Dihydroxyacetone crystallization: process, environmental, health and safety criteria application for solvent selection

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Abstract

Dihydroxyacetone is a good candidate to valorize the excess glycerol obtained as byproduct in biodiesel production. Crystallization is likely the key unit operation to obtain a high quality and pure dihydroxyacetone. The selection of an appropriate solvent for crystallization is not trivial and depends on multiple factors. At the present work a new solvent selection methodology, based on solvents relative comparisons, is described and applied to dihydroxyacetone crystallization as a case study. The procedure accounts not only for process factors such as solubility and yield, but also for cost, recycling, disposal, environmental, health and safety issues. Solubility and theoretical yield data for dihydroxyacetone in methanol, ethanol and 2-propanol were experimentally determined, while cost, life-cycle assessment, environmental, health and safety data of solvents were gathered from different bibliographic sources, software and databases. Among the solvents assessed, methanol resulted as the best overall choice for DHA crystallization. The methodology proved to be a suitable, simple and flexible procedure for solvent selection at the initial stages of the crystallization operation design, being able to be upgraded for advanced stages of the crystallization process development.

Keywords: dihydroxyacetone; crystallization; solvent selection; methanol; ethanol; 2-propanol.

1. Introduction

Nowadays, the necessity of replacing fossil fuels has boosted the search for renewable alternative energy sources and so the development of biofuels such as biodiesel. Nevertheless, the continuous increasing demand for biodiesel has resulted in an excess of glycerol production, obtained as byproduct (10% w/w), causing a significant devaluation in its price (da Silva et al., 2009; Katryniok et al., 2011; Kenar, 2007). Glycerol has a large amount of well-known applications in food, pharmaceuticals, personal care, cosmetics and other industrial applications; however these classical uses are not adequate to absorb the surplus of glycerol and research efforts are being dedicated towards its valorization (da Silva et al., 2009; Katryniok et al., 2011; Kenar, 2007). Moreover, the production of high value-added compounds from glycerol will not only beneficiate its own market but also the biodiesel industry as its economic viability is closely linked to glycerol (Kenar, 2007). In this context the 1,3-dihydroxy-2-propanone, commonly known as dihydroxyacetone (DHA), stands out from other compounds that can be obtained from glycerol, and not only for its relative high price with respect to glycerol, within a 250-500-fold value (Katryniok et al., 2011), but also because, as estimated by the American Chemical Society, the demand of DHA will meaningfully increase in the next years (Ma et al., 2010). The DHA can be used for the organic synthesis of various fine chemicals, but it most remarkable application is in cosmetic formulations as a self-tanning agent, which is based on the Maillard reaction with amino groups of human skin (Bauer et al., 2005; Hekmat et al., 2003; Katryniok et al., 2011; Kenar, 2007).

DHA can be obtained from glycerol via catalytic chemical or biotechnological oxidation processes, but at industrial scale it is generally produced by oxidative fermentation due to economic, safety and quality requirements (Hekmat et al., 2003; Katryniok et al., 2011). *Gluconobacter oxydans* is the most widely used microorganism for this bioprocess (Hekmat et al., 2003; Hekmat et al., 2007; Ma et al., 2010). Many studies deal with the glycerol-DHA fermentation improvement and optimization (Bauer et al., 2005; Hekmat et al., 2003; Hekmat et al., 2007; Hu et al., 2012; Hu and Zheng, 2011; Hu et al., 2011; Li et al., 2010; Ma et al., 2010) but the downstream separation and purification process have received less attention. The downstream process will include several unit operations but crystallization is most likely the key separation/purification step to obtain a pure and high quality DHA.

The selection of an appropriate solvent for crystallization is a critical point in order to achieve optimal process performance. Solute solubility is probably the most important process factor when selecting a solvent, as it will determine the crystallization method and yield; thus, strategies of solvent selection for organic compounds crystallization based on solute solubility prediction have been proposed (Frank et al., 1999; Nass, 1994).

In the last two decades there has been a growing concern about chemistry sustainability and so green chemistry has become a requirement for industrial processes development and chemical compounds obtained or used thereof. The Globally Harmonized System of Classification and Labelling of Chemicals (GHS), created by the United Nations (United Nations, 2003), was the starting point for a global system of information and classification of chemical substances based on their health, physical and environmental hazards. The European Union (EU) has implemented the GHS into the CLP regulation (Regulation on classification, labelling and packaging of substances and mixtures of the European Union) (European Union, 2008), which is complementary to the REACH regulation (Regulation concerning the Registration, Evaluation, Authorization, and Restriction of Chemicals) (European Union, 2006), that addresses chemicals production and use in ways that lead to the minimization of significant adverse effects on human health and the environment. Therefore, in addition to process parameters such as solubility, crystallization solvent selection methodologies need also to include criteria based on environmental, health and safety (EHS) issues. Following this trend, in the last years different pharmaceutical companies such as GlaxoSmithKline (GSK), SANOFI, Pfizer, Astra Zeneca and the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) have developed their own proprietary general guides for solvent selection based on EHS assessment combined with factors relative to their industrial processes (Curzons et al., 1999; Dunn, 2012; Henderson et al., 2011; Prat et al., 2013). These guides are only fully available for internal use within the companies, and although the final rating or solvent classifications have been published, the methodology followed and assessment tools used are completely private. Apart from these proprietary guides other works have proposed different general solvent selection methods (Capello et al., 2007; Slater and Savelski, 2007), intended for fine chemical and

pharmaceutical industries, which have considered environmental, health and/or safety issues, but lack of considerations relative to the crystallization process such as solubility, yield or solvent cost.

Therefore, based on a case study for DHA crystallization, the present work aims to propose a new methodology for crystallization solvent selection that joints together the assessment of fundamental process and economic factors, such as solute solubility, crystallization yield, solvent cost and life-cycle assessment, and EHS hazards inherent to solvents. This methodology will establish a relative comparison between the solvents assessed that will help to select the most appropriate one or ones among the feasible candidates at the initial stages of the crystallization process development, but also will allow for solvent selection improvement as design process advances by upgrading the method. This methodology is a valuable tool that can be applied at any scale of process design: laboratory, pilot and industrial plant.

2. Materials and Methods

2.1. Solubility measurement

DHA solubility was measured in three different alcohols: methanol, ethanol and 2-propanol. This initial set of solvents was selected following the well-known rule of thumb "like dissolves like", and considering that these three alcohols are commonly used as solvents in industrial processes; their assessment provided an appropriate framework to develop, evaluate and explain the novel solvent selection method proposed.

Dihydroxyacetone dimer was purchased from Sigma-Aldrich (lot number: MKBJ4156V), and high purity methanol, absolute ethanol and 2-propanol were purchased from Fisher Chemical.

40 mL of solvent was added to a 45mL septum screw-capped test tube. The test tube was submerged in a bath and brought to the desire temperature within -8 to 30 ºC. Higher temperatures were not assayed as DHA have been found to decompose above 40 ºC (Zhu et al., 2003). The temperature of the bath was controlled with a recirculation cryothermostat Frigiterm-10 (J.P. Selecta). Excess DHA was then added and left to dissolve with magnetic stirring, the dissolved concentration being checked over time; stirring was stopped 10 minutes before sampling and afterwards a 2.5mL sample was withdrawn using a glass syringe with 0.45μm PTFE filter; the

DHA concentration was then determined by HPLC analysis. The DHA concentration was measured until saturation was achieved; saturation time ranged within 96-288h depending on temperature and solvent. Then, the saturated solution density was measured, at the same temperature of the saturated solution, with a 5mL pycnometer, the sample being withdrawn as described before. The saturated solution density was used to express the DHA solubility as grams of DHA per kilogram of solvent. The temperature of all materials and equipment used was controlled throughout the process. Experiments were done by triplicate, the standard deviation being always below 5%.

2.2. DHA HPLC analysis

The DHA concentration HPLC analysis was based on that published by Hekmat et al. (2003) with some modifications. A HPLC Shimadzu VP series, equipped with degasser, auto sampler, pump, column oven, PDA detector and communications bus modules, was used. Chromatograms were analyzed with the LabSolutions LCsolution software. The HPLC column was a Rezex RCM-Monosaccharide Ca+2 (8%) 300x7.8mm (Phenomenex). The operation mode was isocratic, MilliQ water being the eluent. The flow rate, temperature and injection volume were 0.6mL/min, 40 ºC and 10μL, respectively. DHA concentration was measured with the PDA detector at 271nm. A calibration curve with DHA aqueous solutions was constructed, the concentration range being within 0-10g/L.

2.3. DHA X-ray powder diffraction analysis

Four crystalline forms, one monomeric and three dimeric polymorphs (α, β and γ), are known for DHA (Slepokura and Lis, 2004); their crystallographic data are available from the Cambridge Crystallographic Data Center: CCDC 231363, CCDC 231358, CCDC 231359 and CCDC 231360, respectively. Thus, analyses by X-ray powder diffraction (XRPD) were performed to characterize the dimeric DHA purchased.

A DHA sample was passed through a 50 μm sieve followed by 5 minutes micronization to ensure an adequate size for phase quantification. Powder diffraction patterns were recorded at 22 ºC on a BRUKER D8

Advance Series II Vario diffractometer, equipped with a LynxEye detector, in capillary transmission geometry (0.7 mm capillary) with CuKα_1 radiation (λ = 1.540596Å, Ge (111) monochromator), operating at 40kV and 40mA. The scan range was 8-60° 2θ with a step size of 0.015° and a count time of 3s per step. Quantitative phase analysis was done by Rietveld method using TOPAS 4.2 software (Bruker AXS).

The DHA phase quantification resulted as follows: 6.40%, 77.24% and 16.36% for α, β and γ dimeric polymorphs respectively; no monomeric form was detected. The R-values and GOF of the Rietveld analysis were: R_{exp}=3.24, R'_{exp}=4.40, R_{wp}=5.49, R'_{wp}=7.46, R_p=4.29, R'_p=5.99, GOF=1.70, R_{Bragg}-α=2.98, R_{Bragg}-β=3.77, R_{Bragg}-γ=2.54.

2.4. Solvents assessment

Solvent selection was done by relative comparison between the different alcohols studied. Three assessment categories were established for the comparisons: Process&Cost, Health&Safety and Environment. The evaluation of each category was done through different solvent properties associated to the category. These properties were assessed based on different process, cost, environmental, health and safety parameters considered for the solvents. The parameters for assessment were selected according to their major relevance when comparing the solvents within each category. The parameters data were obtained from different sources. Process data were experimentally determined from solubility measurements. Solvent prices were obtained from local chemical suppliers. Life-cycle assessment data were obtained with the Ecosolvent software tool (Capello et al., 2007). EHS data were collected from the materials safety data sheets and the Screening Information Data Set (SIDS) Initial Assessment Reports (SIAR) of the solvents published by the Organisation for Economic Co-operation and Development (OECD). When different values for the same solvent parameter were found their average value was used.

The first step of the evaluation was to calculate the relative values of the parameters according to equations (1) or (2):

$$x_{ijr} = \frac{x_{ij}}{\left(x_{ij}\right)_{\max}} \cdot 100 \quad (1)$$

$$x_{ijr} = \frac{\frac{1}{x_{ij}}}{\left(\frac{1}{x_{ij}}\right)_{\max}} \cdot 100 \quad (2)$$

where:

x_{ij}: numeric value of parameter j for solvent i. The measurement unit depends on the parameter.

x_{ijr}: relative value of parameter j for solvent i, %.

max subscript: the maximum value of the quantity in brackets among all solvents assessed.

If increasing values of the parameter resulted in better solvent characteristics, i.e., better process or cost performance or lower EHS impact/hazard, equation (1) was used; otherwise if decreasing parameter values led to better solvent then equation (2) was used. These equations were applied for $x_{ij} \neq 0$. If $x_{ij}=0$ or there was no data for the solvent considered then:

$$x_{ijr} = 0 \quad (3)$$

Secondly, a property index for each solvent and property was calculated according to the relative values of the parameters related with that property by using equation (4).

$$P_{ik} = \frac{\sum_{j=1}^{n} x_{ijr}}{\left(\sum_{j=1}^{n} x_{ijr}\right)_{\max}} \cdot 100 \quad (4)$$

where:

P_{ik}: index value of property k for solvent i, %

n: number of parameters considered to assess property k.

Thirdly, a category index was calculated for each solvent and category based on the indices of the properties associated to that category by using equation (5).

$$C_{il} = \frac{\sum_{k=1}^{m} P_{ik}}{\left(\sum_{k=1}^{m} P_{ik}\right)_{max}} \cdot 100 \quad (5)$$

where:

C_{il}: index value of category l for solvent i, %

m: number of properties considered to assess category l.

Finally an overall assessment index was determined for each solvent based on the categories indices. A specific weight for each category was defined to determine the relative significance of the category taking in account the circumstances of the system to be evaluated. Therefore, the values of the specific weights are decided by the scientists responsible for the assessment based on their judgment. The overall assessment index was then calculated through equation (6).

$$OA_i = \frac{\sum_{l=1}^{q} sw_l \cdot C_{il}}{\left(\sum_{l=1}^{q} sw_l \cdot C_{il}\right)_{max}} \cdot 100 \quad (6)$$

where:

OA_i: overall assessment index for solvent i, %

sw_l: specific weight for category l.

q: number of categories.

The parameters relative values, properties indices, categories indices and overall assessment indices were always referred to the maximum value calculated among the solvents evaluated, thus providing a relative ranking between the solvents assessed. The higher their values the better the solvent features from a process, cost, environmental, health and safety point of view.

3. Results and Discussion

3.1. Process and Cost Assessment

Relative Solubility (S_r), relative theoretical yield (Y_r), relative theoretical solvent cost (C_{Tr}) and life-cycle assessment (LCA) were the properties considered for the solvents evaluation within the Process&Cost category. The three first properties were evaluated using solubility (S), theoretical yield (Y_r) and solvent cost (C_{Tr}) as parameters; meanwhile, the cumulative energy demand (CED) (Capello et al., 2007; Verein Deutscher Ingenieuere, 2012) was the parameter used to assess LCA (Capello et al., 2007; International Organization for Standardization, 2006).

Solubility is the most important process factor for crystallization solvent selection as commented before. In the case of non-ionic compounds it can be predicted by the van't Hoff equation modified for non-ideal solutions (Mullin, 2001):

$$\ln(\gamma x) = \frac{\Delta H_f}{R}\left[\frac{1}{T_f} - \frac{1}{T}\right] \tag{7}$$

where x is the solubility, expressed as mole fraction of the solute in the solution, T is the solution temperature, T_f is the fusion temperature of the solute, ΔH_f is the molar enthalpy of fusion of the solute, R is the gas constant and γ the activity coefficient for the solute in the solution. To apply this equation, the solubility based solvent selection methods (Frank et al., 1999; Nass,1994) have used methodologies such as UNIFAC to calculate the activity coefficient.

It is known that solid dimeric DHA dissociates in aqueous solutions into two different monomeric species, one of them been a hydrate (Davis, 1973). The rate of dissociation is dependent on the solvent and can be slow as have been found for DMSO (Davis, 1973). In addition, four crystalline forms, one monomeric and three dimeric polymorphs, but no solvates have been described for DHA (Slepokura and Lis, 2004), solubility being also influenced by polymorphism (Beckmann, 2013). Therefore, the DHA solubility prediction in any of the alcohols proposed will depend on the rate and extension of the dimer dissociation, and on the crystalline form considered. Moreover, the calculation methods for activity coefficients used in the previously mentioned works (Frank et al., 1999; Nass,1994) do not take in account any interaction between solutes molecules, which could not be negligible for DHA monomers in solution. Thus, considering all the aforementioned facts, an

accurate solubility for the DHA could not be predicted using equation (7) and so it was experimentally measured. Notwithstanding, for other case studies, where solubility prediction could be possible, it should be advisable to use the predicted solubilities as a first screening step to restrict the wide range of feasible solvent candidates to be tested; afterwards, before taking a final decision, the experimental measurement of solubility will be indispensable in order to corroborate the predicted value and so, the solvent suitability.

The DHA experimental solubility measurements obtained are shown on Figure 1. Solubility data for ethanol agreed with those given by other authors (Zhu et al., 2003). The solubility curves did not show any discontinuity; therefore, only one DHA crystalline form was present in the solid phase in equilibrium with the dissolved DHA under the assayed conditions. The crystalline form and polymorph obtained depends upon experimental crystallization conditions and solvent used (Beckmann, 2013). The DHA dimeric polymorphs α and γ, and the monomeric form have been reported to be produced from recrystallization of Aldrich's DHA in aqueous solutions, where the polymorph γ and the monomeric form were only obtained by lyophilization, i.e. at very low pressures; meanwhile, the dimeric polymorph β has been obtained from DHA recrystallization in 2-propanol at room pressure and temperature (Slepokura and Lis, 2004). Since our experiments were done with alcoholic solvents, including also 2-propanol, and under similar pressure and temperature conditions to those of the dimeric polymorph β, this one should be the DHA crystalline form most likely found in the solid phase under our experimental conditions. In addition, the XRPD analysis of the DHA assayed showed that the dimeric polymorph β was the main crystalline form, close to 80% of the analyzed sample, as commented in section 2.3.

There was a steep solubility decrease with temperature within 10-30 ºC for any of the alcohols assayed (Figure 1), thus being the optimal temperature range for cooling crystallization. At temperatures lower than 10 ºC, solubility change with temperature was very small, and so cooling energetic cost would likely not justify the low crystallization yield obtained under this temperature. Therefore, the theoretical crystallization yield (Y, %), within 10-30ºC was calculated according to equation (8) (Nass, 1994):

$$Y = \left(1 - \frac{S_2}{S_1}\right) \cdot 100 \quad (8)$$

where S_1 and S_2 are the solubilities at the higher (30 ºC) and lower (10 ºC) temperature considered respectively.

Cooling crystallization has been proposed for DHA, but other case studies may consider a drowning-out crystallization process. The solvent selection method described is equally applicable to such processes.

The theoretical solvent cost per kilogram of DHA crystal produced (C_T, €/$kg_{DHAcrystal}$) was calculated according to equation (9):

$$C_T = \frac{C_S \cdot 1000}{\rho_{\text{Solvent}} \cdot (S_1 - S_2)} \quad (9)$$

where C_S is the solvent purchase price and $\rho_{solvent}$ the solvent density at 25 ºC (Table 1).

The theoretical solvent cost associated to its purchase does not account for other costs such as solvent recycling or disposal. Then, the life-cycle assessment was used for their evaluation. In addition, the LCA even covers a wider scope since it assesses the resource use over the full life-cycle of a solvent, including production, use, potential recycling, disposal and impact of emissions to the environment as well (Capello et al., 2007; International Organization for Standardization, 2006). Therefore, LCA is a valuable property to be assessed within the Process&Cost category for solvent selection. The cumulative energy demand of a solvent was calculated with the Ecosolvent software tool to evaluate its LCA (Capello et al., 2007). As solvents could be either recycled or treated in a hazardous waste plant, two CED values were considered as parameters: the CED_{PD} considered the solvent production plus recycling by distillation, while the CED_{PI} considered the solvent production plus elimination by incineration; both CED values were determined taking as calculation basis the use of 1 kg of solvent in the crystallizer.

The values of the parameters used to assess this category, i.e., S_1, Y, C_T, CED_{PD} and CED_{PI} are shown in Table 2. The relative values of the solubility at 30ºC (S_{1r}) and yield were obtained from equation (1). Meanwhile, for the theoretical solvent cost and cumulative energy demands, their relative values were calculated according to equation (2), since lower parameters values means better solvent. As the relative values

of S_1, Y and C_T coincide with their corresponding properties evaluated in this category, the properties indices calculated according to equation (4) were equal to the relative values of these parameters. The four properties indices were used to calculated the category index for each solvent through equation (5). Figure 2 shows the properties and category indices obtained. Methanol was clearly the best solvent within this category caused by its both much higher solubility and much lower theoretical cost compared with the other alcohols, while keeping a reasonable yield close to the other solvents and a similar LCA to ethanol (LCA of 2-propanol was significantly lower).

Finally, as commented before, solubility is the most important process factor, but, of course, not the only one to be considered when designing a crystallization process. For example, the solvent, apart from polymorphism, can also influence the crystal habit, or impurities may affect crystal quality and purity; therefore, these facts could also influence solvent selection depending on the solute crystals specifications required and the process operation conditions. However, at the initial stages of the process development available data will be most likely restricted, and so not all factors could be taken in account for solvent selection at this stage. It has been claimed that the assessment methodology proposed is appropriate specially at these first steps of the crystallization operation development, and so only the main important factors should be considered until no further information is available. Of course, if any other additional important process data are available they could be included in the assessment methodology, as flexibility and upgrade ability is one of the most outstanding characteristic of the solvent selection method proposed. Once the crystallization design project is in an advanced stage all these facts should be taken in account to help to decide about the optimal solvent to be used, and the selection solvent method described can be tailored made to meet these process specifications just by including new properties and parameters, taking in consideration as well the EHS issues assessed in the following sections.

3.2. Health and Safety Assessment

Five different properties were considered to assess the hazards inherent to solvents within this category: occupational exposure limit (OEL), acute toxicity (AT), specific target organ toxicity-single exposure

(STOT-SE) and serious eye damage/eye irritation (SEDI) classifications of the EU CLP regulation (European Union, 2008), and flammability (F). Other properties such as reactivity or chemical stability were not relevant for the alcohols considered and were not taken in account. Notwithstanding these properties or any other ones that could be relevant for other solvents could be used for the assessment of that solvents following the same procedure already described in section 2.4.

The property index for OEL was assessed based on three different parameters: the threshold limit value time-weighted average (TLV-TWA), the threshold limit value short-term exposure limit (TLV-STEL) and the biological exposure index (BEI) given by the American Conference of Governmental Industrial Hygienists (ACGIH) and the Spanish Instituto Nacional de Seguridad e Higiene en el Trabajo (INSHT) (Table 2). AT property index took in account six parameters: oral median lethal dose for rats (LD_{50_Oral}), dermal lethal dose for rabbits (LD_{50_Dermal}), inhalation median lethal concentration for rats ($LC_{50\_Inhalation}$, exposure time 4h), and acute toxicity hazard indices for oral, dermal and inhalation exposure routes ($OATC_h$, $DATC_h$, $IATC_h$, respectively) defined according to their EU CLP regulation classification (Tables 2 and 3). For STOT-SE and SEDI property indices the parameter considered was a hazard index ($STOT\text{-}SE_h$ and $SEDI_h$, respectively) also defined according to their EU CLP classification (Tables 2 and 3). Finally the flammability was assessed taking in account the flash point (FP) and the initial boiling point (IBP) of the solvents (Table 2). Equation (1) was used to calculate the relative values for all the parameters employed in this category.

Ethanol was the best solvent regarding all property indices within this category which turned this solvent as the best choice from a health and safety point of view (Figure 3). Methanol has the lowest indices for all the properties but SEDI, and so it was the worst solvent within this category contrarily to what was observed for the process and cost category. The relative ranking of these alcohols within the health and safety category was in good agreement with that one obtained from GSK and SANOFI solvent selection guides (Henderson et al., 2011; Prat et al., 2013) where ethanol and 2-propanol would be the best choices and methanol the worst one, although ethanol and 2-propanol would be indistinguishable in these guides when considering analogous health and safety issues. In addition, ethanol would also be the best choice within health and safety assessment

304 when considering other different general EHS based solvent selection methods (Capello et al., 2007; Slater and
305 Savelski, 2007), caused by its relative low intrinsic health and safety hazards.
306
307 ***3.3. Environmental Assessment***
308 The environmental hazard inherent to solvents was evaluated considering four properties: aquatic
309 toxicity (AqT), biodegradability (BD), bioaccumulation potential (BAP) and soil mobility (SM). As commented
310 in previous sections, if any other property could be of interest for other solvents comparison it could be added
311 and assessed following the same procedure.
312 AqT property index was computed from three different parameters, the fish median lethal concentration
313 (LC_{50_Fish}, Pimephales promelas 96h), the crustacean median effective concentration for acute immobilization
314 test (EC_{50}, Daphnia magna 24h) and the algae median effective concentration for growth inhibition test (E_rC_{50},
315 96h) (Table 2). The BD property index was calculated considering as parameters the biochemical oxygen
316 demand (after 5 days) ratio with respect to both the chemical and theoretical oxygen demands (BOD_5/COD and
317 BOD_5/ThOD, respectively) (Table 2). For BAP property index two parameters were used, the bioconcentration
318 factor (BCF) and the octanol-water partition coefficient (P_{ow}). To conclude, the property index for SM was
319 calculated from two parameters, the adsorption coefficient normalized to the organic carbon content of the soil
320 (K_{oc}) and the octanol-water partition coefficient. The parameters values for BAP and SM are summarized in
321 Table 2. The relative values of all these parameters were calculated through equation (1), except in case of the
322 parameters for the BAP property index calculation which used equation (2), because BCF and P_{ow} decreasing
323 values means lower bioaccumulation and hence a better solvent behaviour.
324 Figure 4 shows the property and category indices obtained. Methanol had the best behaviour in this
325 category due to its low aquatic toxicity and low bioaccumulation potential while being highly biodegradable
326 when compared with the other alcohols. Ethanol and 2-propanol category indices were close being 2-propanol
327 somewhat better regarding this environmental assessment. For the GSK solvent selection guide (Henderson et
328 al., 2011) similar conclusions can be obtained, being ethanol slightly worse than methanol or 2-propanol.
329 Meanwhile, considering the SANOFI solvent selection guide (Prat et al., 2013), the three alcohols are equally

classified as low impact solvents, and so this criteria would not influence the selection. The SANOFI`s guide assesses the solvents based on range values of the parameters instead of relative comparisons between values, as we have proposed, thus limiting the differentiation among solvents. Finally, methanol would also be the best solvent within the environmental category when considering other different general EHS based solvent selection methods (Capello et al., 2007; Slater and Savelski, 2007), due to its relative low inherent environmental hazards.

3.4. Overall Assessment

A global evaluation of the solvents, involving all the categories indices, was carried out by calculating the overall assessment index through equation (6). None of the values of the parameters used to evaluate the environmental, health and safety properties of the assessed solvents can be considered as a hazard of great concern under adequate process operational and standard safety conditions, and so, in the present case study, process and cost factors should be thought as criteria of higher relevance when comparing these alcohols. Therefore, a specific weight factor equal to 2 was assigned to the Process&Cost category; meanwhile, a value equal to 1 was given to the specific weight factors of the other categories, i.e., Health&Safety and Environment categories. As result, methanol, having the best Process&Cost and Environment category indices, was the best overall choice among the alcohols assessed for cooling crystallization of DHA, followed by ethanol and 2-propanol (Figure 5).

4. Conclusions

A new original methodology for crystallization solvent selection have been described and applied for the case study of DHA crystallization. This assessment methodology improves the selection procedure of those published methods whose decision criteria were exclusively based on solute solubility and process yield (Frank et al., 1999; Nass,1994), allowing to assess solvents from a wider process point of view, including as well environmental, health and safety criteria, which, nowadays, are of growing importance. In addition, the EHS assessment results for the DHA case study have shown this methodology to be generally in good agreement

with the proprietary multipurpose solvent selection guides of pharmaceutical companies such as GSK or SANOFI, and with other general EHS based solvent selection methods, even in some cases allowing for a clearer distinction among solvents.

Finally it is noteworthy to remark that the assessment methodology described is simple and flexible, allowing both for weighing factors and upgrading by addition of assessment for any other category, property or parameter that could be of interest when comparing solvents. Then this methodology is a well-suited tool for solvent selection at the initial stages of the crystallization process design and can be adapted for its use at advanced stages of the process development at any scale of the process design.

5. Nomenclature

Latin symbols

BCF	bioconcentration factor
BEI	biological exposure index, mg/L
BOD_5	biochemical oxygen demand (5 days), mg_{O2}/mg
CED	cumulative energy demand, MJ-eq
CED_{PD}	cumulative energy demand, considering the solvent production plus recycling by distillation, per kg of solvent used in the crystallization, $MJ\text{-}eq/kg_{solvent}$
CED_{PI}	cumulative energy demand, considering the solvent production plus elimination by incineration, per kg of solvent used in the crystallization, $MJ\text{-}eq/kg_{solvent}$
C_{il}	index value of category l for solvent i, %
COD	chemical oxygen demand), mg_{O2}/mg
C_S	solvent purchase price, €/L
C_T	theoretical solvent cost, $€_{solvent}/kg_{DHAcrystal}$
C_{Tr}	relative theoretical solvent cost, %
$DATC_h$	dermal acute toxicity hazard index

EC_{50}	crustacean median effective concentration for acute immobilization test (Daphnia magna 24h), mg/L
E_rC_{50}	algae median effective concentration for growth inhibition test (96h), mg/L
FP	flash point, ºC
ΔH_f	molar enthalpy of fusion of the solute, J/mol
$IATC_h$	inhalation acute toxicity hazard index
IBP	initial boiling point, ºC
K_{oc}	adsorption coefficient normalized to the organic carbon content of the soil, cm^3/g
LD_{50_Dermal}	dermal lethal dose for rabbits, mg/kg
LC_{50_Fish}	fish median lethal concentration (Pimephales promelas 96h), mg/L
$LC_{50\_Inhalation}$	inhalation median lethal concentration for rats (4h), mg/L
LD_{50_Oral}	oral median lethal dose for rats, mg/kg
P_{ik}	index value of property k for solvent i, %
m	number of properties considered to assess category l
n	number of parameters considered to assess property k
OA_i	overall assessment index for solvent i, %
$OATC_h$	oral acute toxicity hazard index
P_{ow}	octanol-water partition coefficient
q	number of categories
R	universal gas constant
S	solubility, $g_{solute}/kg_{solvent}$
S_1	solubility at the higher temperature (30 ºC) within the temperature range considered as optimal for cooling crystallization, $g_{solute}/kg_{solvent}$
S_{1r}	relative solubility at the higher temperature (30 ºC) within the temperature range considered as optimal for cooling crystallization, %

S_2	solubility at the lower temperature (10 ºC) within the temperature range considered as optimal for cooling crystallization, $g_{solute}/kg_{solvent}$
$SEDI_h$	serious eye damage/eye irritation hazard index
$STOT\text{-}SE_h$	specific target organ toxicity-single exposure hazard index
sw_l	specific weight for category l.
T	solution temperature, ºC or K
T_f	fusion temperature of the solute, K
ThOD	chemical and theoretical oxygen demand), mg_{O2}/mg
TLV-STEL	threshold limit value short-term exposure limit, ppm_v
TLV-TWA	threshold limit value time-weighted average, ppm_v
x	solubility, mole fraction of the solute in the solution
x_{ij}	numeric value of parameter j for solvent i. The measurement unit depends on the parameter
x_{ijr}	relative value of parameter j for solvent i, %
Y	theoretical yield, %
Y_r	relative theoretical yield, %

Greek symbols

$\rho_{solvent}$	solvent density at 25 ºC, kg/L
γ	activity coefficient for the solute in the solution

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ACS GCIPR	American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable
AqT	aquatic toxicity
AT	acute toxicity

BAP	bioaccumulation potential
BD	biodegradability
CLP	regulation on classification, labelling and packaging of substances and mixtures of the European Union
DHA	dihydroxyacetone
EHS	environmental, health and safety
F	flammability
GHS	globally harmonized system of classification and labelling of chemicals
GSK	GlaxoSmithKline
INSHT	Instituto Nacional de Seguridad e Higiene en el Trabajo of Spain
LCA	life-cycle assessment
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
REACH	regulation concerning the registration, evaluation, authorization, and restriction of chemicals of the European Union
SIDS	screening information data set
SIAR	screening information data set initial assessment reports
STOT-SE	specific target organ toxicity-single exposure
SEDI	serious eye damage/eye irritation
SM	soil mobility

Subscripts

max	the maximum value of the quantity in brackets among all solvents assessed

6. Acknowledgements

This work was financed by the Precompetitive Research Projects Program 2014 from the University of Granada, Spain.

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533

Figure Captions

Figure 1. Dihydroxyacetone solubility in methanol, ethanol and 2-propanol within -8 to 30 ºC.

Figure 2. Solvents properties and category indices for process and cost assessment.

Figure 3. Solvents properties and category indices for health and safety assessment.

Figure 4. Solvents properties and category indices for environmental assessment.

Figure 5. Solvents overall assessment indices.

Figure1

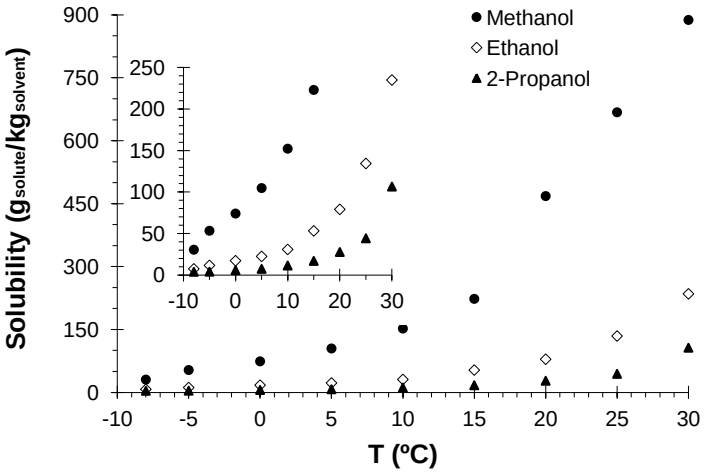
Methanol
Ethanol
2-Propanol
Solubility (g solute/kg solvent)
T (ºC)
900
750
600
450
300
150
0
-10
-5
0
5
10
15
20
25
30
250
200
150
100
50
0
-10
0
10
20
30

Figure2

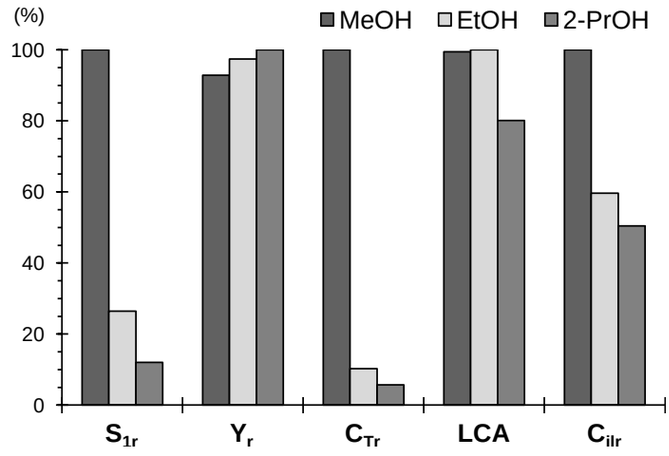

Figure3

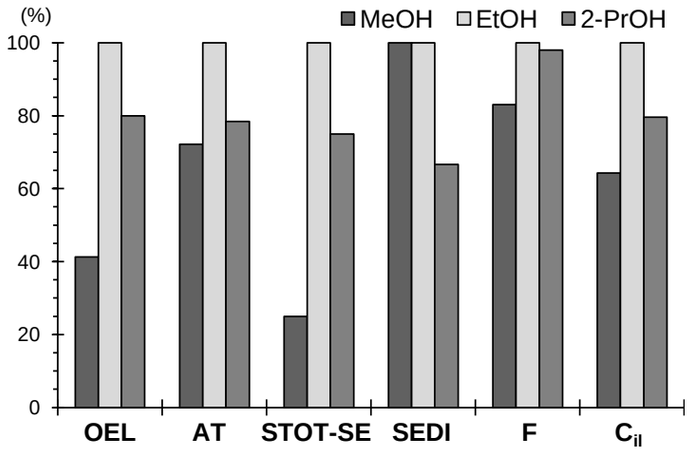

Figure4

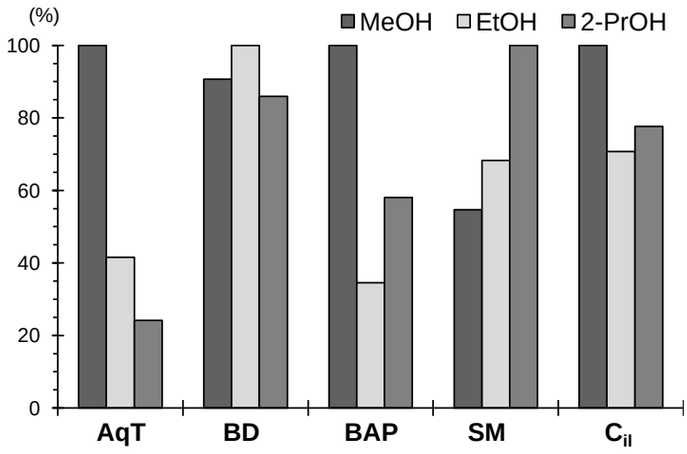

Figure5

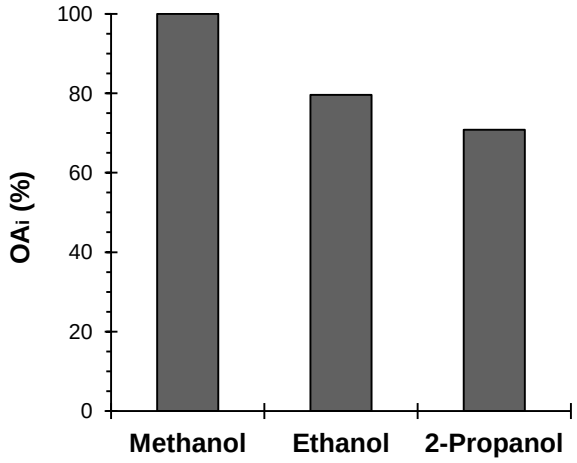

Table1

Table 1. Solvents purchase price and density.

Solvent	C_s (€/L)	$\rho_{solvent}$ (kg/L, at 25ºC)
Methanol	1.48	0.7896
Ethanol	3.97	0.7859
2-Propanol	3.33	0.7818

Table2

Table 2. Categories, properties and parameters (including their values) used for the solvents assessment.

Category	Property	Parameter	Parameter value		
			Methanol	Ethanol	2-Propanol
Process&Cost	S_{1r}	S_1 ($g_{solute}/kg_{solvent}$)	888.0	234.9	106.6
	Y_r	Y (%)	82.9	86.9	89.2
	C_{Tr}	C_T (€$_{solvent}$/$kg_{DHAcrystal}$)	2.6	24.7	44.8
	LCA	CED_{PD} ($MJ\text{-}eq/kg_{solvent}$)	19.0	18.9	19.5
		CED_{PI} ($MJ\text{-}eq/kg_{solvent}$)	18.5	18.4	29.1
Health&Safety	OEL	TLV-TWA (ppm_v)	200	1000	200
		TLV-STEL (ppm_v)	250	1000	400
		BEI (mg/L)	15	-	40
	AT	LD_{50_Oral} (mg/kg)	7388	9254	5275
		LD_{50_Dermal} (mg/kg)	17633	20000	12835
		$LC_{50\_Inhalation}$ (mg/L)	106	125	62
		$OATC_h$[a]	3	5	5
		$DATC_h$[a]	3	5	5
		$IATC_h$[a]	3	5	5
	STOT-SE	$STOT\text{-}SE_h$[b]	1	4	3
	SEDI	$SEDI_h$[b]	3	3	2
	F	FP (ºC)	10.9	13.0	11.9
		IBP (ºC)	64.6	78.3	82.3
Environment	AqT	LC_{50_Fish} (mg/L)	28100	13840	9640
		EC_{50} (mg/L)	21400	10800	7222
		E_rC_{50} (mg/L)	22000	5500	1000
	BD	BOD_5/COD	0.75	0.84	0.72
		$BOD_5/ThOD$	0.71	0.77	0.67
	BAP	BCF	1	3.2	1
		$\log(P_{ow})$[c]	-0.74	-0.32	0.05
	SM	$\log(P_{ow})$[c]	-0.74	-0.32	0.05
		K_{oc} (cm^3/g)	1	1	1.07

[a] Acute toxicity hazard indices values assigned according to Table 3.

[b] STOT-SE and SEDI hazard indices values assigned according to Table 3.

[c] Octanol-water partition coefficient data are usually given in logarithmic scale. Notwithstanding, for calculations their values in linear scale were used.

Table3

Table 3. Hazard indices associated to acute toxicity, STOT-SE, and SEDI according to the EU CLP classification.

Property	EU CLP Classification	Hazard Index[a]
Acute Toxicity[b]	Category 1	1
	Category 2	2
	Category 3	3
	Category 4	4
	Non-classified	5
STOT-SE	Category 1	1
	Category 2	2
	Category 3	3
	Non-classified	4
SEDI	Category 1	1
	Category 2	2
	Non-classified	3

[a]As the CLP category number increases the related risk decreases, so increasing hazard index means lower risk.

[b]For oral, dermal and inhalation exposure routes.