Contents lists available at ScienceDirect

Process Safety and Environmental Protection

journal homepage: www.elsevier.com/locate/psep

Analytical hierarchy processes (AHP) for the selection of solvents in early stages of pharmaceutical process development

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ABSTRACT

The AHP (analytical hierarchy process) mathematical model was implemented into a tool aimed to aid the selection of solvents in the early stages of pharmaceutical process development. The tool assesses environmental implications using the information available in the early stages of development. Solvent properties, characteristics, and their relationship with common operations are exploited. In order to make the approach user-friendly, the tool was incorporated into a VB.NET application. The user obtains a ranked list of potentially good solvents. The result can be used as a starting point in solvent selection. The chemist can explore implications of the solvent selected not only from synthesis perspective, but also from an HSE perspective. A case study is presented for the replacement of benzene, where through a series of steps the chemist inputs ideal solvent characteristics and the importance of each characteristic in the decision. In this case solvent replacement is based in finding a solvent with the same solubility behaviour, but with less toxicity problems and at low cost. The tool considers a wide pool of solvents in a short time and produces ranked choices according to the chemist needs; taking account of both synthesis and HSE perspectives.

Keywords: Solvents; AHP; Decision; Early process development; HSE

1. Introduction

The production of pharmaceuticals is known for its high consumption of raw materials, especially solvents (Constable et al., 2007). Some of the common uses of solvents in the production of pharmaceuticals are (Kolar et al., 2002): entrainers for azeotropic and extractive distillation, absorption, extraction, crystallisation, reaction solvents, catalyst solvents, solvents for coatings and formulations, and cleaning. Solvents represent between 80 and 90% of the mass utilization in the pharmaceutical industry (Constable et al., 2007). Spent solvents constitute a major source of waste in the pharmaceutical industry. The amounts of waste produced can range from 25 to >100 kg waste/kg of product (Sheldon, 2005). Compared to other industries, solvent recycling is not a common practice. While recycling is seen as viable from those outside the pharmaceutical industry, less than 50% is reused and recycled (Constable et al., 2007). Solvents are the source of about 40% of the anthropogenic Volatile Organic Compounds (VOC) entering the atmosphere (Smallwood, 1993). Nowadays, legislation has curbed the use of solvents (Anderson, 2000), demanding that steps should be taken to prevent the release of VOCs to

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Received 4 November 2010; Received in revised form 5 March 2011; Accepted 18 March 2011
0957-5820/$ – see front matter
doi:10.1016/j.psep.2011.03.003

Nomenclature

$P = p_{ij}$	performance matrix
r_i	vector representing basic solvent characteristics
w_i	vector representing criteria weights
$Q = q_{ij}$	normalized performance matrix
$A = a_{ij}$	reciprocal matrix
n	number of solvent properties involved in the evaluation
$V = v_{ij}$	weight normalized matrix
E_i	Euclidean distance
i	matrix row number
j	matrix column number

the atmosphere (Lee and Robinson, 1995). As a consequence, there has been a growing concern about the impact generated before, during, and after the employment of solvents. Solvents present a considerable life cycle impact compared to their impacts in use and final disposal. Solvents cost is considered low; however, the broader total cost caused by resource depletion, life cycle, and societal impact are not (Curzons et al., 2001).

One of the main goals of the pharmaceutical industry is the creation of profit through the discovery and production of drugs that bring benefits to the society. The lengthy process to introduce a pharmaceutical into the market makes the pharmaceutical industry different with respect to other industries. This characteristic has to do with the strict regulations that this industry needs to comply with.

Patent exclusivity also presents a problem. Because of the long periods required for introducing a drug into the market (perhaps 7–8 years from grant of patent) only a few years of patent exclusivity are available for investment recovery. As a consequence, there is a rush for the development of a process able to produce the new drug and introduce it into the market. The discovery and isolation in the laboratory of an active substance is the first step in the development of a new drug. During this stage the chemist will identify synthesis routes for the target molecules. He/she will try to optimise the synthetic route in aspects such as yield, selectivity, solubility, and minimum number of stages. All these factors are driven by time and cost (Anderson, 2000). Regarding solvent selection a typical approach is to maximize yield without fully considering safety, waste minimization, cost, and operability (Basu et al., 1999). As a consequence, the selected solvents may not only lead to faster kinetics or better selectivity, but also to difficulties in the downstream operations (Elgue et al., 2004).

Approaches have been presented to aid the selection of solvents. Theses methodologies vary considerably according to the tools employed. There have been publications about the approaches applied for the selection of solvents (Gani et al., 2006). Approaches such as properties screening, CAMD (Computer Aided Molecular Design), property and solubility estimation through thermodynamic models, reactivity assessment, HSE scoring, and software are some examples of these approaches. Regarding the selection of solvents in the early stages of development, the lack of information is a constraint that in the majority of the cases is not seriously considered. As a result, solvent selection relies on the knowledge and experience of the chemist.

2. Methodology

Basic understanding of the physical and chemical properties is necessary for selecting the best solvent in a process (Wypych, 2006). Typical pharmaceutical processes are carried out at temperatures between −25 and 160 °C, as well as standard pressures (Bennett and Cole, 2003). Solvent phases present under such conditions will dictate potential issues or benefits associated with their performance and handling.

After developing a search for potential solvents for a synthesis the chemist would have a list of solvents to evaluate. Commonly, these solvents present similar properties, so the decision of which solvent should be tested first could be a challenge. In order to reduce the time for deciding which solvents are the ones to test first, a ranking method is proposed.

A feature of this work is that the evaluations can be developed in short time, during the early stages of development. Chemist and chemical engineer can look for solvent replacements or solvents with similar properties; considering basic solvent characteristics required. The Analytic Hierarchy Process methodology (AHP) has been incorporated into a query tool for the ranking of a solvent list produced from a query routine. Databases were developed in order to store important information regarding solvents. Moreover, query procedures were implemented to adapt to the conditions of the early stages of development, this research is presented elsewhere (Perez-Vega and Sharratt, 2007). The mathematical method is a multi-decision criteria approach that has been applied in complex decisions. The method was introduced by Saaty (1977) and examples have been presented elsewhere (Chen et al., 2001; Amna et al., 2004; Venkata, 2007). In addition, the approach has been employed (Chen et al., 2001) for ranking solvents based on economic and environmental criteria. Unlike these examples, the AHP in this work is applied only to the evaluation of solvent properties chosen to describe basic solvent characteristics in the development of pharmaceutical processes. Therefore, no human judgment or calculated indices will be included in the analysis; this to avoid introducing subjectivity in the model. The exploration of a wider pool of alternatives can improve solvent selection, especially in HSE aspects. As a result, the ranked list can be used for the chemist as a starting point for the development of experiments with single solvents or mixtures.

2.1. *Analytic Hierarchy Process (AHP) approach*

The AHP provides a comprehensive and rational framework for structuring a decision problem for representing and quantifying its elements, for relating those elements to overall goals, and for evaluating alternative solutions. The methodology consist of six steps: (1) problem statement, (2) assessment of criteria weights, (3) consistency ratio calculation, (4) construction of a normalized performance matrix, (5) construction of a weighted normalized performance matrix, and (6) calculation of the relative Euclidean distances.

Table 1 – Pair comparison evaluation scale.

Scale	Meaning
1	Equal
3	Slightly favour
5	Strongly favours
7	Very strongly favours
9	Estremely favours

2.1.1. Problem statement

The model begins with the creation of a performance matrix $P = p_{ij}$ of the type:

$$P = \begin{bmatrix} p_{11} & p_{12} & \dots & p_{1n} \\ p_{21} & p_{22} & \dots & p_{2n} \\ \dots & \dots & \dots & \dots \\ p_{m1} & p_{m2} & \dots & p_{mn} \end{bmatrix} \quad (1)$$

Each column of the performance matrix represents a solvent property of the list of solvents selected, and each row represents the available solvents obtained from a query procedure. Chemist requirements (ideal solvent property parameters) are given as a vector of m elements, $r = (r_1, r_2, \dots, r_m)$, where the element r_i represents the basic solvent characteristics. Chemist preferences are assessed and represented as a vector of criteria weights $w = w_1, w_2, \dots, w_m$.

2.1.2. Normalized performance matrix

Since the criteria (based on solvent properties) are measured in different units, the performance matrix P should be converted into a non-dimensional matrix. This is achieved by normalizing each element of the matrix P. As a consequence, the normalized performance matrix Q is obtained as is shown in the following equation.

$$Q = q_{ij} = \frac{p_{ij}}{\sqrt{\sum_{k=1}^{n} p^2}} \quad (2)$$

2.1.3. Assessment of criteria weights

The method of pair wise comparisons developed inside the AHP is applied to provide a reciprocal matrix $A = \{a_{ij}\}$.

$$A = \begin{bmatrix} 1 & a_{12} & \dots & a_{1m} \\ a_{21} & 1 & \dots & a_{2m} \\ \dots & \dots & \dots & \dots \\ a_{m1} & a_{m2} & \dots & 1 \end{bmatrix} \quad (3)$$

If a_{ij} is the element of row i column j of the matrix, then the lower diagonal is filled using this formula:

$$a_{ji} = \frac{1}{aij} \quad (4)$$

In this evaluation the chemist evaluates the importance of each element involved in the decision. In order to produce a matrix A the chemist makes pair comparisons between the different solvent properties taking part of the decision. The number of comparisons to perform can be known with the following relation.

$$\text{No comparisons} = \frac{n(n-1)}{2} \quad (5)$$

where n is the number of solvent properties involved in the evaluation. The pair comparison is developed assigning values from 1 to 9 to express the level importance in the decision of the two solvent properties. Table 1 displays the meaning of the comparison scale used in the weighting of two elements.

Values such as 2, 4, 6, and 8 are considered intermediates values and also are used in the comparison of the pair of properties. After the A matrix has been completed eigen-values are obtained in order to get the weight of each property.

2.1.4. Consistency ratio

A consistency ratio (CR) is calculated to determine inconsistencies in the evaluation. It measures how consistent the judgements have been relative to large samples of purely random judgements. According to the AHP model, if CR is more than 0.1 the judgements are untrustworthy because they are too close for comfort to randomness and the exercise is valueless or must be repeated. In order to calculate CR the principal eigen-value λ_{max} is obtained from the summation of products between each element of eigen-vector and the sum of columns of the reciprocal matrix (A). The degree of consistency (CI) can be estimated as is shown in the following expression.

$$CI = \frac{\lambda_{max} - n}{n - 1} \quad (6)$$

Consistency ratio (CR) can be calculated from the relation of the consistency index (CI) and the random consistency index (RI). The RI values are obtained from Table 2, and its value will depend on the value of n.

$$CR = \frac{CI}{RI} \quad (7)$$

If CR is $\leq$10%, the inconsistency is acceptable. If $CR > 10\%$, it is necessary to revise the subjective judgment.

2.1.5. Weight normalized performance matrix

Weights are used in conjunction with matrix Q to produce the weight normalized matrix V.

$$V = \begin{bmatrix} w_1 q_{11} & w_1 q_{12} & \dots & w_1 q_{1n} \\ w_2 q_{21} & w_1 q_{22} & \dots & w_2 q_{2n} \\ \dots & \dots & \dots & \dots \\ w_m q_{m1} & w_m q_{m2} & \dots & w_m q_{mn} \end{bmatrix} \quad (8)$$

2.1.6. Relative distances

In mathematical terms, the closeness between two objects can be expressed by their Euclidean distance, which geometrically is the straight-line distance between two points. The solvents normalized parameters are measured according to its closeness to the chemist requirements. The relative Euclidean distances are calculated by:

$$E_i = \sqrt{\sum_{j=1}^{m} \left(v_{ij} - \frac{w_j r_j}{\sqrt{\sum_{k=1}^{n} p^2}} \right)^2} \quad (9)$$

The solvent with the smallest Euclidean distance would be the solvent most similar to the solvent requested by the chemist. For its easy application the mathematical model was programmed into a VB.NET framework (Fig. 1).

A query procedure included in this tool is used to obtain a list of potential solvents. This procedure works by exploring properties, characteristics, and operational characteristics of solvents. The list of potential solvents obtained from the query procedure has a link to the AHP analysis tool (Fig. 1). The list of solvents for a desired operation is the performance matrix P; hence, at this point the method can be applied. The procedure consists in two main steps. During the first step the chemist assigns weights to the properties involved in the process. For this purpose, a weight distribution chart informs about the weight of each property in the decision. The default value is that all the properties have the same weight. This

Table 2 – Random consistency index *RI* (Saaty, 1977).

n	1	2	3	4	5	6	7	8	9	10
RI	0	0	0.58	0.9	1.12	1.24	1.32	1.41	1.45	1.49

means that each property has the same importance. If the chemist considers that some properties might be more important than others, the weight distribution control can be used to distribute the importance among the different properties. Moreover, consistency ratio (*CR*) is calculated and displayed. As a consequence, the chemist can obtain feedback about the evaluation process. Different messages such as "Perfect consistency", "Inconsistency acceptable", or "Inconsistency unacceptable, revise the subjective judgment" are displayed depending on the *CR* value.

At the second step ideal property values must be assigned. Here the chemist has to provide properties values that give an approximation of ideal values. Also, if the chemist is looking for a solvent replacement, he/she can provide the values of the solvent to be substituted. For this task the procedure provides alternative criteria for the selection of the ideal values. The first alternative consists of selecting values of a known solvent; the second involves selecting a desired solvent characteristic, and the third one by customizing a specific solvent property value. The mathematical model is run and the program displays the ranked list of solvents. The numeric values shown in the "Rank" column are the Euclidean distances obtained by the mathematical model. Thus, the smaller the Euclidean distance the more similar is the solvent to the desired solvent.

2.2. *Sensitivity analysis*

Final priorities of the alternative solvents depend on the weights given to the main criteria. Changes in the relative weights can cause changes of the final ranking. Since these weights could be based on highly subjective judgments, the stability of the ranking under varying criteria weights has to be tested. Therefore, sensitivity analysis can be performed based on scenarios that reflect alternative future developments or different views on the relative importance of the criteria. Hence, by increasing or decreasing the weight of individual criteria, the resulting changes of the priorities, and the ranking of the alternatives can be observed. This analysis provides information on the stability of the ranking. If the ranking is highly sensitive to small changes in the criteria weights, a review of the weights is recommended (Che-Wei et al., 2007).

3. Study case: benzene replacement

In this case the chemist is trying to find a replacement for benzene. The chemist wants a solvent with the same solubility behaviour but with less toxic effects. In addition, solvent replacement has to be as cheap as benzene (1 £/kg). A list of potential solvents is produced from a query builder, where characteristics such as apolar aprotic, toxicity, and cost are the relevant solvents features for this analysis. To represent apolar aprotic characteristics, properties such as dipole moment, dielectric constant, and solubility parameter ENT were selected. In the case of toxicity and cost the Oral LD50 and bulk cost were selected as the relevant parameters. A list of 22 solvents was obtained from the database.

Fig. 2 shows the output of the AHP tool. The list of 22 solvents and the relevant properties is used as matrix P, so the rest of the matrices are calculated. The different proper-

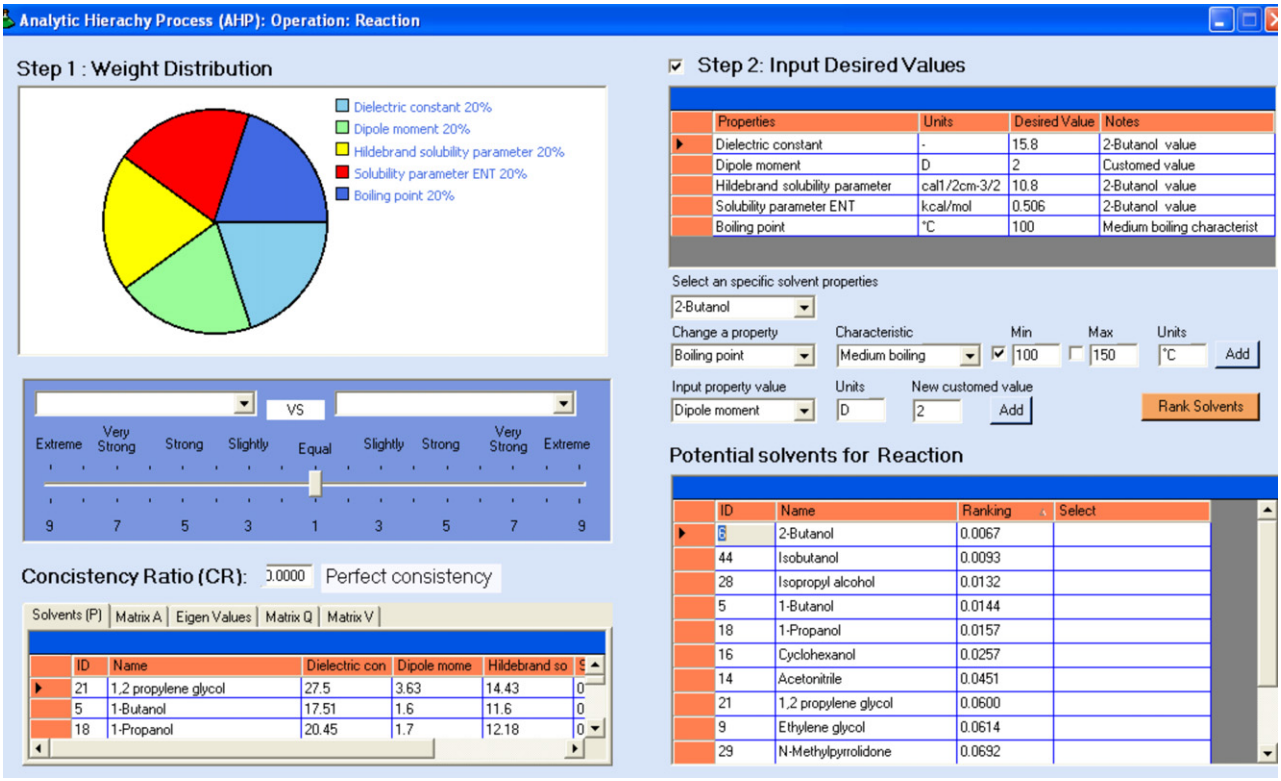

Fig. 1 – AHP tool for the ranking of solvents.

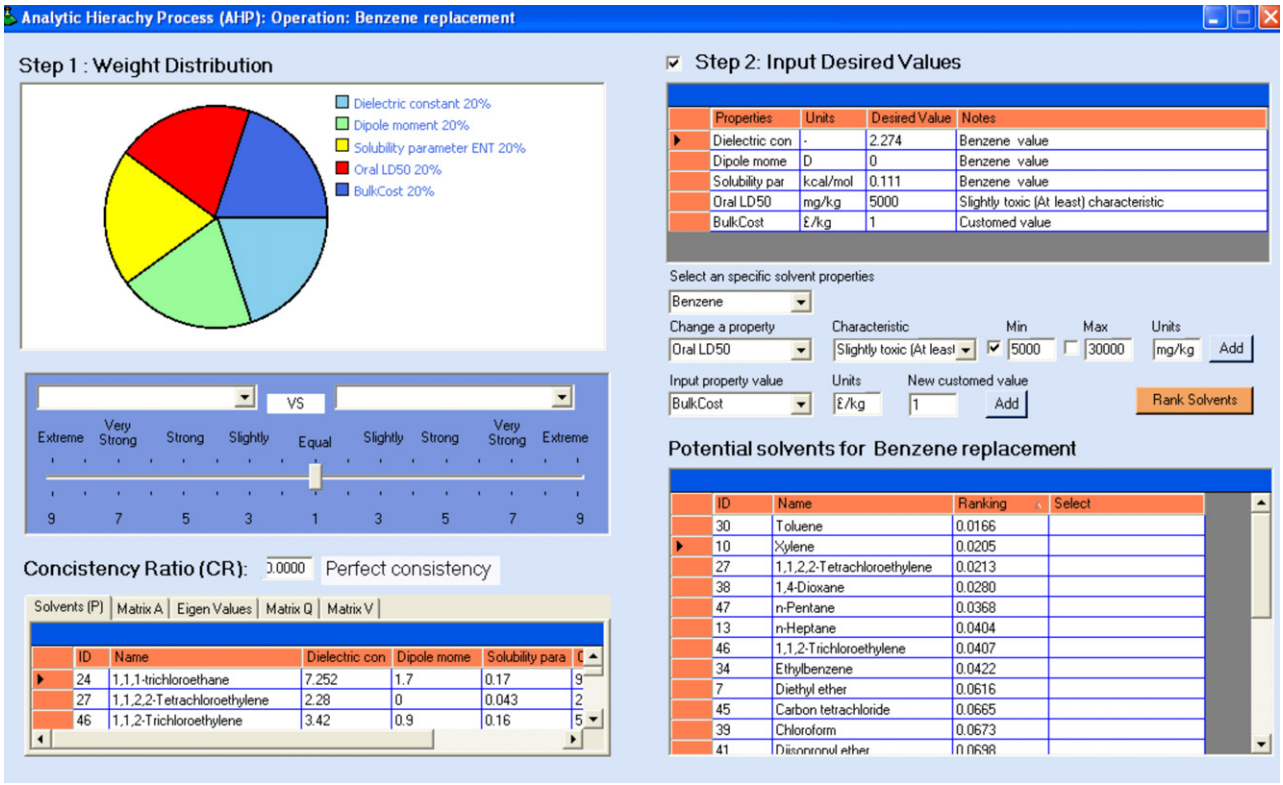

Fig. 2 – AHP tool for benzene replacement.

ties to evaluate (dipole moment, dielectric constant, solubility parameter ENT, Oral LD50, and bulk cost) are displayed in the weight distribution chart. In this case study the same weight was given to all the properties. Since a benzene replacement is needed, the chemist mostly selects benzene's properties as the desired properties. However, in the toxicity and cost aspects new values are input; this to find less toxic solvents at the same or similar cost, but keeping benzene solubility. As a result, a ranked list of the 22 potential solvents is produced. Toluene looks ideal for the replacement; it presents the similar solubility than benzene, but with a better performance in cost and toxicity.

The top row of Table 3 shows the property values of benzene, the solvent to be replaced. The second row shows the property values of the ideal solvent and below that are the top four solvents obtained from the AHP tool evaluation. As can be seen, benzene toxicity and cost parameter were replaced with new values for the ideal solvent. From the analysis, toluene was the first choice followed by xylene, 1,1,2,2-tetrachloroethylene, and 1,4-dioxane. Toluene has solubility property values similar to benzene. Moreover, its toxicity and cost also are similar than the ideal value. Xylene also has similar solubility parameters, together with an oral LD50 of 4300 mg/kg, and a bulk cost of 1.9 £/kg. 1,1,2,2-Tetrachloroethylene presented similar solubility and toxicity values than benzene. However, its oral LD50 was lower (more toxic) than the other choices. With 1,4-dioxane, the solubility is similar to benzene, and its oral LD50 was higher than the other solvents (less toxic). However, its cost was higher than the other choices.

3.1. *Sensitivity analysis*

Extra weight was given to the different criteria (properties); this in order to test the sensitivity in the benzene replacement case. Fig. 3 shows the results of the sensitivity analysis.

The first graph (Fig. 3a) shows the first four solvent choices when the criteria had the same weight: 20% each. The solvent with the minimum Euclidean distance is the most similar solvent to benzene; considering the desired properties and the weights assigned. The rest of the graphs (Fig. 3b–f) display the top four choices and their Euclidean distances when double weight (more importance) was given to one property. In other words, each highly weighted property had 33% of weight in the decision while the rest of the properties had 16.75%. When dielectric constant was highly weighted (Fig. 3b), toluene was the solvent with more similarities than the ideal solvent, followed by 1,1,2,2-tetrachloroethylene, xylene and 1,4-dioxane. Dielectric constant values for the four solvents were found near the ideal value. Attaching double weight to dipole moment (Fig. 3c) moved 1,1,2,2-tetrachoroethylene to the top rank. 1,1,2,2-Tetrachoroethylene presents a very similar dipole moment to benzene. Xylene and toluene were also highly ranked. A different solvent, n-pentane, was fourth in the ranking. Its low polarity moved it above dioxane in the ranking. When applying double weight to the solubility parameter ENT (Fig. 3d) toluene, xylene, 1,4-dioxane, and 1,1,2,2-tetrachloroethylene appeared at the top of the ranked list. For this property the first two solvents were found close to the ideal behaviour, while 1,4-dioxine and 1,1,2,2-tetrachloroethylene were more distant. Toluene, xylene, 1,1,2,2-tetrachloroethylene, and 1,4-dioxane were the top solvents in the ranked list when double weight was given to the OralLD50 (Fig. 3e). In the case of toluene the solvent presented similar toxicity to the ideal behaviour; hence, the solvent was found as number one in the ranked list. Xylene presented the highest OralLD50, whereas 1,1,2,2-tetrachloroethylene was more toxic than the ideal behaviour (5000 mg/kg). 1.4-Dioxane presented an Oral LD50 similar to

Table 3 – Top four solvents of the ranking in the benzene replacement.

Solvent	Parameters involved in the decision				
	Solubility			Toxicity	Cost
	Dielectric constant	Dipole moment (D)	Sohibility paramenter ENT (kcal/mol)	Oral LD50 (mg kg)	Bulk cost (£/kg)
Benzene*	2.27	0.00	0.111	930	**1.68**
Ideal solvent	2.27	0.00	0.111	5000	1.00
Toluene	2.38	0.40	0.099	5000	1.23
Xylene	2.60	030	0.123	4300	1.90
1.1.2.2-Tetrachloroethylene	2.28	0.00	0.043	2629	0.90
1,4-Dioxane	2.20	0.40	0.164	5700	2 03

Asterisk means that this is the solvent to be replaced.

the ideal value; however, its cost was higher than the rest of the choices, and this parameter still had a strong influence on the overall result. Toluene was found the solvent most similar to the ideal in terms of cost criterion (Fig. 3f). 1,1,2,2-Tetrachloroethylene is a less expensive solvent; however, its other parameters – especially solubility parameter ENT and oralLD50 – are not so close to the ideal. Therefore, weighting the cost more highly makes toluene the best choice followed by 1,1,2,2-tetrachloroethylene, benzene and xylene. Toluene was found slightly more expensive than the ideal solvent; nev-

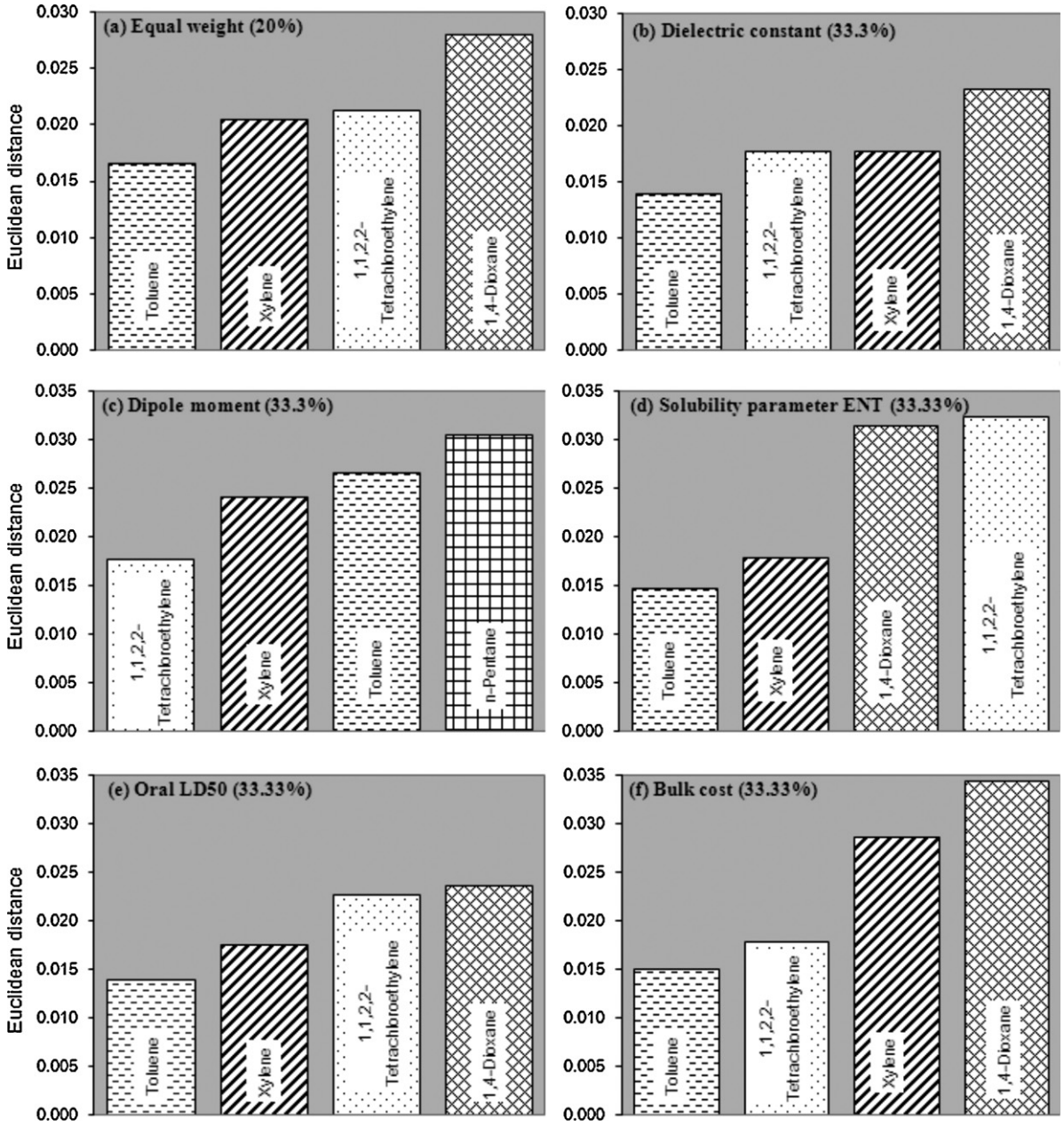

Fig. 3 – Benzene replacement sensitivity analysis.

ertheless, the rest of its parameters also are closes to the ideal behaviour.

As seen in this sensitivity analysis solvents were favoured depending on the weight given to the criteria. However, toluene, xylene, and 1,1,2,2-tetrachloroethylene were found as top choices in almost all the different sensitivity scenarios. Therefore the three solvents can be explored for application in future trials. They are all similar solvents to benzene, but with better oral LD50 and cost criteria.

It is true that other HSE properties must be consulted to verify the friendliness of the solvents. For instance, toluene's boiling point is higher (110.6 °C) than benzene (80.09 °C). As result its volatility (relative to diethyl ether) is also higher (4.6) compared to benzene (2.6). This is important if an exothermic runaway take place affecting the maximum pressure and the design of any pressure relief system. Another important aspect is that toluene is not miscible with water, so it can be removed by oil scrubbing. Also it can be removed by activated carbon satisfactorily (does not need drying when the carbon bed is regenerated) and it is stable at recovery process temperatures (Smallwood, 1993).

4. Conclusions

The AHP tool provides the chemist with a tool that can be applied during the early stages of development for the selection of solvents. The tool aids to obtain a ranked list of solvents to try in experimental trials. It also aids the chemist to replace or look for solvent alternatives. The case presented in this paper was run with a database of 60 solvents. Of course more extensive databases would increase the capabilities of the analysis. The tool also helps the user to customise the solvent characteristics and replace characteristics that might bring future issues. This could be the case when solvents do not present good HSE characteristics. Generally, all solvents will present some benefits and some disadvantages. Therefore, it is the scope of this tool to develop alternatives for exploring a wide pool of choices in the early stages of development. This should lead to a more sustainable process development regarding solvent selection.

Acknowledgements

The author would like to thank the CONACYT for providing the funding for the development of this research project.

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