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Tools for an enhanced solvent properties screening in the early stages of pharmaceutical process development

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ABSTRACT

The objective of this research was the implementation of tools for the evaluation of solvents trough property screening in the early stages of process development. An important feature of the tools is that the implementation of indexes, scores, or weights is avoided. Information already available from the literature was stored in a database in order to turn raw data into decision making information. As a result, a solvent radar chart, a solvent representation table, and a solvent telescopying tool were developed in an ASP.NET application. The synthesis of Propranolol was used as study case in order to explore the selection of solvents in the early stages of process development. The replacement of diethyl ether was possible in the extraction step, while solvent choices were detected for potential telescoping for extraction and crystallisation steps. Solubility was found as a critical parameter in telescoping analysis. The methodology proposed enhanced the view towards a more holistic perspective and a more robust solvent screening process. As a consequence, the next steps into solvent evaluation and process development can be reduced.

1. Introduction

Solvent selection is considered an important step in the development of sustainable pharmaceutical process. When selecting solvents, property screening can be considered as a first activity. The purpose of this task is to have a multiple property evaluation (Zhao & Cabezas, 1998). Basic understanding of the physical and chemical properties is necessary for selecting the best solvent in a process (Wypych, 2006). Solvent properties are available in a great deal of books and databases (Gani et al., 2006). Moreover, there is plenty of literature describing the properties of solvents (Marcus, 1999; Smallwood, 1996; Wypych, 2000; Zhao & Cabezas, 1998). Typical pharmaceutical processes are carried out at temperatures between −25 and 160 °C, as well as standard pressures (Bennett & Cole, 2003, chap. 5). Solvent phases present at such condition will dictate potential issues or benefits associated with their performance and handling. If physical properties are available the selection of solvents can be narrowed down, this is possible by evaluating the chemical behaviour of solvents in a process (Wypych, 2006). Literature have explained solvent implications in process development (Constable, Jimenez-Gonzales, & Henderson, 2007) and how solvent selection has not been seriously considered. A common issue with solvent selection relies in the differences of opinion inside the industry about which solvents are considered sustainable and which are not. Such difference can be attributed to the different perspectives of the people in charge of process development and the lack of tools aimed to a more holistic evaluation.

Approaches based on solvent properties have been developed (Curzons, Constable, & Cunningham, 1999; Gani et al., 2006; Slater & Savelski, 2007). A common feature of these methodologies is the development of indexes, scores, or weights for the representation of a group of properties. Currently, there is a lack of friendly procedures for using this information in a more efficient way. New trends in information and the use Data Base Management Systems (DBMS) allows for a more efficient use of data. For instance, the storage of information regarding operations involving the use of solvents (i.e. extraction, distillation, reaction, etc.), or

Abbreviations: CAMD, computer aided molecular design; DBMS, database management system; ASP.NET, active server pages in NET framework; AHP, analytical hierarchy processes; HSE, health, safety, and environment; LD50, letal dose 50; BOD, biological oxigen demand; MTBE, tert-butyl-methyl-ether; VOCs, volatile organic compounds; ENT, normalized transition energy.

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characteristics of solvents (i.e. polar, water soluble, easy to recover, cheap, etc.) can be stored in a DBMS, handling this information more efficiently. This will be a step into filling the gap regarding that computer searches need to be more fine-tuned to match the detailed requirements of a given process (Wypych, 2006). One example would be to store different solubility parameters and define their ranges according to their classification: non polar, polar, protic, apolar aprotic, dipolar aprotic. A benefit of this is that the chemist can easily find solvents with similar polarity using different solubility parameters. For instance, Hildebrand solubility parameter can be used as general solubility parameter when is more applicable when selecting non polar solvents; this is because this parameter only takes into account molecular dimensions or segments that take part in the solvation process (Wypych, 2006). The use of a group of solubility properties might help to fine tune this search.

As stated above the majority of the property screening methodologies available are based on global indexes, weights or scores to represent solvent behaviour. Nevertheless, it might be confusing for someone without experience. It can be difficult to understand which properties are involved and how properties were handled to get the score, index, or weight. As stated for some authors (Sharratt, 1999) the complexity of environmental effects are difficult to consider from an environmental and process design perspective. Because of this, there is a lack of tools to aid chemist exploring solvent choices from a properties perspective where the influence of each property is evident during the evaluation process. Moreover, the majority of the tools available are aimed to discharge solvents with no "green" characteristics leading into wrong assumptions. As stated by some authors (Tucker, 2006) replacing a toxic solvent for a "green solvent" and reducing yield is not green chemistry.

The objective of this work was the development of tools for an enhanced selection and evaluation of solvents based on information available in the early stage of process development. The benefits of this research relied in the optimisation and improvement of solvent selection through the development of a friendly web tool. As a result of this, the next evaluation stages can be more efficient and target oriented.

2. Methodology

A web tool was developed for an environment where the chemist provides information about potential basic solvent characteristics. The goal of the tools is to provide guidance and advice to the chemist about future solvent implications, as well providing solvent alternatives. For achieving such goal a database and a web application in ASP.NET.4 were proposed.

Table 1
Database main contents.

Entity	Features
Properties	Contains all solvents properties
Properties Description	Describes the property: name, units, database, information.
Characteristics	Characteristics related to properties and their ranges.
Operations	Operations related to their relevant properties.

Fig. 1 shows a selection and evaluation procedure. A query procedure was implemented for generating solvent choices for different operations. Solvent representation and telescoping analysis were incorporated for analysing solvent choices. Also, a ranking tool based on Analytical Hierarchy Processes (AHP) was included in the evaluation process, although its implementation and use has been explained elsewhere (Perez-Vega, Senior, Salmeron-Ochoa, Nieva-de la Hidalga, & Sharratt, 2011).

2.1. Solvents database design

A database is a collection of related data. According to some authors (Elmasri & Nevathe, 2006) it has the following implicit properties: represents some aspect of the real world, contains a logical coherent collection of data with some inherent meaning, it is designed, built, and populated with data specific for some purpose. The database construction task consists in turning non-structured data into information. Some of the benefits of such task are the power of handling information and decision making improvement. By analysing data, companies have the advantage of taking corrective actions when a problem is discovered (Petersen, 2002). As result, a database was designed in Microsoft Access and its main content is explained in table 1.

The "Properties" entity contains solvent properties, this is the common structure of a solvents database and they are already available. This entity do not intended to replace available database, but it was designed to test the web tool. This entity was filled with common solvents used by the industry (Smallwood, 1993, 1996). The "Properties Description" entity was designed to store information regarding the description and location of solvent properties. Currently there are databases available; hence, this entity will allow working with different solvent databases. The "Characteristics" entity contains different characteristics of solvents and their related properties. The goal of having this entity is to store solvent characteristics that can be interpreted as specific property ranges available in the literature (Marcus, 1999; Smallwood, 1993; Wypych, 2001, 2006 chap. 2,). The "Operation" entity contains the names of operations typically developed in the pharmaceutical

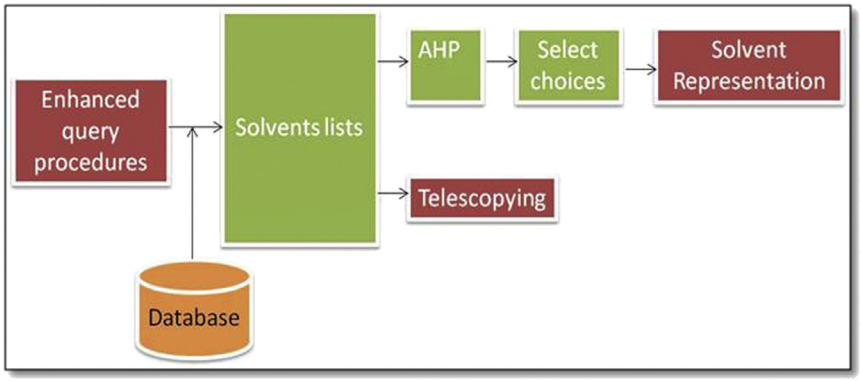

Fig. 1. Evaluation procedure.