17th European Symposium on Computer Aided Process Engineering – ESCAPE17
V. Plesu and P.S. Agachi (Editors)

Solvent selection evaluation tools for an early stage at pharmaceutical process

Samuel PEREZ and Paul SHARRATT

School of Chemical Engineering and Analytical Science, The University of Manchester, PO Box 88, Sackville St, Manchester, M60 1QD, UK
Samuel.Perez-vega@postgrad.manchester.ac.uk
paul.sharratt@manchester.ac.uk

Abstract

A first level of a methodology for the selection and evaluation of solvent at an early stage is presented inside a programming tool for its systematic and friendly application. This first level is based on properties and characteristics of solvents for their selection. Different tools are integrated into the program to aid the evaluation of the group of solvents selected. A case study is presented to highlight the most important aspects of the methodology. As a result, this kind of analysis can be useful to determine where the efforts related with solvent selection at an early stage should be aim.

Keywords: solvents, system, systematic, early stage, selection, and evaluation.

1. Introduction

Throughout the years solvent selection has been a difficult activity to do in the pharmaceutical industry. This is because there is not a complete understanding of the effects that this decision has on the complete process. One of the principal concerns of this industry is the lack of time to introduce a drug into the market; as a result, there is a need to create methodologies to appreciate future implications related with solvents at early stage.

2. Problem Statement, background

Because of the regulations concerning the approval of pharmaceutical process, early stage of development it is the best time to highlight potential issues concerning solvents. There had been recently reviews [1] about approaches available to aid the selection of solvents. Nevertheless, it is a fact that these approaches are in a early stage of development [2]. Among these approaches we find software for the selection of solvents. However, it is necessary that solvent search software behave more specifically according with the requirements, of a given production process [3]. Some property-based methodologies have been introduced [4-6] for the selection and design of solvents. A common characteristic of these approaches is the simulation of properties through thermodynamic models when properties are not available. Because of the molecular complexity of the pharmaceuticals the models have a limited application [7]. Recently new models have been developed more according to the needs of the pharmaceutical industry [8, 9]; nevertheless, there is a need to produce knowledge about when these models can be specifically applied and what is the reliability for its application for new molecules.
There is a need of software management tools where systematic evaluations for the selection of solvents it is evaluated. At the same time, the tool should exploit the reality of the conditions and information available at an early stage. Also, solvent should be evaluated not only from operation perspective (reaction, extraction, crystallisation, etc), but also from a system perspective (as a whole). Evaluation tools should promote the participation of the stakeholders involved (chemist, chemical engineer, contractors, suppliers, etc). Another characteristic is that this kind of tools should tell the user what kind of tools and evaluations are more convenient to apply in order to appreciate future cost implications related with solvents in a complete system.

3. Paper approach

The methodology applied in this approach consists of three levels for the evaluation. Each level start from information that can be provided from the chemist at this stage: level 1 “What solvents are you planning to apply?”, level 2 “What lab procedures do you intend to follow? ”, and level 3 “What is the synthesis recipe?”. Level 1 is presented on this paper with the aim of helping the user to select and evaluate solvents from property-based knowledge. After the solvent has been selected a series of evaluation are carried. Results at this stage should be considered just as potential implications with solvents. Further levels (2 and 3) will be in charge of producing more information for supporting the advantages or disadvantages of solvents performance on a system.

Solvent characteristics, properties, and tools belonging to the first level of evaluation are structured into a Visual Basic.Net framework. Fig. 1 shows some

of the most important steps to follow at level 1 as well as some of the tools that interact along the approach.

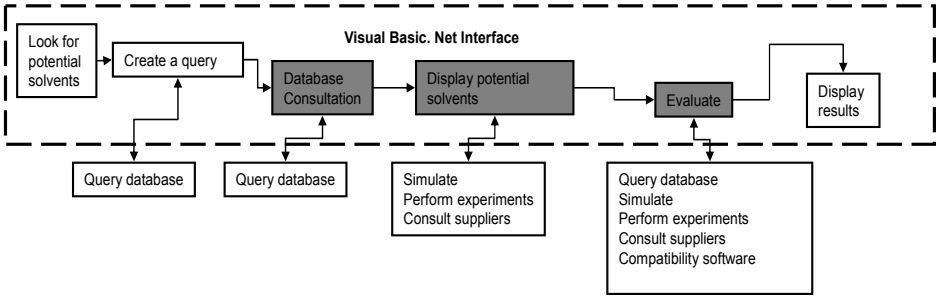

Figure 1. First level of evaluation "properties and characteristics based"

3.1. Methodology

The main goal at this stage is to develop a framework where the user can establish different queries (Fig. 2) to search for a potential solvent for a specific task.

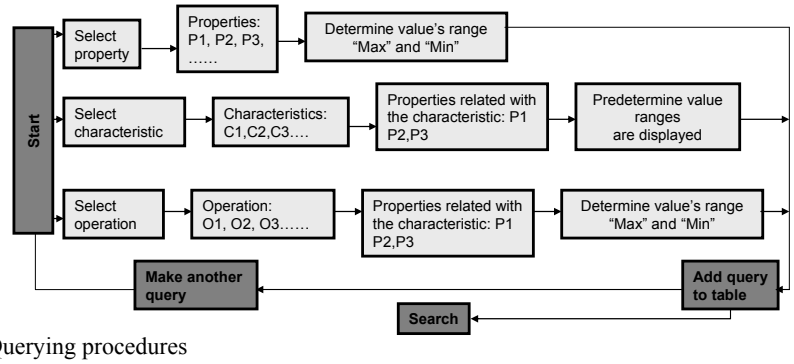

Figure 2. Querying procedures

Fig. 2 represents the behaviour of the routines at the time of creating a query based on properties selected. Query by property is available for the user to determine desire properties. Query by characteristics it is aimed to aid the user about properties related with certain characteristics. An example would be that the user it is looking for a solvent "easy to handle" as a result the program will display properties and parameters related with the easier handling of solvents such as: boiling point, density, and flammability limits among others. Query by operations is a procedure where the user might be interested in certain operation such as: reaction, crystallisation, liquid extraction, and drying among others. To develop this query routine it is important to analyse which properties are relevant for certain unit operations; work has been presented about this kind of properties[10]. After potential solvents are retrieved, evaluation procedures are developed.

3.2. Case study

The synthesis of propranolol was taken as a case study to highlight the principal aspects of our methodology. The information was treated as an early development stage.

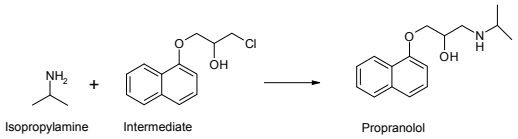

Figure 3. Propranolol potential synthesis reaction

Fig. 3 displays the potential main reaction for the synthesis of propranolol. The chemists assume that they require four solvents to achieve the drug synthesis. Fig. 4 shows the form to develop the query procedures proposed in Fig. 2.

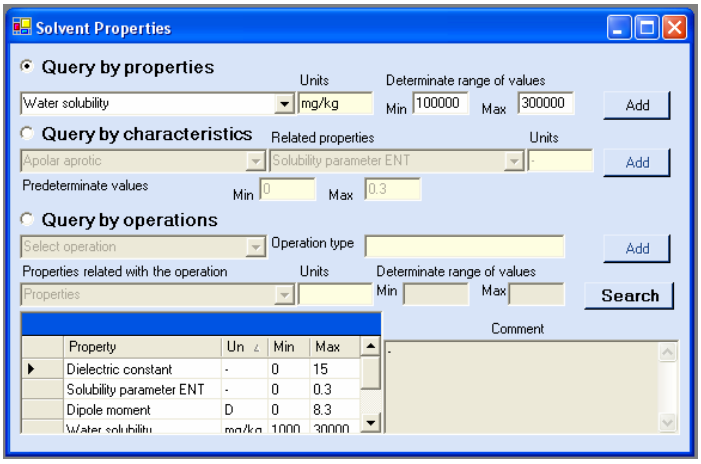

Figure 4. Query form

The query is added into the grid and the search into the database is performed. As a result, potential solvents for the desired operations are retrieved from the database (Fig. 5). In this case, the solvents selected were: isopropylamine, diethyl ether, water, and cyclohexane. The next step is to take the solvents selected into the evaluation assessment. Tools such as: databases, evaluation programs, contractor contact, correlations, and web service are employed. The criteria available for the evaluation of solvents are displayed in the bottom of the form (Fig. 5). Because the chemist wants to know about potential implications regarding the handling of these groups of solvents the “Handling” check box is selected as is shown in Fig. 5.

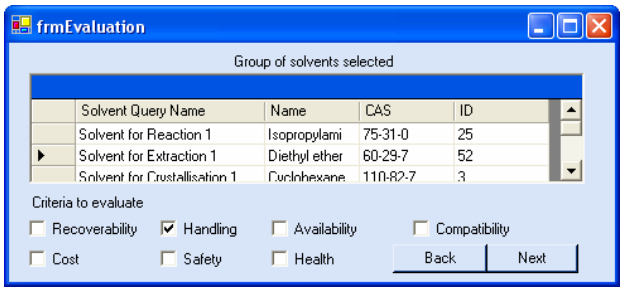

Figure 5. Evaluation form

After the user selects the criteria to evaluate, the tool selector is display (Fig. 6) with the tools available for the evaluation of the criteria selected. As a result, the user selects the tools to make the evaluation. In the case of our case study the user selects query of database, use of software, and experiment.

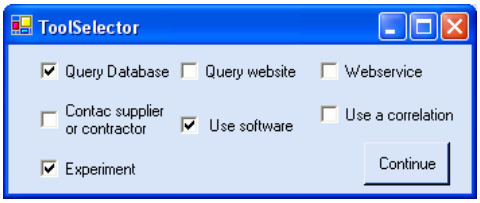

Figure 6. Tools selector form

In the case of "query of database" the system retrieves relevant notes and properties related with the handling of the solvents selected (if they are available). One important aspect about these databases is that they must be design in a friendly way in order to be useful for different applications.

Software such as the "chemical reactivity worksheet" created by the NOAA [11] can be linked to consult an check reactivity and compatibility among the solvents. Also, the program can suggest experiments such as calorimetric evaluations in order to evaluate the compatibility and other potential issues related with the SHE performance of the group of solvents. Since many of the solvents used at the pharmaceutical industry are disposed, another important tool to select might be to contact a waste disposal contractor. This with the aim of assessing potential implications with the disposal of the solvents selected.
Regarding the evaluation of the solvents selected at this level and handling characteristics; we found that solvents such as isopropylamine and diethyl ether do not have very favourable handling properties and characteristics. Because of this, more evaluations included on the levels 2 and 3 is required in order to determine the principal cost implication related with such issues. An important aspect it is that the friendly structure of the approach presented allows to guide the chemist through the evaluations. Also, the approach permits to visualize

very early potential issues related with solvents and where the research and development efforts should be aimed.

4. Conclusions

A first level for the systematic selection and evaluation of solvents was presented. The programming tool provides the user with a series of different procedures to create queries and select desired properties for the solvents required for an operation. Moreover, the program provides guidance for the evaluation of the group of solvents selected and interaction with different tools and stakeholders. The aim of this level would be to detect advantages and disadvantages related with the use of a group of solvents in early stage. Future work will integrate the second and third level in to the program with the aim to evaluate solvent selection cost implications on a system.

References

1. Gani, R., Jimenez-Gonzalez, C., ten Kate, A., Crafts, P.A., Powell, M.J., Powell, L., Atherton, J.H., and Cordiner, J.L., *A modern approach to solvent selection.* Chemical Engineering (Rockville, MD, United States). **113**(3):(2006) p. 30-43.
2. Constable, D.J.C., Jimenez-Gonzales, C., and Henderson, R.K., *Perspective on solvent use in the pharmaceutical industry.* Organic Process Research and Development. **11**(1):(2007) p. 133-137.
3. Wypych, G., *Important determinants of solvent selection.* Chemical Engineering (Rockville, MD, United States). **113**(6):(2006) p. 54-60.
4. Modi, A., Aumond, J.P., Mavrovouniotis, M., and Stephanopoulos, G., *Rapid plant-wide sscreening of solvents for batch processes.* Computers Chem. Eng., **20**:(1996) p. S375-S380.
5. Li, M., Harten, P., F., and Cabezas, H., *Experiences in designing solvents for the environment.* Ind. Eng. Chem. Res., **41**:(2002) p. 5867-5877.
6. Gani, R., Jimenez-Gonzales, C., and Constable, D., J.C., *Method for selection of solvents for promotion of organic reactions.* Computers and Chemical Engineering, (29):(2005) p. 1661-1676.
7. BRITEST, *Solvent selection current practice*, in *Solvent Selection*, B.Q.W. Project, Editor. (2004).
8. Chen, C.-C. and Crafts, P.A., *Correlation and prediction of drug molecule solubility in mixed solvent systems with the nonrandom two-liquid segment activity coefficient (NRTL-SAC).* Ind. Eng. Chem. Res. **45**:(2006) p. 4816-4824.
9. Chau-Chyun, C. and Song, Y., *Extension of nonrandom two-liquid segment activity coefficient model for electrolytes.* American Chemical Society:(2005)
10. Jaksland, C.A., Gani, R., and Lien, K., M, *Separation process design and synthesis based on thermodynamic insights.* Chemical Engineering Science. **50**(3):(1995)
11. ChemicalReactivityWorksheet, a database of reactivity information. http://response.restoration.noaa.gov/index.php:(2006)