost estimation where identified such as the case of the USEPA (USEPA 2002) for the determination of cost related to the abatement of emissions. Other examples of cost estimation tools are contractor, heuristics, and solvent price databases (Chemical Reporter 2007).

2.2.7 Tools

The VB.NET programming language was applied for developing tools required for the easier analysis of solvent selection and evaluation. Some of the developed tools are:

Query Builder

A query builder was developed at VB.NET with the aim of provider the user frienly query options for establishing criteria for searching solvents. This query tool is link to databases and can withdraw solventes after establish the criteria desired. The tool was introduced in other work (Perez-Vega and Sharratt 2007). The tool consist of three different criteria for the search of a potential solvents. The criteria were developed with the aim that the chemist could carry out an easy search.

Telescoping tool

Solvent swap it is a common activity in the pharmaceutical industry where great deal of solvent is employed. Exploring the use of solvents for more than one task (solvent telescoping) might offer benefits for the synthesis since the potential reduction in the number of solvents employed will reduce the amount of waste produced. An algorithm (Fig. 3) for exploring solvent telescoping was developed in VB.NET. Even a small reduction in the used of solvents is reflected in a reduced effect in the solvent life impacts (Constable, Jimenez-Gonzales et al. 2007).

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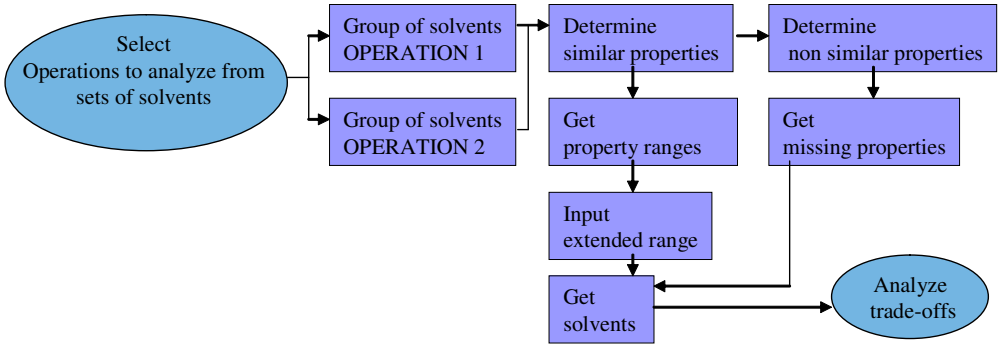
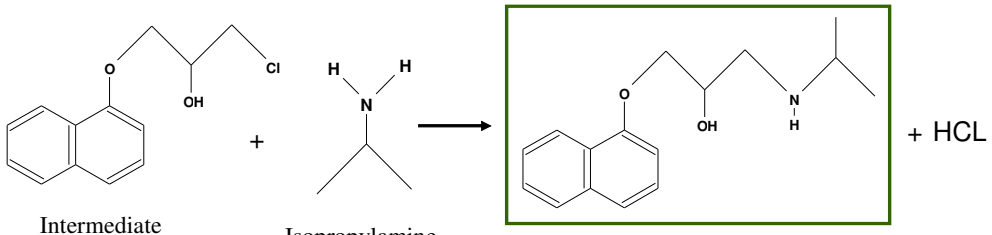


Figure 3. Telescoping algorithm

3. Propranolol case study

3.1 First level

The synthesis of Propranolol (Inderal) was treated as if it was an early stage synthesis in order to evaluate the methodology. Starting from a first level of evaluation the chemist has an idea about the potential synthesis of the drug as presented in the main reaction below.



Intermediate Isopropylamine Propranolol

Figure 4. Potential synthesis route

At this stage the chemist is about to explore the potential solvents at the different potential stages of the synthesis. The first task at this level is to developed a “property based” search for potential solvents to developed the synthesis. The chemist considers that four solvents are required for the potential synthesis. Some of the information provided by the chemist for creating the queries and obtain potential solvents for the different operations are show below :

Reaction: As can be seen in the potential reaction (Fig. 4) Isopropylamine is a strong candidate for the synthesis. Since isoproplamine is among the reactants it might present good solubility for the solute. The use of this solvent might present great advantages. Nevertheless, solvents with similar properties were also explored. To

achieve this, characteristics such as polarity in the ranges of low-medium polarity are input through the query tool.

Dissolution: A dissolution will take place in order to create a liquid phase for further work-up. As a consequence, a polar solvent with a liquid phase present at standart conditions is desired.

Extraction: Once the phase from dissolution has been form and extraction is considered with the aim of removing impurities. For such a task a solvent with low polarity, and low density is required.

Crystalisation: Crystalisation is considered as one of the common last steps of the synthesis to achieve efficient impurity removal. Hence, a non-polar, low toxicity, medium boiling point solvent is necessary.

3.1.1 Solvent search

These queryes are introduced into the query builder (Fig 5), to produce lists of potential solvents having the appropriate properties for each operation.

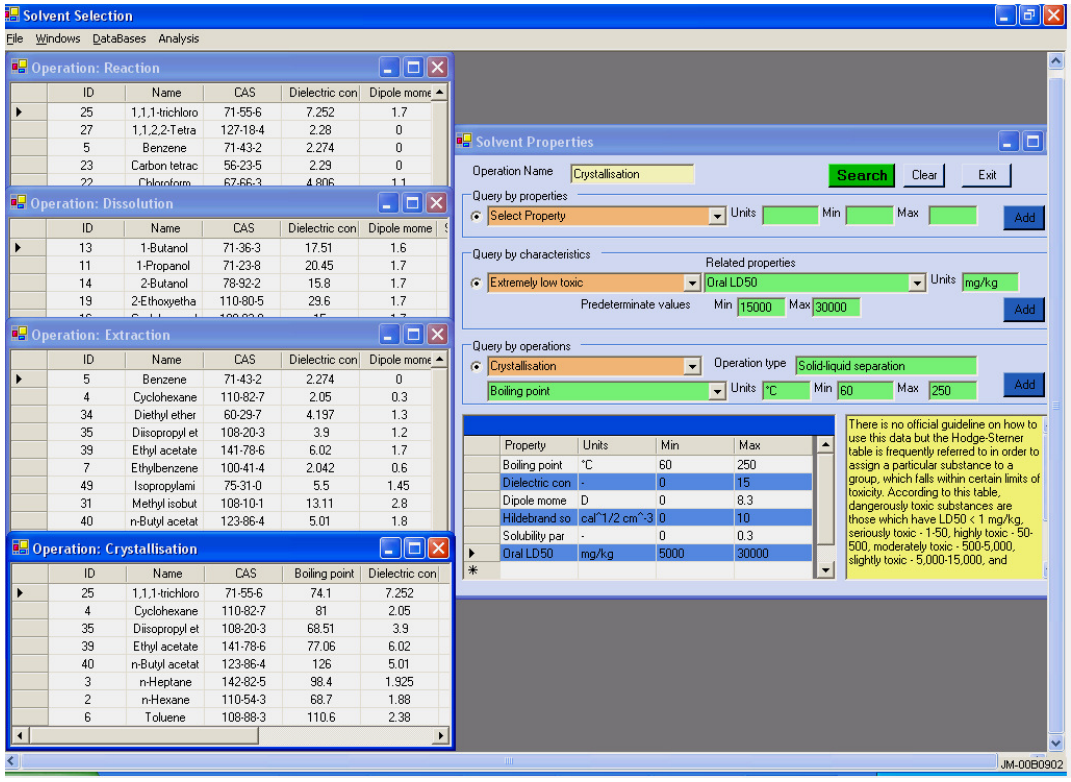


Figure 5. Query builder and lists of potential solvents

The next step might be to assess which solvents better suit the different operations from among the list obtained.The list of solvents obtained from the query builder are taken into the AHP (Fig. 6) tool where the chemist gives weight to the different properties. At the same time he provides the values of the parameters for the “ideal” solvents.

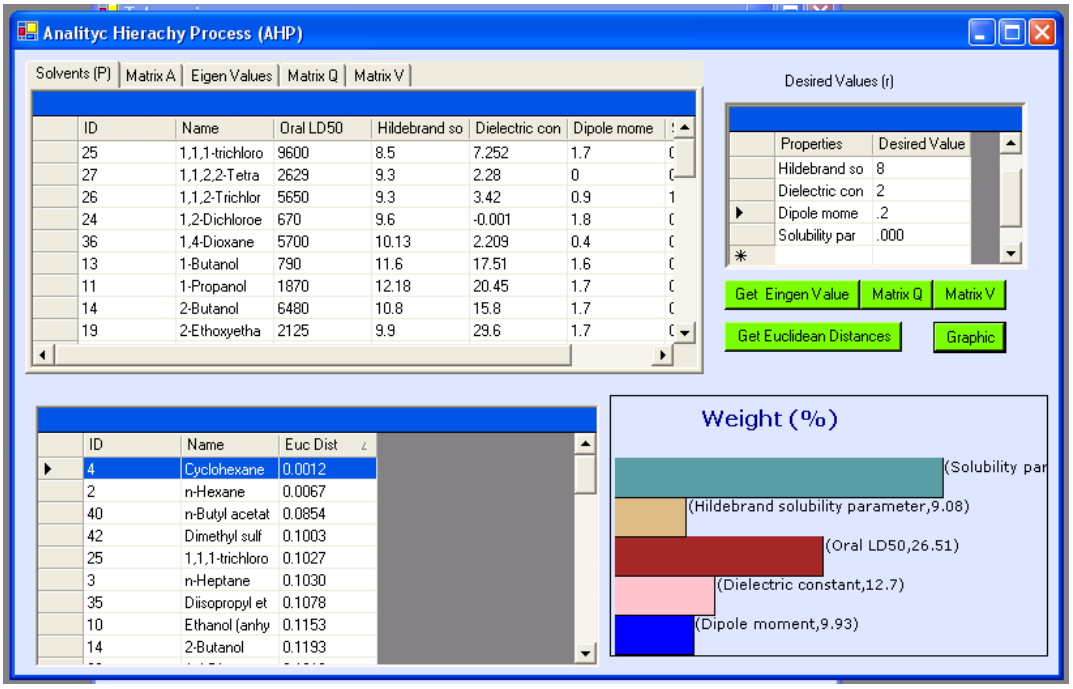


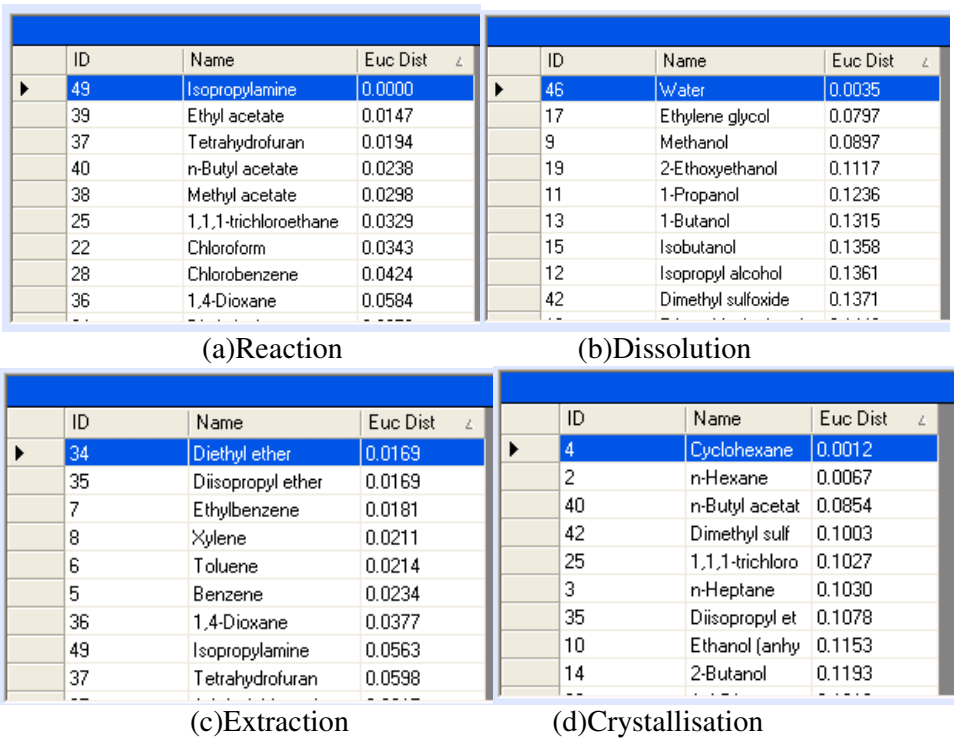
Figure 6. Multi-desicion AHP tool

At the top of the form (Fig. 6) the different matrices required for the analysis are displayed. At the same time a graphic is displayed to show the user the importance of each property at the decision. Figure 6 shows the analysis of the list of potential solvents for the crystallisation operations, where solubility parameter ENT and toxicity (LD50) are the parameters with more weight in the decision. As suggested by the chemist; for the crystallisation of propranolol a non-polar solvent might be required. Another important aspect is that crystallisation usually is one of the last operations in the synthesis of pharmaceutics. Toxic solvent impurities contained in the pharmaceutical represent an important issue. Because of this, it is recommended to use low toxicity solvents in the last stages of the synthesis. After the user inputs the information required, the Euclidean distances are displayed. The solvents with the smallest Euclidean distance values are displayed at the top of the list, telling the user that the solvents with parametes more similar that the ideal parameter are the ones at the top of the list. This analysis provides guidance to the chemist about what kind of solvents might be worth trying in the laboratory.

The same procedure was repeted for the different operations in order to obtained the best potential solvents for the different operations. Figure 7 shows the different lists

of solvents for the synthesis of each operations. In the case of reaction isopropylamine is the solvent to test, for dissolution water looks as the best option. For extraction the best option diethyl ether is also selected. In the case of crystalisation cyclohexane is the solvent to test.

Having seleted the potential solvents for the synthesis, different evaluations were performed with the aimed of exploring alternatives and provide decision-making information about the penalities and advantages of using the selected group of solvents in a system.



ID	Name	Euc Dist
49	Isopropylamine	0.0000
39	Ethyl acetate	0.0147
37	Tetrahydrofuran	0.0194
40	n-Butyl acetate	0.0238
38	Methyl acetate	0.0298
25	1,1,1-trichloroethane	0.0329
22	Chloroform	0.0343
28	Chlorobenzene	0.0424
36	1,4-Dioxane	0.0584

(a)Reaction

ID	Name	Euc Dist
46	Water	0.0035
17	Ethylene glycol	0.0797
9	Methanol	0.0897
19	2-Ethoxyethanol	0.1117
11	1-Propanol	0.1236
13	1-Butanol	0.1315
15	Isobutanol	0.1358
12	Isopropyl alcohol	0.1361
42	Dimethyl sulfoxide	0.1371

(b)Dissolution

ID	Name	Euc Dist
34	Diethyl ether	0.0169
35	Diisopropyl ether	0.0169
7	Ethylbenzene	0.0181
8	Xylene	0.0211
6	Toluene	0.0214
5	Benzene	0.0234
36	1,4-Dioxane	0.0377
49	Isopropylamine	0.0563
37	Tetrahydrofuran	0.0598

(c)Extraction

ID	Name	Euc Dist
4	Cyclohexane	0.0012
2	n-Hexane	0.0067
40	n-Butyl acetat	0.0854
42	Dimethyl sulf	0.1003
25	1,1,1-trichloro	0.1027
3	n-Heptane	0.1030
35	Diisopropyl et	0.1078
10	Ethanol (anhy	0.1153
14	2-Butanol	0.1193

(d)Crystallisation

Figure 7. List of solvents available for the different operations

3.1.2 Solvent telescoping

The solvent telescoping tool (Fig. 8) was applied to explore the reduction in the number of solvents for the synthesis.

The tool compares the properties contained on each operation. Similar properties between the two operations are detected by comparing the needs of the consecutive operations in a pairwise manner. In this case, *Reaction* operation was compared against *Dissolution* and *Extraction* against *Crystallisation*

Analysing telescoping oportunities for the operations *Reaction-Dissolution* none of the solvents contained in the options for both operations presents characterisitcs for a

potential solvent telescoping. This is because the polarity requirements differ a lot. Since *Reaction* operations requires a solvent with medium polarity, *Dissolution* requires a solvent with very high polarity such as water in order to form an aqueous phase for further work up.

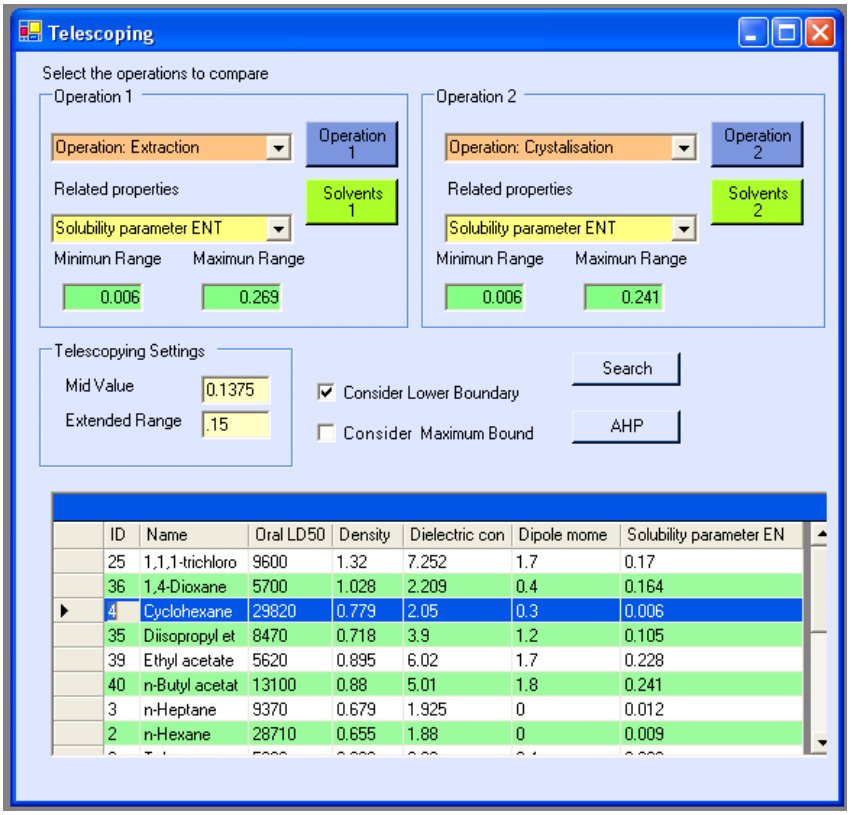


Figure 8. Telescoping tool

In the case of *Extraction-Crystallisation* and since for these operations required non-polar and low polar solvents, the extended range for the solublity parameter ETN is set to .15 in order to give some flexibility and find solvents located among the two sets of solvents. As a result, potential solvents for exploring the performance of both operations with a single solvent are displayed. Propeties such as LD50 and density were incorporated into the analysis. For including the importance of such properties into the analysis the AHP tool was employed (Fig 9), giving weight to the desicion for obtaining solvents with desired solubility, density (phase separation for extraction) and LD50 (low toxicity for crystallisation).

A list of potential solvents for exploring solvent telescoping between Extraction and Crystallisation are provided. As a consequence, the chemist can judge and spot very early in design about opportunities for selecting the best solvents for the performance of the system. Another important aspect of the analysis is that the user can detect very

early on design where do the efforts should be aimed. The other levels presented in this work continue with the selection and evaluations developed at this point.

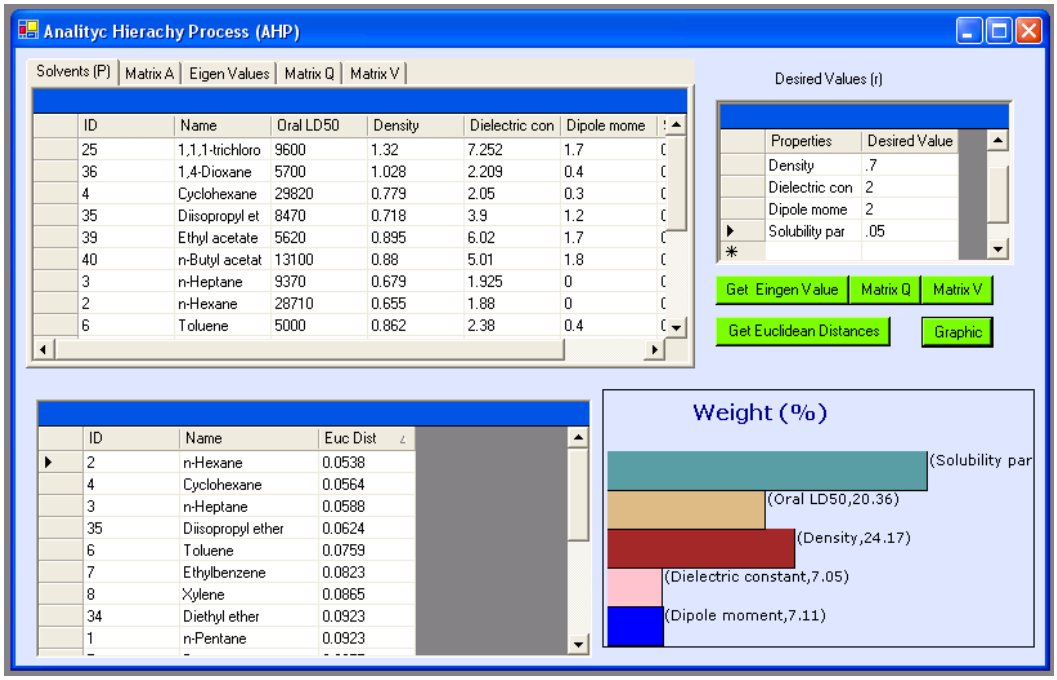


Figure 9. AHP for the Extraction-Crystallisation telescoping analysis

3.2 Second level

3.2.1 Phase analysis

Phase analysis was developed with the aim of exploring potential phase formation into the synthesis. This analysis aids to give an idea about potential issues related with issues such as: solvent handling, potential mixture formation, waste disposal issues, and potential VOC produced along the process. This analysis uses tools such as process heuristics and information provided by process developers as well as information coming from the chemist. At this stage more information about the synthesis stages are provided from the laboratory (Fig. 10).

Compound	Water solublily
Propranolol	Soluble (pH < 6)
Byproduct 1	Sparinlgy (pH 1-10)
Byproduct 2	Sparinlgy (pH 1-10)

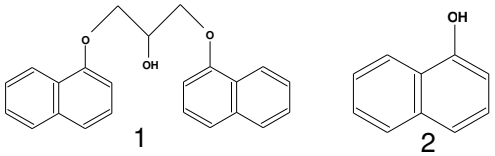


Figure 10. By-products and solubility data provided by the chemist

Main by-products identification as well as water solubility behaviour plays and important role for the effective separation in the synthesis, as a consequence,

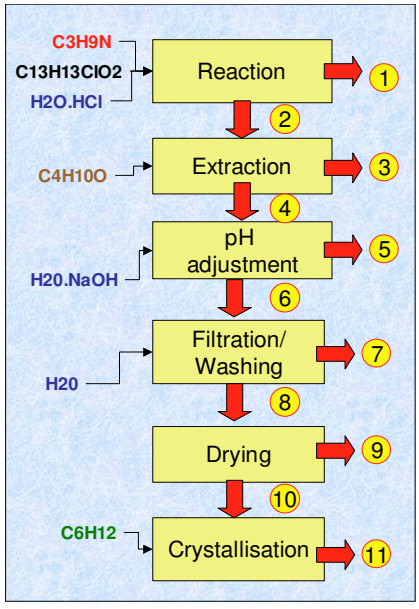
operations such as pH adjustment, Filtration/Washing, and Drying are also introduced into the potential synthesis in order to favour an effective by-product separation.

With the information provided at these stage potential streams formed in the synthesis are identified for the process. Potential process conditions (Fig. 11) are also identified. Having this information is possible to determine qualitatively the possible main streams formed (Fig. 12a) and their potential components ((Fig. 12b).

Operation	Temperature (℃)	Pressure (bar)
Reaction	80	>5
Extraction	23	<5
pH Adjustment	23	<5
Filtration/Washing	23	<5
Drying	>100	<5
Crystallisation	<80	<5

Figure 11. Potential process conditions

One aspect to highlight from the process conditions applied at laboratory scale is that the reaction takes place at high pressure, something not very common at industrial scale in the pharmaceutical industry. However, this condition is necessary to keep the isopropylamine at liquid phase at reaction temperature. Potential phases presented at the process are obtained (Fig. 12b), where V= Vapour, L=Liquid and S= Solid.



(a)

	Potential Phases	Main Components
1	V	C3H9N
2	V,L	C3H9N, H2O.HCl, Inderal, By-products
3	V,L,S	H2O.HCl, C4H10O, Inderal, By-products
4	V,L,S	H2O.HCl, C3H9N, C4H10O, Inderal, By-products
5	V	C3H9N, C4H10O
6	V,L,S	H2O.HCl, H20.NaOH, C3H9N, C4H10O, Inderal, By-products
7	V,L	H2O.HCl, H20.NaOH, C3H9N, C4H10O, By-products
8	V,L,S	C3H9N, Inderal, By-products
9	V	H20, C3H9N, C4H10O
10	S	Inderal, By-products
11	S,L	C6H12, Inderal, By-products

(b)

Figure 12. Streams and main components

In order to obtain more information about the performance of the solvents at industrial scale some SHE related properties are consulted for each solvent (Fig. 13).

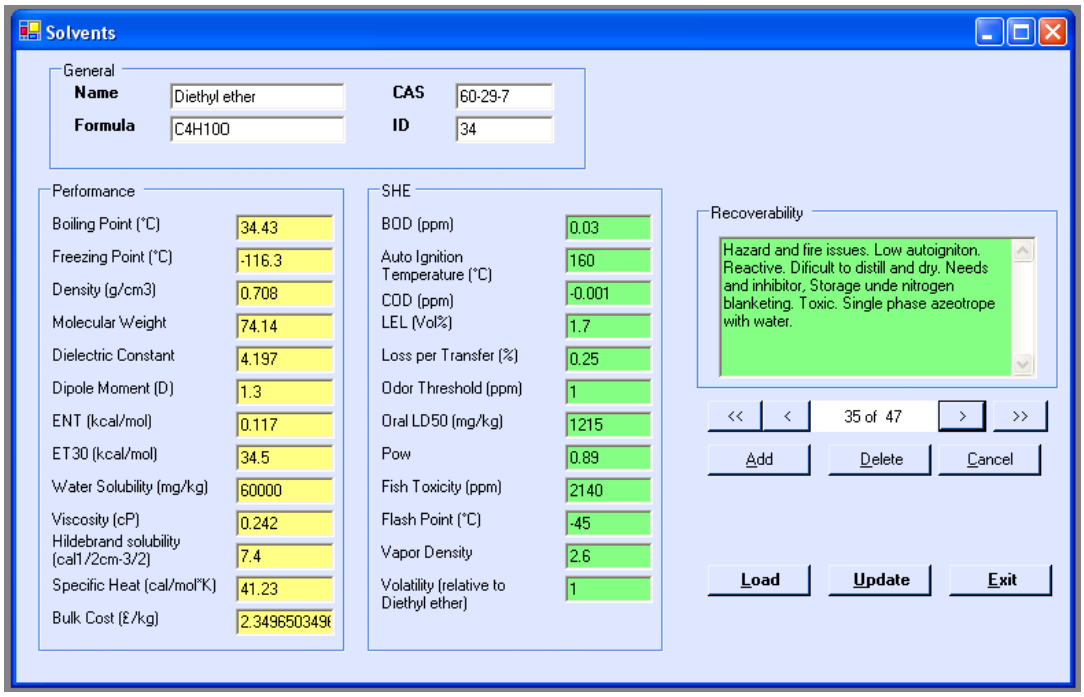


Figure 13. Properties and recovery notes

Another important aspect at this stage is that the chemist and chemical engineer can start to predict which kind of mixtures would be present in the system, and decide which experiments can be more suitable in the laboratory to obtain information. Consulting some properties related with SHE from the database it is visible that solvents such as isopropylamine, and diethyl ether will present issues at industrial scale in aspects such as: VOC, toxicity, flammability, corrosivity, azeotropy and explosivity. These issues will represent a potential cost implication for the process. Nevertheless, some other characteristics such as solubility and density are ideal for the perfomance of the synthesis. After the most important trade-offs are identified the next step is to analyze the cost implication for such trade-offs.

Another important aspect at this stage is to evaluate future implications related with waste and VOC generation. A typical characteristic of the pharmaceutical industry id that it disposes huge amounts of solvent. Many times, disposal contractors do not have a choice other than to incinerate these mixtures due to the mixture characteristics. As a consequence, the disposal cost it is elevated. At this stage and with the generated information disposal contractor can look for opportunities to reuse waste in activities such as solvents for car washing and cement kiln fuel. Interacting with disposal contractors at this stage might open new possibilities for the future disposal of solvent wastes. As a result, win-win situations are created and the pharmaceutical industry reduces considerably waste disposal cost, and the disposal

contractors generate more profit at the time of find an alternative use for the waste solvents.

3.3 Third level

3.3.1 Cost analysis

Recipe simulation and cost estimation was applied for the determination of the mass balance of the solvents at industrial scale. The Aspen Batch Plus simulator was applied for simulating the recipe provided by the chemist. The simulation was carried out with the aid of process development knowledge in aspects such as; amount of drug produced, charging times, equipment selection, scheduling, operations, campaign behaviour, and draft layout (Fig. 14), This was done with the aim of producing a simulation closer to the reality. Phase analysis had previously shown potential issues related with the low boiling point of isopropylamine and diethyl ether. Therefore, the VOC abatement cost can be calculated at this third stage.

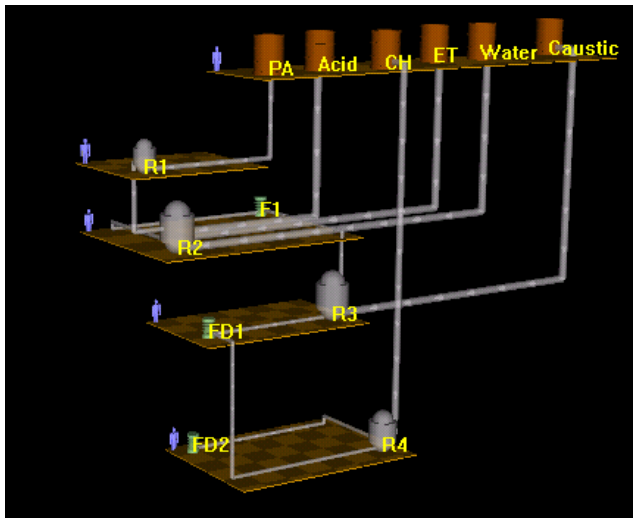


Figure 14. Draft Layout of the Propanolol Plant

After the simulation a profile of the behaviour of the emissions throughout the campaign was obtained (Fig. 15a). The peaks produced in the emission behaviour come from the use of isopropylamine and diethyl ether into the process. Cost estimation for the abatement of the emission was calculated applying an EPA method (USEPA 2002).

The costs obtained in Figure 15b are the costs assumed to abate the emissions of the whole process at 90% efficiency. Capital (TCI) and Operation (TOC) costs can vary considerably from one technology to another. Water absorption seems the cheapest option. Nevertheless, the water solubility of cyclohexane and diethyl ether is not as higher at the one presented by isopropylamine. It might be necessary to explore other absorbents and not only water. Another aspect to consider will be to abate the emissions in separate equipment. Catalytic incineration presents higher TOC and TCI;

this might be because of the technology required as well as fuel and catalyst. Thermal incinerators show less cost than the catalytic incinerators, while condensation is the second cheapest option.

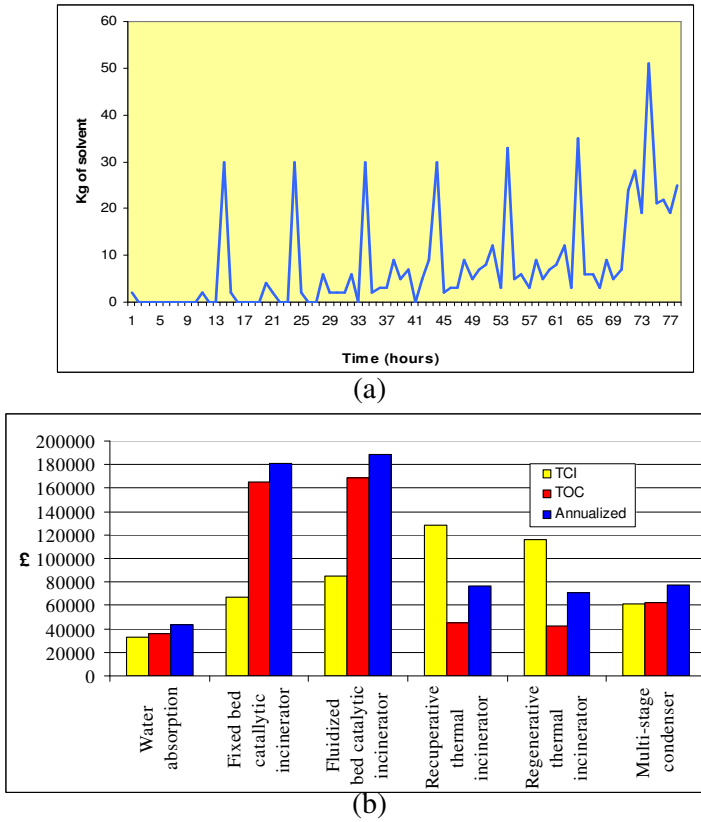


Figure 15. VOC emission profile (a) and Abatement cost (b) for the Propranolol Plant

All these decisions are strongly dictated for the characteristics of the emission. These analyses give hints about what kind of tools should be employed in order to validate and obtain more robust data. One example would be to contact a contractor to estimate the cost and validate our results at the same time. At this stage the cost evaluations can continue in order to evaluate other the cost implications related with managing the solvent at industrial scale.

4. Summary and Conclusions

During the first level of evaluation potential solvents were identified. This gives the chemist the opportunity to explore available solvent alternatives very early at design. Also, solvent telescoping was introduced at this level with the aim of exploring candidate solvents for the reduction in the number of solvents employed during the synthesis. In the second level the solvents selected by the chemist were analyzed from a phase formation perspective. This gives the chemical engineer information about the potential phases present in the process as well as potential qualitative composition. As

a result early interaction is generated with important stakeholders related with the performance of the solvent in the system. The third level explored the simulation of the synthesis lab recipe in order to estimate cost implications related with the use of solvents at the system. The systematic analysis presented provides tools for the analysis of solvents performance on a system very early at design; as a result, chemist and chemical engineer can be aware about potential implications. Moreover, the analysis aids to weight such implication. As a result good decisions are expected at the time of selecting solvents in order to develop more sustainable process at the pharmaceutical industry.

Respecting the *Propranolol* synthesis future SHE issues are detected with the use of isopropylamine and diethyl ether. Nevertheless, in aspects such as performance the solvents present ideal characteristics. However, the cost implications related with the SHE might suggest to the chemist to explore other of the potential available solvents obtained at level one. Solvent presenting similar performance characteristics such as solubility and density, but different properties related with SHE.

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