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Solvent impact assessment for the "One-Flow Functional Solvent Factory"

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ABSTRACT

In the ONE-FLOW project, the concept of a "Functional Solvent Factory" is proposed, in which designer and conventional solvents are used to transform a multiphase system into a single phase system. This change of phases is alike to the creation and the disruption of compartmented spaces, which will be used for conducting multi-step reactions in a continuous flow. Due to the large availability to a great number of solvents, it is imperative to make a holistic solvent selection. Selection which must be in line with the environmental targets of the pharmaceutical industry. Herein, it is elaborated a methodology to assess common and neoteric solvents for its application in the Functional Solvent Factory. Solubility is taken as the main criterion for the assessment in the Functional Solvent Factory case; however, the solubility of a chemical in a particular solvent is not always known. Therefore, a method to circumvent the lack of solubility data, from an environmental perspective, is proposed. Afterwards, the methodology is applied to assess common solvents. The assessment considered economic and safety constraints. Decan-1-oic acid and 2-octanone were found to be the best solvents for the cascade selected. Thereafter, the environmental assessment showed that Decan-1-oic acid is the best option for the cascade. The aim of this methodology was also to include and compare ionic liquids with conventional solvents, and find the most sustainable option. Applying the methodology to compare an ionic liquid with a conventional solvent was found that the environmental impact of an ionic liquid can be lower to that of a conventional solvent. This is possible when the compound of interest has a higher solubility in the ionic liquid compared with the conventional solvent.

1. Introduction

Solvents play a determinant role in the pharmaceutical industry (Byrne et al., 2016). They take part in reactions affecting the selectivity and conversion towards a certain product. Also, they are used in workup procedures to ease separation processes such as in crystallization (Abou-Shehada et al., 2016; Raymond et al., 2010). In 2005 the American Chemical Society (ACS), the Green Chemistry Institute (GCI) and global pharmaceutical companies founded the ACS GCI Pharmaceutical Roundtable (ACS GCIPR) (Jiménez-González et al., 2011; Prat et al., 2016). This Round table quantified the materials used to produce a drug including the solvents used in the synthesis and the purification. They reported that the process mass intensity of solvents in drug synthesis is over 56%, followed by water with 32% and the reactants with only 7% (Jimenez-Gonzalez et al., 2011). This reflects the extensive amounts of solvents used mainly in the purification stages. Drugs are washed with large amounts of different solvents and water to remove any kind of impurity that remains on the drugs after the synthesis. These washings produce mixed aqueous-organic waste, which due to environmental regulations must be treated before conducting any wastewater treatment operation. Incineration is proposed as an alternative method to manage mixed aqueous-organic wastes. However, incineration requires high amounts of energy due to the high water content and produces undesirable NO_X emissions (Constable et al., 2007; Dunn et al., 2010; Gadipelly et al., 2014).

Recently, pharmaceutical companies have increased their efforts to become more sustainable by incorporating green chemistry and green engineering into their daily practices (Jimenez-Gonzalez et al., 2011; Roschangar et al., 2017). It is of special interest to reduce the environmental impact caused by the use of solvents. Hence, two approaches have been considered by the pharmaceutical companies: (a) solvent reduction and (b) solvent

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selection methodologies (Constable et al., 2007; Prat et al., 2014). These methodologies select the solvents based on their physicochemical properties and/or environmental profile. Several methodologies that target the selection of the greenest solvent are at hand. A type of these methodologies is the SHE assessment guidelines, where SHE stands for Safety (S), Occupational Health (H) and Environment (E). As the name states, the main criteria used to define the greenest solvent is based on three categories: safety, health and environment. Other criteria that can be included in these guidelines are regulations (e.g. REACH), industrial constraints (e.g. freezing temperature) and cost. Examples of these methodologies were developed by many pharmaceutical companies and institutions (Clark and Tavener, 2007; Diorazio et al., 2016; Henderson et al., 2011; Isnard et al., 2013; Jiménez-Gonzalez et al., 2004; Mahmoodani et al., 2017; Prat et al., 2016; Tobiszewski et al., 2015). These help to classify common solvents into a traffic light system (Prat et al., 2014). Another methodology is the Life Cycle Assessment (LCA) of a solvent. The LCA is a detailed and precise environmental assessment methodology that considers the complete life cycle of a material (i.e. from the extraction of the resources, the manufacture, the use, the disposal and the recycle of the material) (Capello et al., 2007; Jimenez-Gonzalez et al., 2011). The methodology is based on the ISO standards ISO-14040, ISO-14044, and ISO-14047; and consists in the following steps: goal definition, scope determination, inventory analysis (LCI), impact assessment and finally the interpretation of the results (Raymond et al., 2010). LCA should preferably be conducted in the early stages of research and development, rather than after prototypes or plants have been constructed (Shonnard et al., 2012), where changes are more difficult to implement. The LCA methodology is not commonly applied in solvent selection guidelines because of the long-time invested in acquiring all the data for the assessment (Alder et al., 2016; Capello et al., 2007).

The combination of the environmental assessment together with the physicochemical properties opens a vast solvent design space, but increases the complexity of the solvent selection. Consequently, the use of computational methods have been suggested (Gani et al., 2006; Slater and Savelski, 2007). Computational tools can open new windows of opportunities for solvents that otherwise would have never been considered (Constable et al., 2007). Moreover, this can aid in the search for substitutes to hazardous solvents, evaluate the use of solvents produced with renewable resources (bio-solvents) and evaluate the use of neoteric solvents (Capello et al., 2007).

The interest in neoteric solvents, particularly in ionic liquids (ILs) and their application in the pharmaceutical industry have increased in the past years (Cvjetko Bubalo et al., 2014; Monti et al., 2017). ILs are defined as organic salts with a melting point below 100 °C, i.e. they are liquids at room temperature (Brennecke and JMaginn, 2004; Welton, 1999). They consist of an organic cation and an anion, which can be inorganic or organic. They have low vapour pressure, are normally not flammable, have high solubility, and high thermal stability. Moreover, they are designer solvents which means they can be tailored to address a particular function (Mizuuchi et al., 2008; Moniruzzaman and Goto, 2011; Monti et al., 2017). Because of those characteristics they are perceived to be green and of an environmentally benign nature (Dharaskar et al., 2013; Frade and Afonso, 2010). This green nature has increased the interest in them as potential replacements for volatile organic solvents (Joglekar et al., 2007).

ONE-FLOW is a FET-Open EU project that aims to use conventional and neoteric solvents in a far more fetching context. The Solvents will be used to develop a Functional Solvent Factory (FSF), where these solvents will essentially replace the functions of the reactor and the purification equipment (One-Flow, 2017). The solvents will be used to create a bi-phasic or multiphasic system, and by tuning the environment this multiphasic system will be switched to a single phase system and vice-versa. This switching behaviour will form temporary compartments where reactions and purifications will be conducted. Single phase systems will be used to conduct the reactions, while multiphasic systems to conduct the separation processes (see Fig. 1).

These advanced separation functions are a central part of the ONE-FLOW approach. Therefore it is necessary to design a solvent selection methodology that proposes solvents that create up to three fluidic phases, each solvent tailored to trap the reactants, the product, and the catalyst (Hessel, 2018; Zhang et al., 2018b). That would allow an advanced and simplified purification and recycling while achieving multi-step processing. In view of the latter, there is biomimetic potential to translate the 'vertical hierarchy' of multistep flow reactors and separators into a self-organizing 'horizontal hierarchy' of one compartmentalized flow reactor system (Hessel, 2018; One-Flow, 2017; Zhang et al., 2018b).

In this study, the first sustainability assessment for the ONE-FLOW is presented, based on the first step that is the solvent selection. The focus will be to assess a solvent for the recovery of the product (as shown in Fig. 1). The solvents used for the recovery of the catalyst and reactants will be presented elsewhere (Zhang et al., 2018a, 2018b). In order to have a holistic selection, it is necessary to include an economic, environmental, and safety evaluation to the physicochemical properties assessment (Hessel, 2018; Zhang et al., 2018a). This paper elaborates on the sustainability part of the solvent selection.

2. Methodology

The schematic diagram of the Functional Solvent Factory solvent selection methodology is presented in Scheme 1. It consists of the following steps:

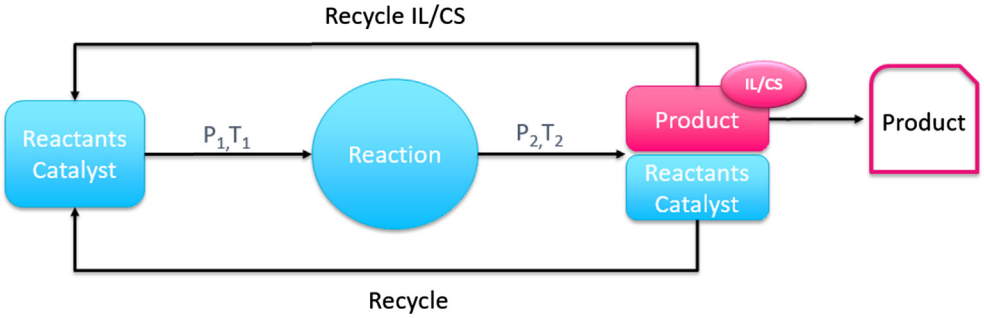
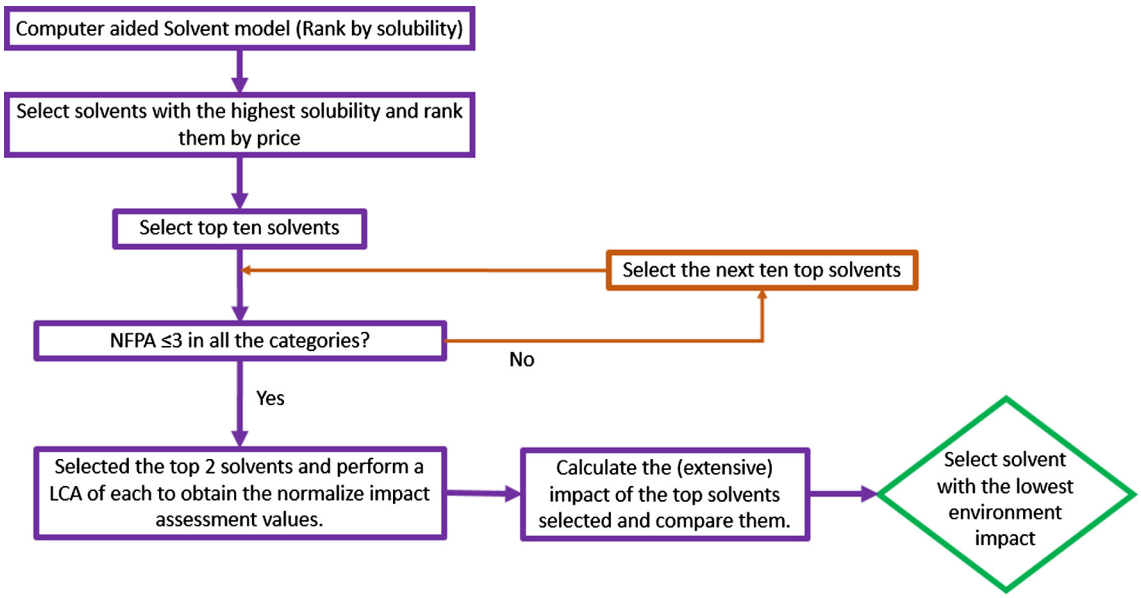


Fig. 1. ONE-FLOW Functional Solvent Factory outline. IL stands for ionic liquid and CS for common solvent. This is the most general and ideal scheme, based on modern biphasic catalysis. The real flow scheme might be more complex, depending on the number of solvents and additional workup steps needed (yet all based on neoteric solvents).



Scheme 1. Functional Solvent Factory Solvent Assessment Methodology.

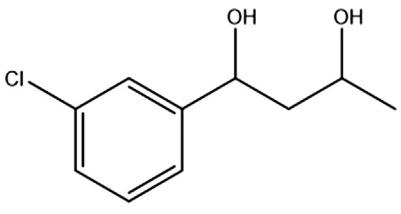
2.1. Solvent selection

Firstly, a cascade is selected as a case study, from which a list of solvents will be obtained from COSMO-RS (Zhang et al., 2018b). In this particular study, the methodology targeted the selection of a functional solvent for the bio-chemo cascade reaction developed by Gröger et al. to synthesize of a 1-(3(chlorophenyl)butan-1,3-diol (see Fig. 2) (Rulli et al., 2017, 2011). As explained before, in order to develop the FSF the solvent selected should extract the product from the reaction media as pure as possible just by changing the physical conditions. Therefore, the desired product should have high solubility in that solvent. The result of this modelling work in COSMO-RS generated a list of over a thousand solvents. These solvents were then ranked based on the capacity to dissolve the main product of the reaction.

Due to the vast number of solvents, it was opted to develop a methodology in which the solvents were discarded if they do not fulfil pre-established criteria rather than applying a multicriteria assessment. These criteria are the cost, the safety and the environmental impact. The assessment of the solvents in each criterion is presented below. In case that fewer solvents than the expected pass the assessment, then the next solvents on the top of the list will be considered. This process of looping back to next solvents on the list is applied only in the safety criterion.

2.2. Price rank

From the list of solvents ranked by solubility the first 50 are selected. These 50 solvents are ranked by the price. The top 10 solvents are selected for the next stage. The economic constraints were aimed for future economic assessments to the FSF, rather than aimed at making a hard cut. Prices were obtained from E. Merck KGaA (formerly Sigma-Aldrich).



1-(3-chlorophenyl)butane-1,3-diol

Fig. 2. Product of the chemoenzymatic tandem-type one-pot synthesis cascade.

2.3. Safety rank

The top 10 solvents undergo a safety evaluation, in which the NFPA rating is used. The NFPA rating aims to advise on the potential hazards that may be encountered due to the use of a certain chemical. There the chemicals are rated on a numeric scale from zero to four, with zero being the lowest (no hazard) and four the highest level of risk (severe hazard) (Melorose et al., 2015). Only the solvents with a score below or equal to three in all of the categories will be considered for the next step. If the solvents are peroxidizable or polymerizable will be discarded as well. Solvents without NFPA data will not be considered due to safety reasons.

2.4. Calculation of amount of solvent

The top four solvents from the safety rank are selected. For each it is calculated the amount of solvent needed to solubilize one mol of product.

2.5. Environmental assessment

The top two solvents undergo a Simplified Life Cycle Assessment (SLCA). An SLCA was conducted to identify ecological hotspots when data gaps and uncertainties are unavoidable. Furthermore, this assessment allows the opportunity of assessing and quantifying the potential environmental impact of the solvents, i.e. rank the impact on a quantitative scale. However, as mentioned before this step can be very time consuming. Accordingly, it was limited to only two solvents.

For the SLCA the solvents were assessed from a cradle-to-gate approach, which means the assessment was conducted starting from the raw materials until obtaining of the solvent. The functional unit selected for the SLCA is 1 kg of solvent.

The inventory for the conventional solvents was constructed from the LCI database Ecoinvent 2.2. This database is incorporated in Umberto NXT LCA, software used for the SLCA. In the case that

the solvent was not found in the database, a retrosynthesis was conducted until the base starting bulk materials were found. Information regarding the manufacturing process for the retrosynthesis was obtained from SciFinder® and relevant literature (Girard, 1980; Miwa et al., 1964; Righi et al., 2016; Shaabani et al., 2014).

If a component needed for the synthesis of a solvent was not present in the database a proxy was used. For example, 2-Octanol, the precursor of 2-Octanone was not found in the database; thus the proxy fatty alcohols was used instead (USDA and Agricultural Marketing Service, 2016).

The fourteen ReCiPe Midpoint impact factors were used to evaluate the solvents, namely: Urban Land Occupation [ULOP m^2/yr], Natural Land Transformation [NLTP m^2], Climate change [GWP 100 kg CO_2 Eq], Ozone Depletion [ODP kg CFC-11-Eq], Particulate Matter Formation [PMFP kg PM10-Eq], Photochemical Oxidant Formation [POFP kg NMVOC], Marine Eutrophication [MEP kg N-Eq], Marine Ecotoxicity [METP kg 1,4-DCB-Eq], Freshwater Eutrophication [FEP kg P-Eq], Freshwater Ecotoxicity [FETP kg 1,4-DBC], Cumulative Energy Demand [CED Folsil Fuels MJ-Eq], Water Depletion [WDP m3], Fossil depletion [FDP kg oil-Eq]), and Human Health (Human Toxicity [HTP kg 1,4-DCB-Eq]). All impact factors were considered with the same weighting factor. The total impact of the solvent was obtained by multiplying the impact factor (per kilogram of solvent) times the amount of solvent needed to dissolve one mol of product. Then the total impact factor was normalized with respect to a selected solvent, in this case was acetic acid, in order to obtain dimensionless impacts. Consequently, each category can be added to obtain the overall impact of the solvent. The solvent with the lowest value will correspond to the lowest environmental impact, thus it will be rated as the best solvent.

A sensitivity assessment was conducted by analysing possible synthetic routes present in the market. Two scenarios were developed for the solvents for which a retrosynthesis was conducted. These scenarios consisted in two different production routes, to assess how these routes affect the environmental impact of the solvents.

Finally the solvent with the lowest impact is selected for the experimental trials.

3. Results and discussion

Solubility data of pharmaceuticals is rarely available. Thus selecting the best solvents requires experience and experimental testing. This testing may lead to a poor solvent selection, especially when time and economic constraints obstruct the possibility of trying an extensive number of solvents. Solubility is of crucial importance for the FSF concept, and selective solubility in the different a multiphase system is the prerequisite for the functioning of the whole concept. Therefore this parameter was used to determine possible solvents and calculate the amount of solvent needed. Herein we present how solubility can aid in the solvent selection process from an environmental perspective.

In the first case study we discuss how the employment of the solubility can help in finding a more environmentally friendly solvent, even when the solubility in a particular solvent is unknown. Then we apply the methodology developed for the assessment of common solvents for the Functional Solvent Factory. Finally, we conclude with a case study where we present how this methodology is flexible enough to be applied to neoteric solvents, particularly ILs, and compare them with common solvents.

3.1. Unknown solubility

Solvents with different capacities to dissolve 1-(3 (chlorophenyl)butan-1,3-diol were obtained from COSMO-RS. Based on the solubility the amount of solvent needed was calculated. The result is plotted in Fig. 3. This plot shows how the amount of solvent increases exponentially when the solubility of the product in the solvent decreases.

To evaluate how the environmental impact of a solvent is influenced by the solubility 3 solvents were selected, namely: acetic acid, acetonitrile and acetone. These solvents are rated within the same category in existing solvent guides (Prat et al., 2014). An SLCA study was performed for each solvent, only the following impact categories were evaluated: CED, FEP, GWP and WDP. In Fig. 4, the impact of the solvents in all the categories are presented. These impacts were calculated at different solubilities, hence the logarithmic behaviour. The environmental impact in each category increases with the increasing amount of solvent needed, which is caused by the decreases of solubility of the product in the solvent. Consequently, selecting the solvent with the highest solubility will lead to the lowest impact.

Besides being able to select a solvent, environmental hot spots can be identified. These can be used later for the environmental management in the process design stages, and design strategies to abate the categories where the solvent has a high impact.

If the solubility of the product, catalyst, or any other compound that wants to be recovered in a particular solvent is known. Then the impact in each category can be calculated and compared for different solvents. However, this is not the standard case, the solubility of pharma compounds is rarely known (Kolář et al., 2002). With these in mind, two assessments are proposed to compare different solvents, namely: single point and a multiobjective comparison. These will allow to compare the solvents when the solubility is unknown.

The single point comparison refers to the comparison of the environmental impact of two solvents at the same point (same solubility) in the same impact category. To perform this comparison Eq. (1) was used.

$$R_{IF,j} = \frac{IF_{j,i} - IF_{r,i}}{M_{j,i} - M_{r,i}} \quad (1)$$

where R is the rate of change, IF the impact category selected (e.g. GWP) and M the mass of solvents (selected and reference *r*) at solubility *i*.

The results are presented in Table 1. These show that acetone GWP is 6.5 fold lower than acetic acid, while it is only 1.3 times lower with respect to acetonitrile. The results in the other cate-

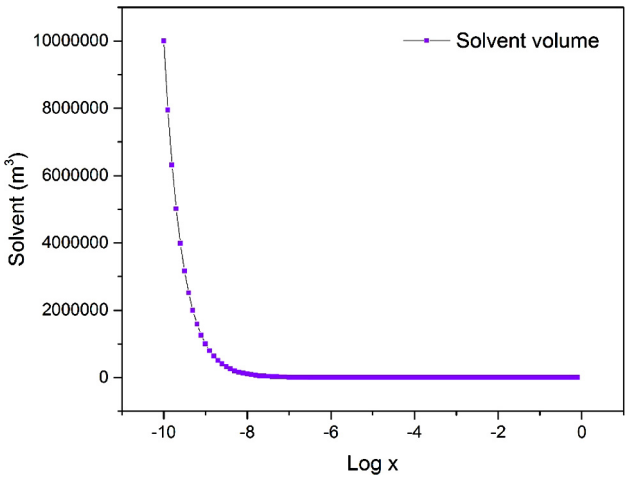


Fig. 3. Solvent needed, in volume, as a function of its capacity to solubilize one mol of product. Log x refers to the solubility expressed in a logarithm scale, with zero being the highest solubility.

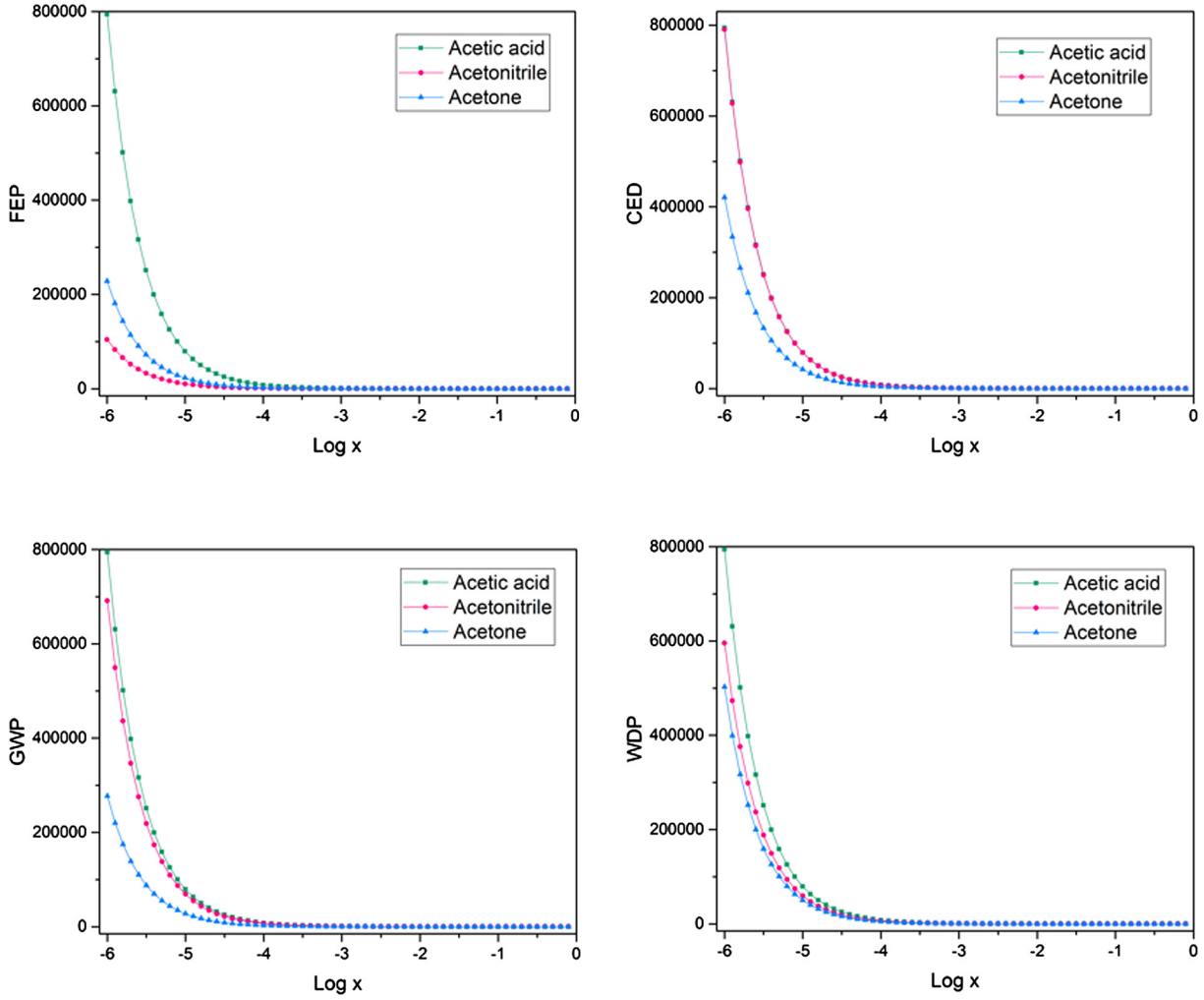


Fig. 4. Environmental impact of acetic acid, acetonitrile and acetone in the FEP, CED, GWP and WDP categories.

Table 1
Single Point comparison for acetone-acetic acid and acetonitrile-acetic acid in the GWP, CED, HTP and FEP categories.

LCA Factor	Solvent	Reference Solvent	Fixed Point Assessment
GWP	acetone	acetic acid	6.5
GWP	acetonitrile	acetic acid	1.3
CED	acetone	acetic acid	110.9
CED	acetonitrile	acetic acid	1.2
HTP	acetone	acetic acid	0.3
HTP	acetonitrile	acetic acid	0.3
FEP	acetone	acetic acid	3.3×10^{-04}
FEP	acetonitrile	acetic acid	4.1×10^{-04}

gories indicate a similar trend. Acetone rates better than acetic acid, while acetonitrile has an impact comparable to acetic acid. The only category for which acetic acid has a lower impact than the other two solvents is FEP.

A set of solvents can be judged with this assessment. However, this assessment can only compare one point, encumbering the evaluation through the whole solubility range. To encompass the possible range of solubilities a multiobjective comparison is suggested. In this, small variations of solubility can be studied simultaneously (see Fig. 5). It can be applied to compare two solvents simultaneously. By employing this assessment it will be possible to determine how many times higher the solubility of the second solvent needs to be to replace the solvent for which the solubility in is known.

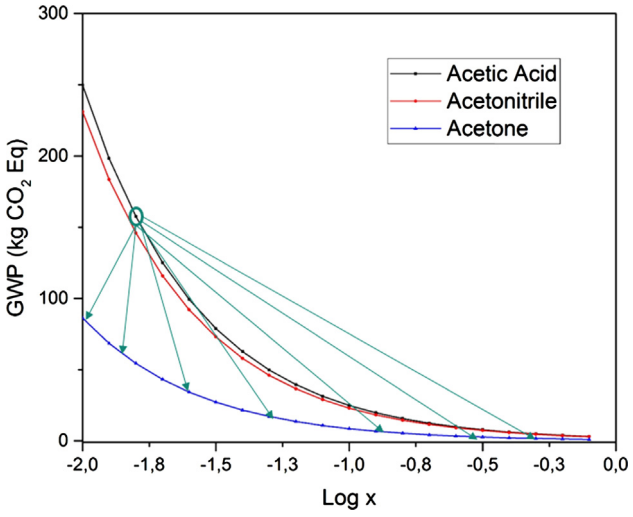


Fig. 5. Graphical visualization of the multiobjective comparison assessment.

Eq. (2) was used to perform this assessment for the solvent sets of acetone-acetic acid and acetonitrile-acetic acid. The results are displayed in Figs. 7 and 8.

$$\Delta IF_{j,} = IF_{j,i} - IF_{r,n} \quad (2)$$

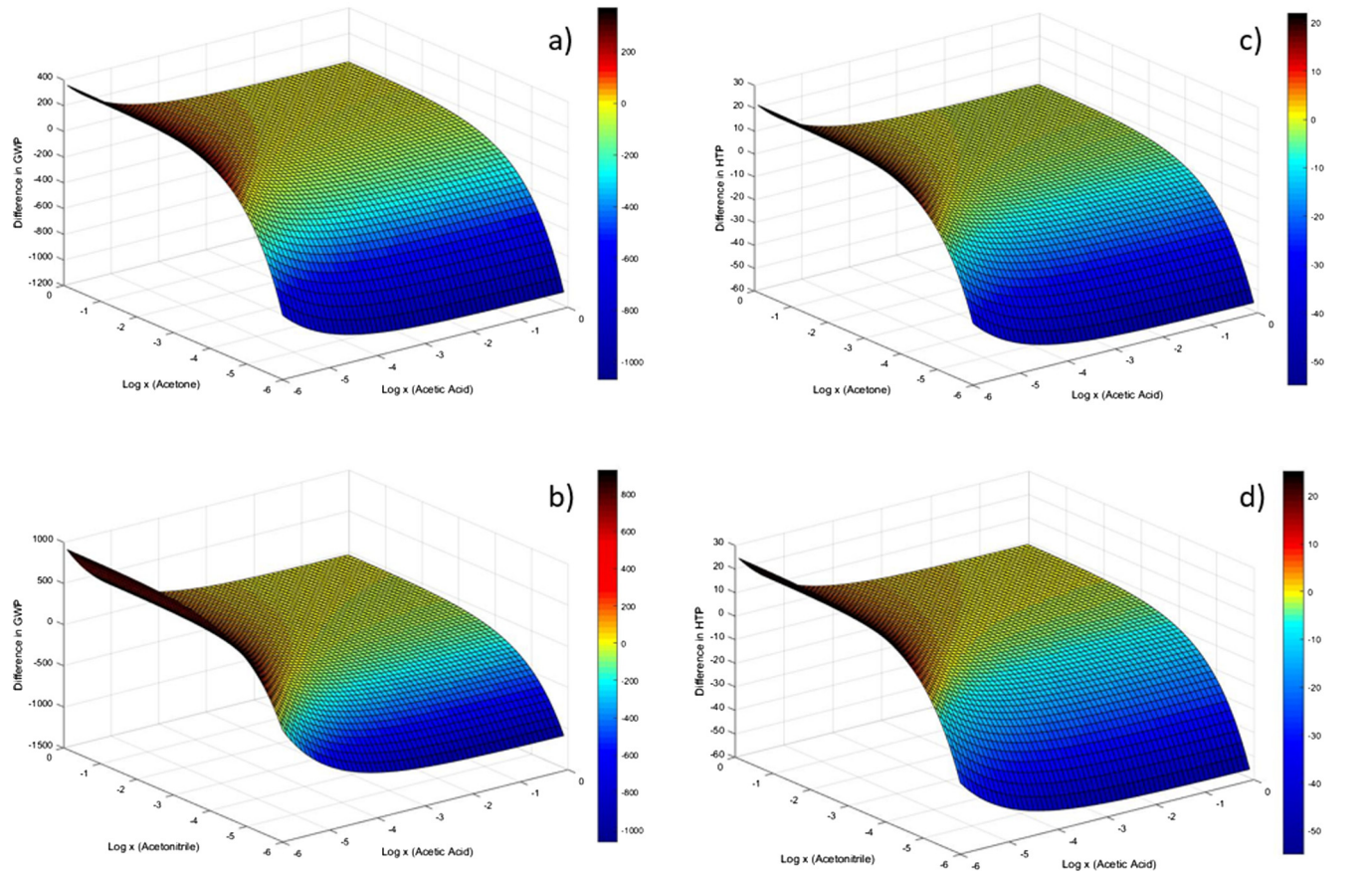


Fig. 6. Graphical representation of multiobjective assessments for (a) acetone-acetic acid GWP category, (b) acetonitrile-acetic acid GWP category, (c) acetone-acetic acid HTP category, (d) acetonitrile-acetic acid HTP category.

where *IF* is the impact factor of interest (e.g. GWP), *r* is the reference solvent (i.e. reference solvent), j refers to the solvent of interest and *i* to the point of comparison (solubility expressed logarithmically). Applied to n ⊇ Log x. By applying Eq. (2) a surface plot is created. Flat areas represent the points where the impact (in that particular category) of the solvents is relatively the same; while cleft areas represent the solubilities in which the reference solvent (solvent one) is better than the solvent of interest. For example, in Fig. 6 the GWP category is plotted. In the case of acetonitrile-acetic acid, the cleft areas are smaller compared with the cleft areas of the set acetone-acetic acid. Steep points are overserved in the case of the acetonitrile-acetic acid set. Without any knowledge of the solubility of a compound in any of these solvents, the experimenter can check how greater the solubility in the solvent of interest need to be compared with the reference solvent in order to select the greenest solvent. It can also be observed that some impact factors differ greatly from solvent to solvent. This is the case of GWP and CED, where delta is in the order of hundreds; while for HTP and FEP the delta is in the order of tens. This difference can aid in the selection of impact factors with greater influence for the evaluation of the solvents.

3.2. Case study Functional Solvent Factory

Due to the importance of the solubility for the FSF, it was elaborated from that a methodology to assess and select the solvents for the FSF. Below it is presented how the methodology is applied for the cascade to synthesize 1-(3(chlorophenyl)butan-1,3-diol. An extensive list of solvents was obtained from COSMO-RS and ranked by solubility to obtain the solvents with the highest values. The top 50 were selected and ranked by price, for which the top ten solvents are presented in Table 2.

It is important to note that the solvents given here are specialities, i.e. not in the group of bulk solvents such as ethanol or methanol. For comparison purposes, the common solvents: ethanol, methanol, acetic acid and methyl ether ketone were included in the environmental assessment section.

After the price ranking, solvents were ranked based on safety consideration. The safety assessment considered first the flammability, followed by instability and finally health. Less importance was given to the health score considering that it is also evaluated in the environmental assessment (HTP category). The top three solvents after the safety assessment are presented in Table 3. Decan-1-oic acid scored the highest due to its low flammability; however, it ranks level 2 in the health category because it can cause incapacitation after continuous or intense exposure of the operators to it (Melorose et al., 2015). After decan-1-oic acid, the next solvent with the highest rating was 2-ocatanone.

Afterwards, an SLCA of the top-2 solvents and the common solvents (EtOH, MeOH, Acetic acid and MEK) was done. The impact factors were obtained as extensive properties, i.e. dependent on the mass (e.g. per kg). These results were adjusted with the mass of the solvent needed to extract one mole of product, which was calculated from the solubility results. The solubility in this common solvent had to be assumed, in this case equal to decan-1-oic acid. Fig. 8 presents the results from the common solvents (EtOH, MeOH, acetic acid and MEK). These results were normalized with respect to acetic acid (as it has the highest impact of the common solvents). The results show that MeOH is the solvent with the lowest environmental impact, with the majority of it caused by the emissions produced during its synthesis. MeOH is followed by MEK, which has a greater impact in the water compartment (WDP).

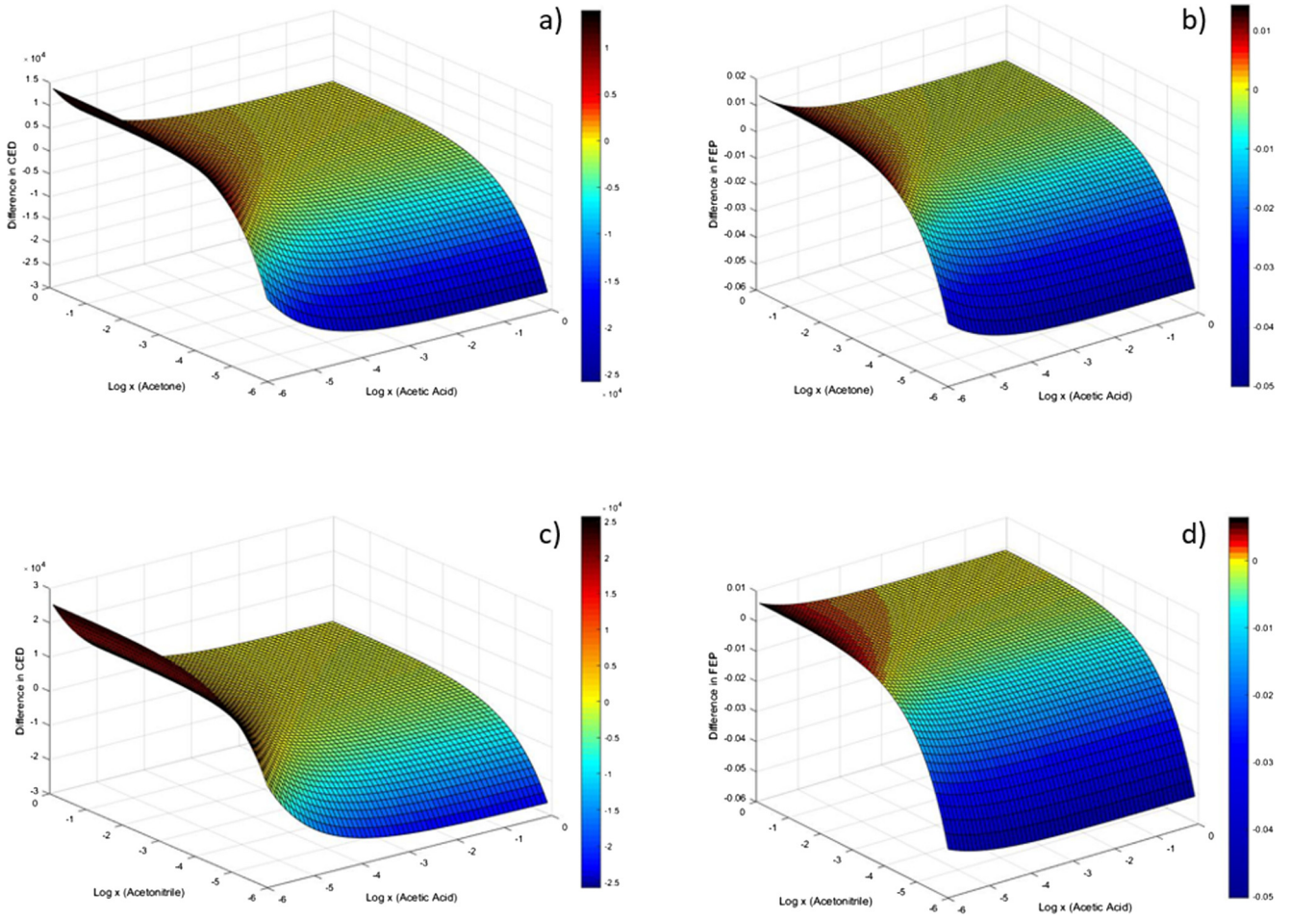


Fig. 7. Graphical representation of multiobjective assessments for (a) acetone-acetic acid CED category, (b) acetonitrile-acetic acid CED category, (c) acetone-acetic acid FEP category, (d) acetonitrile-acetic acid FEP category.

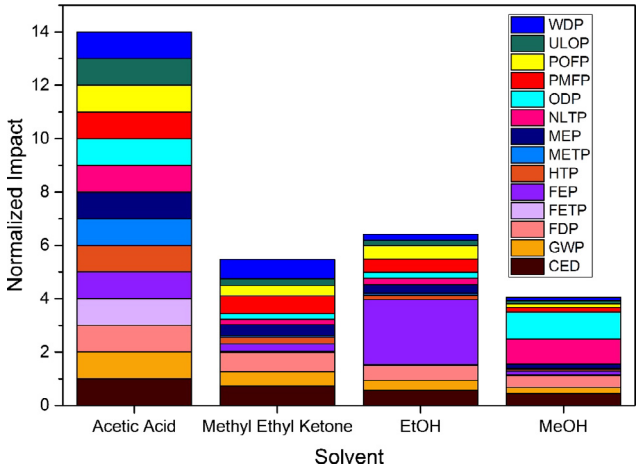


Fig. 8. Environmental impact results of conventional solvents normalized with respect to the impact of acetic acid.

A retrosynthesis was conducted for 2-octanone. Two synthetic routes were studied to analyse different pathways and reduce uncertainties. These routes or scenarios are named "a" and "b" respectively (see Fig. 9). For example, 2-Octanone is synthesized by the oxidation of secondary alcohols. Traditionally such class of reactions are performed using inorganic oxidants, particularly chromium, which cause great environmental damage (Sheldon et al., 2002). Consequently, alternatives for this synthesis have been proposed (Ballarin et al., 2017; Pagliaro et al., 2005; Shaabani et al., 2014; Sheldon et al., 2002). A greener alternative was compared with the traditional synthesis, in this manganese is used as oxidation agent. In Fig. 9 it is shown that the manganese-based process "a" is indeed greener than the state of the art process. However, the remarkable difference is caused by the large amounts of diethyl ether used in the synthesis and in the separation stage, rather than caused by the materials used.

The two scenarios modelled for the synthesis of decan-1-oic acid exhibit less discrepancy in the impact, with most of it attributed to the use of fatty acids as starting material in both cases.

After the assessment, it can be concluded that unless 2-octanone is synthesized with a greener procedure, the best solvent

Table 2
Top ten common solvents after price rank.

Solvent	Solubility Rate	Rank
2,2-Diethoxypropane	Maximum	1
1-Propanol	Maximum	2
decan-1-oic acid	Maximum	3
Lactic acid	Maximum	4
Propanal	Maximum	5
4-Methyl-2-Pentanone	Maximum	6
Isophorone	Maximum	7
2-Methyl-2,4-Pentanediol	Maximum	8
2-Octanone	Maximum	9
Formic acid	Maximum	10

Table 3
Top-3 solvents according to safety ranking (NFPA), as expressed by flammability, instability, and health.

Solvent	CAS	Flammability	Instability	Health	Safety[a]
Decan-1-oic acid	334-48-5	0	0	2	accepted
2-Octanone	111-13-7	2	0	1	accepted
2-Methyl-2,4-pentanediol (hexylene glycol)	107-41-5	2	0	2	accepted

[a] Solvents that successfully passed the evaluation are marked as accepted. Otherwise, it is marked as rejected.

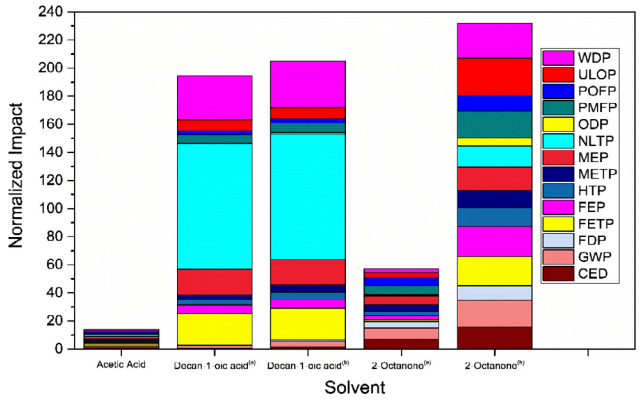


Fig. 9. Decan-1-oic acid and 2-octanone (common solvents) environmental impact results normalize with respect to the impact of acetic acid.

is decan-1-oic acid. However, compatibility issues must be checked. Decan-1-oic acid is incompatible with the temperature at which the reaction is conducted due to the high melting point of it; therefore, it has to be discarded. Other compatibility matters will be considered and assessed during experimental stages.

On the other side, when if compared with the most conventional solvents (e.g. acetic acid), the impact of decan-1-oic acid is larger.

3.3. Case study ionic liquids as functional solvents

There is a great interest in ionic liquids (ILs) for pharmaceutical applications (Brennecke and JMaginn, 2004; Smith et al., 2011). This interest is due to their performance properties, that allow them to conduct a wide range of chemical reactions (Amde et al., 2015). In the particular case of the Functional Solvent Factory, they are functional solvents; i.e. in combination with other(s) solvent(s) they can develop a multiphase system that can be switched to a single phase system by changing the conditions (e.g. temperature) (Liu et al., 2004).

Ionic liquids are commonly perceived as more environmentally friendly with respect to conventional organic solvents. This is because they have a low vapour pressure, and near zero flammability (Petkovic et al., 2011). However, the synthesis of ILs requires extensive amounts of reagents, energy and solvents, and generates large amounts of waste (Costa et al., 2017). Therefore, if it is aimed to use them in the Functional Solvent Factory it is imperative to select the best IL with the lowest environmental impact. However, their assessment and selection pose a great challenge. It has been reported that there are over 10^{18} ILs as a result of the possible cation-anion combinations (Sangoro et al., 2016). The methodology developed for conventional solvents can be applied to ILs. Nonetheless, despite the extensive amounts of ILs not all of them are commercially available. In 2018 E. E. Merck KGaA KGaA counted in their portfolio with over 200 ILs (Merck, 2018). For ILs not available commercially, it is possible to get an estimation of the cost based on a laboratory scale production. However, using laboratory data may lead to inaccurate cost evaluations.

Therefore the final case elaborates on how the methodology developed can be applied when the ILs have been identified. This is the case when some ILs are known to be compatible with the cascade but the solubility is unknown, then it is possible to assess them by evaluating the ILs at different solubilities.

A commercial IL, 1-butyl-3-methylimidazolium chloride [Bmim] [Cl], was selected. Imidazolium-type ILs are among the most commercially available ILs (Merck, 2018). These kinds of ILs are known to have negligible volatility, high stability, good solubility with many compounds (Wang and Wang, 2016). Moreover, the safety data for this particular solvent is available. The evaluation parameters considered in this assessment are only the safety and the environmental evaluation of the solvents. From the material safety data sheet of the solvent the NFPA rating was obtained (Thermo Fisher SCIENTIFIC, 2012) (see Table 4). Contrary to what would be expected, the flammability level of this solvent is one and not zero. This is due to the hazardous products that may be formed during the combustion of the solvent. Yet its flammability is still lower than of 2-octanone or hexylene glycol. In the health rating it scores Level 2, meaning that the solvent can cause incapacitation to the operator after continuous or intense exposure to it. Despite the health rating, the solvent rates satisfactorily, and the SLCA can be conducted.

Two scenarios were developed for the assessment of this IL focusing on its solubility rather than different production pathways. Scenario "a" assumes that the solubility in the IL is the same as in acetic acid, and scenario "b" assumes that the solubility of the IL is 5 times higher than in acetic acid. The results are presented in Fig. 10. The environmental impact of the IL is three times larger than the impact of the acetic acid in scenario "a". NLTP, ODP and

Table 4
NFPA rating of [Bmim] [Cl].

Flammability	Instability	Health
1	1	2

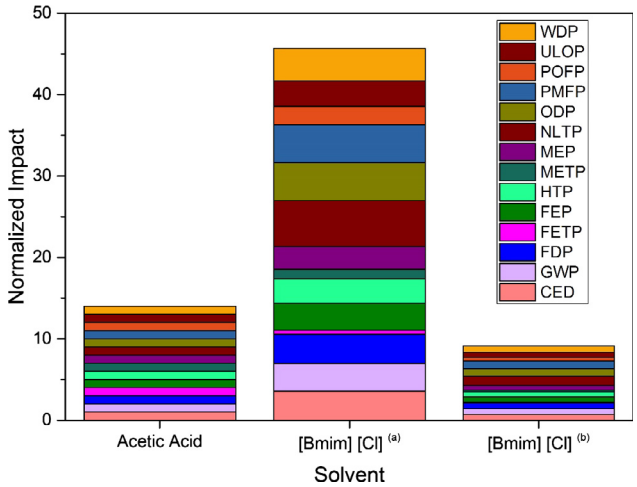


Fig. 10. Environmental impact of the Ionic Liquid [Bmim] [Cl] compared with acetic acid. Scenario (a) assumes the same solubility as acetic acid, and (b) assumes that the solubility of the product in [Bmim] [Cl] is 5 times greater than in acetic acid. Results were normalize with respect to the impact of acetic acid.

PMFP are the categories with the largest impact. In scenario b, the environmental profile of this IL improved dramatically. This scenario shows that this IL could potentially be a better alternative to a common solvent such as acetic acid, depending on the solubility in it. Even though, the environmental impact of the IL is greater than the environmental impact of the conventional solvent, when compared only in terms of the same mass. When the performance properties are accounted, e.g. solubility, a greener solvent can be found. This was also found before in a comparison of two ILs (Amado Alviz and Alvarez, 2017). There it was corroborated that despite the difference in the environmental impact of the solvents when their performance in the process was compared the results presented a similar profile. Moreover, they also highlight the importance of including these performance properties in the assessment of a solvent.

In order to improve the solubility in the IL the anion can be tune (Moniruzzaman and Goto, 2011; Smith et al., 2011). However, the anion also influences the toxicity of the IL. Meaning that a careful assessment and selection needs to be done.

4. Conclusions

It was presented the key statement of this research, i.e. aid of performance parameters in the selection of the greenest solvent. Solubility, in this case is used as the key parameter for the solvent assessment.

Firstly, it was introduced two simple methods to evaluate the solubility variations: the single point and the multiobjective comparison. Then, it was presented a more comprehensive solvent assessment methodology that targets the Functional Solvent Factory. This methodology was designed considering its future application towards neoteric solvents. It integrates a series of screenings (the environmental impact, the economic and the safety) together with the physical property of interest, the solubility. The second case study shows how the methodology is applied to normal solvents. Yet these normal solvents are not as conventional as methanol or ethanol. For purposes of comparison the conventional solvents also were assessed and compared against the normal solvents. For the cascade selected it can be concluded that decan-1-oic acid is potentially the greenest alternative. Especially if the synthesis pathway of 2-octanone is unknown. However, when compatibility in the reaction is added, then the best solvent is 2-octanone.

The advantage of this methodology was showed in the third case study, where it was used to assess and compare neoteric solvents to conventional solvents. Two aspects are noteworthy, the first is the safety of the ionic liquids. They are believed to be non-flammable and in general safer to conventional solvents. However, the safety data sheet presented a safety hazard comparable with conventional solvents. Secondly, when the solubility of the ionic liquids is the same as conventional solvents, the environmental impact of the ionic liquid is greater than the conventional. Nevertheless, as the solubility in the ionic liquid increases the environmental impact is greatly reduced, to the point where the ionic liquid is the greener candidate.

This methodology is the first step towards a green design of the Functional Solvent Factory, where the aim was to select and assess the solvents. As an outlook it is aimed to improve the methodology with a multicriteria perspective that includes the process and compatibility issues in detail. Evaluating how the solvent impacts the process and recyclability options are necessary for the green design of the Functional Solvent Factory.

Conflict of interest

The authors declare no competing financial interest

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