Green Chemistry

PAPER

View Article Online
View Journal

CrossMark click for updates

Cite this: DOI: 10.1039/c6gc00261g

Recovery of ibuprofen from pharmaceutical wastes using ionic liquids†

Francisca A. e Silva,[a] Magda Caban,[b] Piotr Stepnowski,[b] João A. P. Coutinho[a] and Sónia P. M. Ventura*[a]

Received 27th January 2016,
Accepted 22nd March 2016

DOI: 10.1039/c6gc00261g

www.rsc.org/greenchem

This work aims at developing a process to valorise pharmaceutical wastes through the recovery of pharmaceutically active compounds. The ibuprofen extraction and isolation from solid pharmaceutical wastes is used here as a case study and an integrated approach comprising the ibuprofen solid–liquid extraction, the removal of the insoluble excipients present in the pills, the target drug recovery and the recycling of the aqueous solutions is proposed. The present work is centred on the optimization of the first (solid–liquid extraction) and third (drug recovery) steps mentioned above. For the solid–liquid extraction step, various ionic liquid aqueous solutions were tested, tetrabutylammonium chloride ($[N_{4444}]Cl$) being adopted to further optimize the process. A solution composed of 45 wt% of $[N_{4444}]Cl$ + 5 wt% of citrate buffer + 50 wt% of H_2O led to the highest ibuprofen extraction efficiency (EE_{IBU} = 97.92 ± 2.65%) while in the absence of citrate the extraction efficiency was somewhat lower (EE_{IBU} = 93.53 ± 0.62%). The polishing task was affected by the type of aqueous solution utilized during the solid–liquid extraction step: in the presence of citrate buffer water was not prone to induce significant ibuprofen precipitation (maximum RE_{IBU} of 34.71 ± 4.00%) the aqueous KCl solution being the best option (maximum RE_{IBU} of 87.97 ± 1.00%); when no citrate buffer is used water can be used as an anti-solvent with a maximum RE_{IBU} of 91.60 ± 0.19% while aqueous KCl solutions lead to an RE_{IBU} up to 97.07 ± 0.14%. Based on these results an integrated process is proposed for the ibuprofen recovery and isolation aimed at adding value to pharmaceutical wastes.

Introduction

Inspired by the principles of Green Chemistry[1] and sustainability,[2] academia and industry are modifying the way new products and processes are developed. As suggested by the 5th principle of Green Chemistry,[1] the replacement of the widely used hazardous organic solvents by safer alternatives is of utmost importance. Recently, Kerton and Marriott in their book[3] further stressed the importance of promoting a more sustainable approach in industrial processes. Alternative solvents for Green Chemistry comprise water, supercritical fluids and ionic liquids, there being a number of novel industrial processes based on these solvents proposed and implemented in the last few decades.[3,4] Bayer's polyurethane coatings nowadays use water instead of organic solvents, the coffee decaffeination process is carried out using supercritical carbon dioxide[3] and, as detailed by Plechkova and Seddon,[4] a number of industrial processes and commercial products based on ionic liquids have been implemented. BASIL™ owned by the German company BASF,[5] the *ionikylation* process of PetroChina,[6] Linde's ionic compressor[7] and IL1000 commercialized by Hitachi to perform microscopy of biological samples[8] are very good examples.

Ionic liquids are salts with melting temperatures lower than 100 °C, formed by the combination of a large organic cation and an organic or inorganic anion, and have been proposed as alternatives to conventional solvents.[9] They present a set of unique properties such as negligible vapour pressure, non-flammability, high chemical and thermal stabilities, and high solvation ability for a wide range of solutes.[10–12] The possibility of playing with their structural features to fit the requirements of a given application, *i.e.* their designer solvent nature,[13] has driven their successful application in an extensive range of fields such as catalysis,[14] electrochemistry,[15,16] biotechnology[17] and separation processes.[18–20]

Another important guideline of the sustainability concept,[2] further stressed by the Horizon 2020 societal challenges, is the

[a]CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal. E-mail: spventura@ua.pt
[b]Department of Environmental Analysis, Institute for Environmental and Human Health Protection, Faculty of Chemistry, University of Gdańsk, ul. Wita Stwosza 63, 80-308 Gdańsk, Poland

† Electronic supplementary information (ESI) available: Detailed data for extraction and recovery efficiencies, ^{1}H NMR data and alternative representation of the integrated process. See DOI: 10.1039/c6gc00261g

valorisation of wastes. This comprises looking at waste as a source of raw materials or energy, minimizing release to the environment and their impact.[21] Wastes from food,[22–24] agro-industrial[25,26] and pharmaceutical[27] origins have been studied. Of particular interest is the recovery of valuable compounds from waste streams or solid residues using separation approaches based on greener solvents.[23,24,27–31]

This work is aimed at coupling these two concepts through the development of a sustainable extraction and purification process for the recovery of pharmaceutically active ingredients from household pharmaceutical wastes. Pharmaceutical wastes of domestic origin are a direct result of the increasing lifespan of population and disease treatment incidence worldwide. These wastes result from different situations, such as the end of the shelf life of drugs making them unsuitable for human therapy, the inadequacy of the package size, and changes in posology or even failure in the treatment guidelines.[32,33] However, even expired drugs still hold *circa* 90% of the active principle in a stable form,[34] representing an attractive source of valuable chemicals. These could be further used for a wide range of applications in the chemical industry. Pharmaceutical wastes are currently being managed through their collection in local pharmacies and further treated by incineration.[35]

Ionic liquids have been envisaged as powerful solvents for the extraction of several important molecules due to the unique array of intermolecular interactions that they can establish. The underlying molecular level mechanisms suggest that a judicious selection of the ionic liquid structure is vital to achieve efficient extractions, as recognized for phenolic compounds.[36–38] Mostly hydrogen-bonding, hydrophobic and electrostatic interactions were shown to play vital roles in the extraction phenomenon.[36–38] Within the framework of pharmaceutical processing, the boosted solvency of these neoteric solvents for drugs (*e.g.* analgesic, non-steroidal anti-inflammatory drugs and antibiotics) has been systematically studied.[39–41] Again, a significant dependence on both the ionic liquid and drug hydrophobicity/hydrophilicity and hydrogen-bonding ability was observed. Additional insights were gathered on how to finely-tune "ionic liquid–paracetamol–anti-solvent" hydrogen-bonding interactions for purification purposes and how to manipulate the "hydrophilic–lipophilic" balance of an ionic liquid for drug delivery applications.[42,43]

Recent studies have shown the ability of aqueous solutions of ionic liquids in the extraction of value-added compounds from biomass[19] as a result of their hydrotropic nature as revealed lately by Cláudio *et al.*[44] Moreover, they have also been successfully applied in the purification of a wide range of (bio)molecules[18] including drugs.[27] Based on these previous studies a more sustainable route for the valorisation of pharmaceutical wastes is investigated here. For this purpose, aqueous solutions of ionic liquids in combination with the potassium citrate buffer (from now on referred to as citrate buffer) normally used as a hydrotrope in the pharmaceutical industry[45–47] will be studied. Initially, an evaluation of the performance of three ionic liquids will be carried out aiming at perceiving its capacity to extract ibuprofen, a hydrophobic non-steroidal anti-inflammatory drug, sparingly soluble in water, from a real pharmaceutical matrix (*i.e.* pills). After identifying the most effective ionic liquid, this will be applied in an optimization study regarding the selection of the optimal ionic liquid/citrate buffer ratio to enhance the extractive capacity of the aqueous solution. Finally, the isolation/recovery of ibuprofen from the aqueous solution will be described. A conceptual integrated process for the extraction, purification and solvent recovery will be proposed.

Experimental

Materials

The ionic liquids studied were tetrabutylammonium chloride, $[N_{4444}]Cl$ (purity ≥ 97 wt%), 1-butyl-3-methylimidazolium chloride, $[C_4mim]Cl$ (purity = 99 wt%) and benzyldimethyl(2-hydroxyethyl)ammonium chloride, [BzCh]Cl (purity ≥ 97 wt%), which were supplied by Sigma-Aldrich, Iolitec and Fluka, respectively. The potassium citrate tribasic monohydrate, $C_6H_5K_3O_7{\cdot}H_2O$ (purity = 99 wt%) and citric acid monohydrate, $C_6H_8O_7{\cdot}H_2O$ (purity = 100 wt%), used to prepare the citrate buffer at pH 7, were acquired from Acros Organics and Fischer-Scientific, respectively. The ibuprofen (IBU) pills, Brufen® 200 [*active principle*: ibuprofen, 200 mg *per* 1 capsule; *excipients*: microcrystalline cellulose, sodium croscarmellose, lactose monohydrate, anhydrous colloidal silicon dioxide, sodium lauryl sulfate, magnesium stearate, hypromellose 2910 (5 cp), hypromellose 2910 (6 cp), talc and titanium dioxide], were purchased from a local pharmacy (Aveiro, Portugal). The molecular structures of the three ionic liquids and ibuprofen are depicted in Fig. 1. Potassium chloride, KCl (purity = 99.5 wt%) was supplied by Chem-Lab.

The mobile phase used in the HPLC analysis was composed of ammonium acetate, $NH_4C_2H_3O_2$ (purity ≥ 99.99 wt%) and acetic acid, $C_2H_4O_2$ (purity ≥ 99.99 wt%), both from Sigma-Aldrich, HPLC grade acetonitrile, C_2H_3N from HiPerSolv Chromanorm and ultrapure water treated using a Milli-Q 185 water purification apparatus. Syringe filters (0.45 μm) and regenerated cellulose membrane filters (0.45 μm) respectively

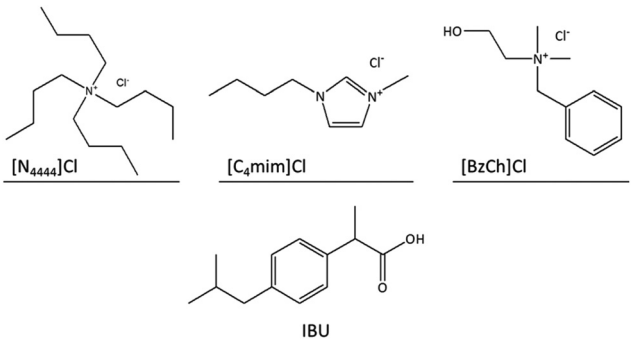

Fig. 1 Chemical structures and acronyms of the ionic liquids and non-steroidal anti-inflammatory drug (ibuprofen) investigated in this work.

acquired at Specanalitica and Sartorius Stedim Biotech were used during the filtration steps.

Solid–liquid extraction

For the initial evaluation of the ionic liquid structure on their ability to extract ibuprofen, solutions composed of 45 wt% of each ionic liquid ([C_4mim]Cl, [N_{4444}]Cl and [BzCh]Cl) + 0 or 5 wt% of citrate buffer + 55 or 50 wt% of H_2O were prepared. The best ionic liquid was then fixed for the evaluation of the impact of [N_{4444}]Cl + citrate buffer compositions on the extractive performance. The compositions presented in Table 1 were investigated during these optimization studies. The citrate buffer at pH 7 was prepared by adding the appropriate amounts of potassium citrate tribasic and citric acid at *circa* 50 wt% according to a well-established protocol.[48] It should be underlined that when the amount of citrate buffer added in each experiment is defined, it describes the salt and acid contents ($C_6H_5K_3O_7$ + $C_6H_8O_7$), meaning without the water content. All the aqueous solution compositions selected were placed in the monophasic region of the ternary phase diagrams reported for aqueous biphasic systems composed of [N_{4444}]Cl,[27] [C_4mim]Cl [49] and [BzCh]Cl [50] + citrate buffer at pH 7. By taking into consideration the total mass of ibuprofen and excipients present in the ground pill (as described in the pharmaceutical flyer), 20 mg of ibuprofen were added to 3 mL of each solution. All extraction assays were conducted under constant stirring at a controlled temperature of 298 (±1) K for at least 12 hours. After this period, the solutions were filtered using syringe filters in order to remove all the solids in suspension, the ibuprofen content being further assayed in the clean solution by HPLC-DAD. Triplicates were performed in order to estimate the average extraction efficiencies attained using each one of the aqueous solutions and the respective standard deviations (σ).

Table 1 Compositions of the [N_{4444}]Cl and citrate buffer salt aqueous solutions tested during the optimization studies of solid–liquid extraction

100 × mass fraction composition (wt%)		
[N_{4444}]Cl	Citrate buffer salt	H_2O
0	0	100
15	0	85
25	0	75
35	0	65
45	0	55
50	0	50
55	0	45
0	5	95
0	15	85
0	25	75
0	35	65
15	5	80
25	5	70
35	5	60
45	5	50
25	10	65
10	25	65
15	15	70
5	15	80

The extraction efficiencies of ibuprofen (EE_{IBU}, %) were calculated according to eqn (1):

$$EE_{IBU},\% = \frac{m^{IBU}_{aq.\ sol}}{m^{IBU}_{0}} \times 100 \quad (1)$$

where $m^{IBU}_{aq.\ sol}$ and m^{IBU}_{0} are the mass of ibuprofen on the aqueous solution after the solid–liquid extraction assay and filtration stage and that initially added to the system, respectively.

Ibuprofen purification

The ibuprofen purification assays were carried out by means of precipitation with an anti-solvent. For this purpose, aqueous solutions of KCl at 25 wt% or water were added in the proportions 1 : 1, 1 : 2, 1 : 3, 1 : 4 and 1 : 5 (volume of drug extract : volume of anti-solvent) to the extract obtained from the solid–liquid extraction (with 45 wt% of [N_{4444}]Cl + 5 wt% of citrate buffer + 50 wt% of H_2O and with 45 wt% of [N_{4444}]Cl + 55 wt% of H_2O). After the addition of the anti-solvent, the solutions became cloudy due to the formation of a precipitate, which was then filtered using syringe filters. The concentration of ibuprofen remaining in solution was further assessed by HPLC-DAD. All the assays were performed in triplicate to determine the recovery efficiencies of ibuprofen and the corresponding standard deviations (σ).

The recovery efficiencies of ibuprofen (RE_{IBU}, %) from the aqueous solutions were calculated following eqn (2).

$$RE_{IBU},\% = 100 - \left(\frac{m^{IBU}_{anti\text{-}solvent}}{m^{IBU}_{aqueous\ solution}} \times 100\right) \quad (2)$$

where $m^{IBU}_{anti\text{-}solvent}$ and $m^{IBU}_{aqueous\ solution}$ are the mass of ibuprofen present in the filtered solution after the addition of the anti-solvent and that of the initial aqueous solution after the solid–liquid extraction assay and filtration step, respectively.

Ibuprofen quantification

The concentration of ibuprofen was determined by HPLC-DAD using an analytical method developed and validated by us. The liquid chromatograph HPLC Elite LaChrom (VWR Hitachi) was composed of a diode array detector (DAD) l-2455, column oven l-2300, auto-sampler l-2200 and pump l-2130. A 5 μm, 250 mm × 4 mm i.d. C_{18} reversed-phase column (LiChrospher 100 RP-18) linked to a 5 μm, 4 mm × 4 mm guard column with the same stationary phase was used. The column oven and the autosampler were operated at controlled temperatures of 27 and 25 °C, respectively. The mobile phase was formed from an organic phase, *i.e.* C_2H_3N, and an aqueous phase, *i.e.* 5 mM of $NH_4C_2H_3O_2$ at pH 4.02 (the pH adjustment was made by the addition of $C_2H_4O_2$) and 5 wt% of C_2H_3N. The separation was conducted in gradient elution mode as follows: 0–4 min 30% of C_2H_3N, 4–11 min from 30 to 60% of C_2H_3N, 11–18 min 60% of C_2H_3N, 18–21 min from 60 to 30% of C_2H_3N, 21–24 min 30% of C_2H_3N, at a flow rate of 1 mL min^{-1} and using an

injection volume of 10 μL. DAD was set to measure at 230 nm. Each sample was analysed at least two times. The validation parameters acquired through an external standard method were the following: retention time of 16.48 min, R^2 of 0.9999, linearity range of 10–750 μg mL^{-1} (stock solutions prepared in C_2H_3N), LOQ of 10 μg mL^{-1} (with assumed precision lower than 5% and accuracy between 80 and 120%), LOD of 1 μg mL^{-1} (using a signal : noise ratio of 3), accuracy intra-day of 83.1–101.0%, accuracy inter-day of 88.7–109.7%, precision intra-day of 0.15–3.00% and precision inter-day of 0.01–1.93%. The samples coming from the solid–liquid experiments or isolation assays were diluted in a mixture of C_2H_3N and H_2O in a volumetric ratio of 30 : 70, when required.

Results and discussion

The conception and development of an integrated process for the efficient and sustainable extraction and isolation of ibuprofen from pharmaceutical wastes is the objective of this work. The conceptual process diagram proposed comprising four main steps: (1) solid–liquid extraction using aqueous solutions of ionic liquids, (2) removal of the insoluble contaminants, *e.g.* excipients, by filtration, (3) recovery of the ibuprofen through precipitation by an anti-solvent, and (4) recycling of the aqueous solutions and reuse of the anti-solvent, is depicted in Fig. 2.

This work will focus on the optimization of steps (1) and (3) of the proposed process. Regarding step (1), an initial evaluation aimed at selecting the most suitable ionic liquid cation was performed in the presence or absence of citrate buffer. Subsequently, the most effective ionic liquid was used to carry out a study aimed at optimizing the conditions for the solid–liquid extraction process. Having established those variables, the concentrations of aqueous KCl solution and water, used as anti-solvents in step (3), which maximize the recovery of ibuprofen, are gauged.

Selecting the best ionic liquid

The capability of three ionic liquids with cations of distinct nature, namely $[N_{4444}]Cl$, $[C_4mim]Cl$ and [BzCh]Cl, for extracting ibuprofen from solid wastes was assessed. These were chosen taking into account our previous experience in solid–liquid and liquid–liquid extraction using aqueous solutions of ionic liquids[18,51] and studies on the hydrotropic nature of ionic liquid cations[44] while trying to keep the anion as simple as possible (chloride) to minimize the process operational costs and environmental risk. These cations were combined with the citrate buffer, a known anionic hydrotropic agent used in the pharmaceutical industry[45–47] allowing the study of the synergies of the two compounds in the extraction process. Fig. 3 shows the results obtained using solutions composed of 45 wt% of ionic liquid + 0 or 5 wt% of citrate buffer + 50 or 55 wt% of H_2O along with those gathered using only H_2O and 5 wt% of citrate buffer. The detailed data obtained are provided in Table S1 in the ESI.† The ability of (i) ionic liquids and (ii) ionic liquids + citrate buffer aqueous solutions to extract ibuprofen can be ranked as follows: water < [BzCh]Cl < 5 wt% citrate buffer ≈ $[C_4mim]Cl \ll [C_4mim]Cl$ + citrate buffer < [BzCh]Cl + citrate buffer < $[N_{4444}]Cl$ < $[N_{4444}]Cl$ + citrate buffer.

While both citrate buffer and the ionic liquids show a higher capacity for extraction of ibuprofen than water alone, only $[N_{4444}]Cl$ or the combined action of the citrate buffer with the ionic liquids achieves extraction efficiencies higher than 90%. The synergetic effect is quite dramatic on the $[C_4mim]Cl$ + citrate buffer and [BzCh]Cl + citrate buffer systems, and less important for the $[N_{4444}]Cl$ as this salt alone is able to achieve very high extraction efficiencies (EE_{IBU} = 93.73 ± 1.62%) that are somewhat enhanced by the presence of the citrate buffer (EE_{IBU} = 97.92 ± 2.65%). The information on ionic liquids as hydrotropic agents is still scarce,[44] and thus it is difficult to anticipate how they will impact on the solubility of a compound and, consequently, on its extraction. Previous

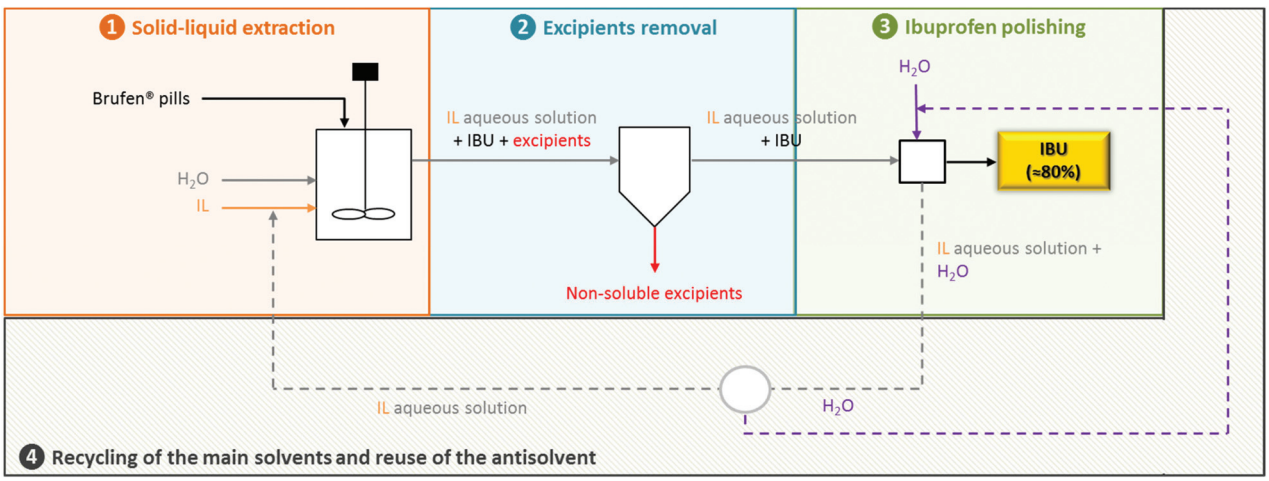

Fig. 2 Schematic representation of the integrated process of extraction, purification, ibuprofen recovery and recycling of the main solvents based on the use of aqueous $[N_{4444}]Cl$ solution and water as the solvent and anti-solvent, respectively.

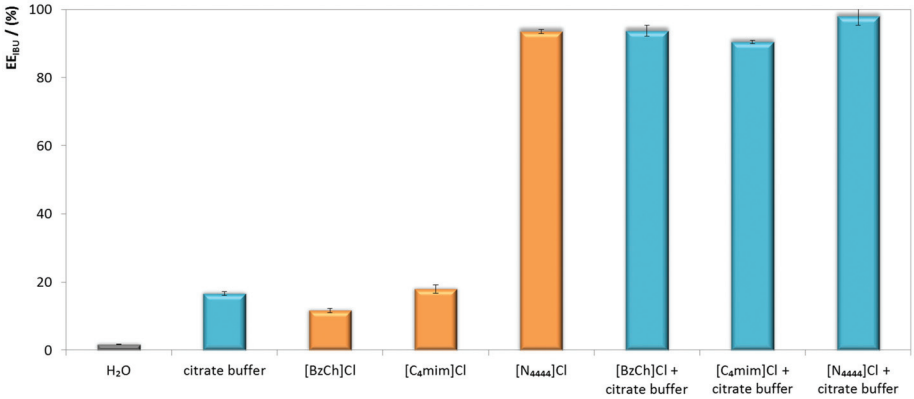

Fig. 3 Extraction efficiencies of ibuprofen (EE_{IBU}, %) achieved in the solid–liquid extractions carried out with aqueous solutions of three ionic liquids (45 wt%) in the absence (orange bars) and presence (blue bars) of 5 wt% of citrate buffer. The data obtained for the experiments with water and citrate buffer at 5 wt% are depicted for comparison purposes.

studies show that the same hydrotrope may affect similar molecules very differently.[44] In this work,[44] the authors have shown that the hydrotropy could be a synergistic phenomenon with the cation and the anion working together to enhance the solubility of a given solute. Moreover, they mentioned that neither the π···π interactions nor the formation of complexes were enough to explain the hydrotropic nature of the ionic liquids, since the non-aromatic nature was also responsible for the enhancement of the solubility of both vanillin and gallic acid, nor the formation of complexes was proved by UV spectroscopy analysis.[44] However, and in contrast to what happened in our recent paper,[44] the results obtained here can be interpreted in the light of the hydrophobic interactions known to be relevant in the hydrotropic agent action.[44]

The extraction efficiencies of the ionic liquids alone correlate well with the ionic liquids' hydrophobicity. Ibuprofen being a hydrophobic drug, as suggested by its octanol–water partition coefficient ($\log K_{ow}$ of 2.48 [52]), has its solubility enhanced in aqueous solutions of the most hydrophobic ionic liquid, $[N_{4444}]Cl$. The other ionic liquids being more hydrophilic exhibit similar but much lower extraction efficiencies (EE_{IBU} = 11.58 ± 0.63% for [BzCh]Cl and EE_{IBU} = 17.94 ± 1.20% for $[C_4mim]Cl$). A similar dependency of ibuprofen's extraction on the ionic liquid hydrophobicity was observed by Pei *et al.* in liquid–liquid extraction systems.[53] Since all three ionic liquids investigated are water-miscible in an extended concentration range, their hydrophobicity was inferred from two perspectives: their $\log K_{ow}$ (values retrieved from Chemspider[54]) and their ability to undergo liquid–liquid demixing in aqueous biphasic systems.

Taking into account the octanol–water partition coefficient values, $[N_{4444}]Cl$ possesses a $\log K_{ow}$ of 1.32, indicating its higher affinity for the octanol phase and thus, its higher hydrophobicity. The remaining two ionic compounds, *i.e.* $[C_4mim]Cl$ and [BzCh]Cl, with negative $\log K_{ow}$ values of −2.15 and −2.94, respectively, are identified as more hydrophilic than the ammonium. Moreover, and consistent with this pattern is their improved ability to generate ABS with salts according to the following hierarchy, $[C_4mim]Cl \approx [BzCh]Cl \ll [N_{4444}]Cl$,[50] which is also based on the increased hydrophobicity of the ionic liquids' cations.[18] Given the good extraction capabilities demonstrated by the $[N_{4444}]Cl$ it will be selected here for further optimization studies described below.

Optimization of the ratio $[N_{4444}]Cl$: citrate buffer

Based on its ability for extracting ibuprofen from the Brufen® 200 pills, both in the presence or absence of citrate buffer as well as its low cost[19] and toxicity,[55] $[N_{4444}]Cl$ was selected to conduct a concentration optimization study. Aqueous solutions formed by the addition of distinct amounts of $[N_{4444}]Cl$ and/or citrate buffer at pH 7 at concentrations where no liquid–liquid phase separation occurs[27] were tested. The data gathered in this study are presented in Fig. 4. To simplify the analysis and discussion of the results, these were grouped according to the impact of $[N_{4444}]Cl$ and citrate buffer on the solid–liquid extraction efficiency, either individually or combined. These results are compiled in Table S2 in the ESI.† The results plotted in Fig. 4 show that high concentrations of $[N_{4444}]Cl$ (in the range of 35–55 wt%) and low concentrations of citrate buffer (in the range of 0–10 wt%) are the conditions that favour ibuprofen extraction. A synergistic effect of the hydrotropic effect of $[N_{4444}]Cl$ and of citrate buffer is observed.

The conditions that maximize the extraction efficiencies, while minimizing the cost of the extraction solution are composed of 45 wt% of $[N_{4444}]Cl$ and 5 wt% of citrate buffer and of $[N_{4444}]Cl$ alone (a concentration of 45 wt% was adopted as it allows direct comparison at the same time that maintains the extractive performance higher than 90%). These will be used in subsequent studies concerning the definition of the operating conditions for the proposed conceptual process for the recovery of ibuprofen from pharmaceutical wastes.

Precipitating agents for ibuprofen recovery

The recovery of ibuprofen (task 3 of the integrated process proposed, Fig. 2) from the extraction solutions with concentrations previously fixed at 45 wt% of $[N_{4444}]Cl$ + 5 wt% of

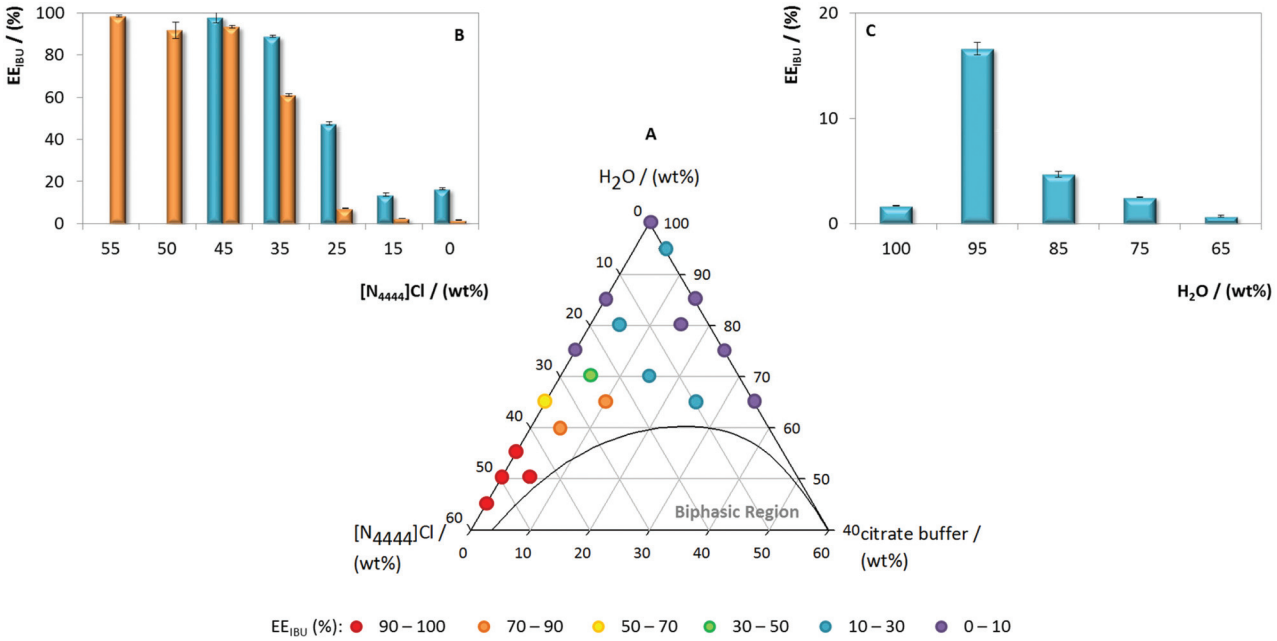

Fig. 4 Extraction efficiencies of ibuprofen (EE_{IBU}, %) attained for the optimization study of the solid–liquid extraction carried out with aqueous solutions of [N_{4444}]Cl and citrate buffer (A). The black line[27] denotes the boundary between the monophasic and the biphasic regions. To facilitate the results perception, the extraction efficiencies of ibuprofen (EE_{IBU}, %) results were grouped according to (i) the [N_{4444}]Cl concentration impact (55, 50, 45, 35, 25, 15 and 0 wt%) in the presence (5 wt%) (blue bars) and absence (0 wt%) (orange bars) of citrate buffer (B) and (ii) the citrate concentration effect (0, 5, 15, 25 and 35 wt%, *i.e.* 100, 95, 85, 75 and 65 wt% of H_2O) in the absence of [N_{4444}]Cl (blue bars) (C).

citrate buffer + 50 wt% of H_2O and 45 wt% of [N_{4444}]Cl + 55 wt% of H_2O was studied using KCl and water as precipitating agents and attempting at optimizing their concentration. The KCl was selected to avoid introduction of new ionic species into the solution, since K^+ and Cl^- were already part of the extraction system. An aqueous solution of KCl at 25 wt% was added in different proportions of 1 : 1, 1 : 2, 1 : 3, 1 : 4 and 1 : 5, these ratios representing the volume of extract : volume of aqueous KCl solution. The same procedure was adopted for water as the anti-solvent. The recovery results obtained are graphically displayed in Fig. 5, whilst the detailed data are reported in Table S3 in the ESI.† At first glance, the influence of citrate buffer present in the solid–liquid extraction solution is notorious, as it hampers the precipitation phenomenon. Recovery efficiencies of ibuprofen up to 97.07 ± 0.14% and 91.60 ± 0.19% were achieved by the addition of aqueous KCl solution in a proportion of 1 : 5 and water in a ratio of 1 : 3, respectively, having as the starting point the extraction conducted with 45 wt% of [N_{4444}]Cl + 55 wt% of H_2O. Lower maxima of 87.97 ± 1.00% and 34.71 ± 4.00% of the recovery efficiencies of ibuprofen were instead assessed when applying KCl and water in the same ratios aforementioned, using the initial solution containing 5 wt% of citrate buffer. This boosted aptitude of water to precipitate ibuprofen from the solutions free of citrate buffer is justified by the hydrophobic character of this drug. Another aspect of relevance is the enhanced power of aqueous KCl solution as an anti-solvent, more preponderant for higher volumes of anti-solvent added and in the presence of citrate buffer in solution. The change in

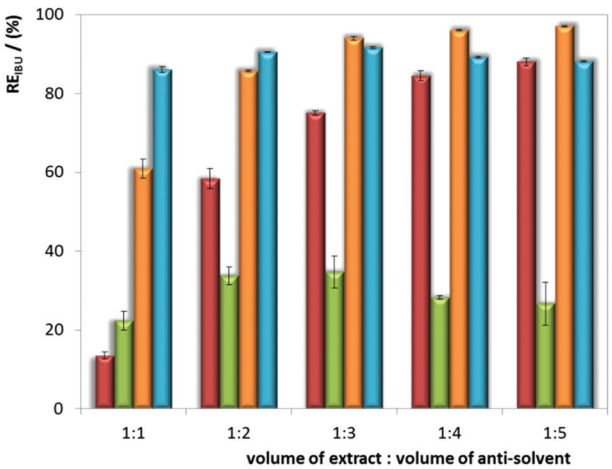

Fig. 5 Recovery efficiencies of ibuprofen (RE_{IBU}, %) attained for the isolation assays carried out by adding distinct proportions of anti-solvent: aqueous solution of KCl at *circa* 25 wt% to the solid–liquid extraction aqueous solutions composed of 45 wt% of [N_{4444}]Cl with citrate buffer (red bars) and without citrate buffer (orange bars); water to the solid–liquid extraction aqueous solutions composed of 45 wt% of [N_{4444}]Cl with citrate buffer (green bars) and without citrate buffer (blue bars).

the ionic strength of the medium, and the speciation in solution caused by the introduction of KCl in the system reduce the interactions between ibuprofen and the components of the extractive solution leading to its precipitation. Arising from these data is the possibility of creating/destroying strong

hydrotropes (*i.e.* citrate salts and ionic liquids) with the judicious choice of the solvent and anti-solvent adopted.

The precipitates obtained were subjected to ^{1}H NMR spectroscopy along with separated samples of the main component of the aqueous solution, $[N_{4444}]Cl$, and the ibuprofen pure standard. Separate analyses were performed for the powders isolated from the processes starting with either $[N_{4444}]Cl$ + citrate buffer or aqueous $[N_{4444}]Cl$ solutions at the level of solid–liquid extraction. The NMR spectra are provided in Fig. S1 in the ESI,† demonstrating the presence of ibuprofen with purities of *circa* 70% and 80% on a molar basis, respectively, due to the contamination with the ionic liquid. This suggests the need for a further polishing step, that, given the differences in solubility between ibuprofen and $[N_{4444}]Cl$, could be a simple washing step with cold water to remove the ionic liquid content from the drug precipitate.

Although water-insoluble (or poorly soluble) excipients contained in Brufen 200 pills were likely removed in step (2) by filtration (microcrystalline cellulose, sodium croscarmellose, anhydrous colloidal silicon dioxide, magnesium stearate, talc and titanium dioxide), attention must be called to the possibility of co-extracting water-soluble compounds (lactose monohydrate, sodium lauryl sulfate, hypromellose). As discussed above, it is known that ionic liquids may have a significant impact upon the solubilities of a wide range of solutes,[43,44,51] and the presence of traces of some insoluble excipients cannot be fully discarded. The presence of such contaminants, even if anticipated as being present in very low concentrations, will affect the ibuprofen's final purity. Beyond $[N_{4444}]Cl$, no other organic contamination was found to a considerable extent by ^{1}H NMR spectral analysis (Fig. S1 in the ESI†), supporting the idea that the main bulk of excipients was removed.

In spite of the improved extraction and recovery efficiencies of ibuprofen obtained with a process based on the $[N_{4444}]Cl$ + citrate buffer and precipitations with aqueous solution and KCl, respectively as the solvent and the anti-solvent, this was dropped as a desirable approach due to the higher degree of operational complexity (*cf.* Fig. S2 in the ESI†). Remarkably, the selection of water as the anti-solvent in the integrated process presented in Fig. 2 gives rise to a simpler approach for which a further step of KCl removal is not required. Having most of the ibuprofen recovered from the aqueous $[N_{4444}]Cl$ solution, this can be recycled and reused within the integrated process proposed herein (step 4). For this, it would be necessary to remove the excess amount of water added during step (3) through evaporation or a membrane-based process. It should be pointed out that the ibuprofen content remaining in solution even after the precipitation step (around 8.4% of the IBU feed into the process) will be recycled to step (1), then increasing the ibuprofen content at the feed and enhancing the recovery in the following steps until a steady state is reached where the ibuprofen feed into the process equals its amount recovered in each cycle.

The industrial relevance of the process proposed here can be gauged from the overview of processes for ibuprofen production or purification previously reported presented hereafter. Firstly prepared and patented in 1961, ibuprofen has seen its production processes evolving in the light of the Green Chemistry principles. The former synthetic route involved six steps, including the use of aluminium trichloride, which cannot be reused, to trigger the reaction.[56] The massive amounts of wastes generated along with the excessive quantities of aluminium trichloride required forced changes in this synthetic route. A "greener route" developed by BASF decreases both the (i) waste generation (*i.e.* uses small amounts of the recyclable catalyst hydrofluoric acid as an alternative to aluminium trichloride) and the (ii) synthesis complexity (only three steps) and at the same time manufacturers' profits are enhanced.[56] An isolation method of ibuprofen from tablets was patented in 1994.[57] According to the inventors,[57] recycling ibuprofen reduces wastes and costs, but it is only worthwhile if ibuprofen is separated from the excipients in a low cost process. The process proposed involves alkanes or cycloalkanes as solvents at temperatures higher than 35 °C, a filtration step to remove undissolved solids, followed by the ibuprofen separation from the solvent through crystallization or solvent evaporation and by solvent recycling and reuse.[57] Another approach proposed addresses the purification of ibuprofen from reaction product mixtures and relies on the use of selective ibuprofen crystallization from a hydrocarbon solvent, keeping the impurities in solution.[58] The mixtures need to be pre-treated (heating and/or washing) and/or to be subjected to sequential crystallizations for impurity removal. Overall, the process proposed here allows replacing volatile organic solvents by an ionic liquid aqueous solution and operating under ambient conditions, thus representing a greener approach to this problem.

Conclusions

The current study addresses the development of a conceptual process, and the optimization of its most relevant steps, for the recovery of ibuprofen from solid pharmaceutical wastes. The proposed integrated process comprises four steps, starting from the solid–liquid extraction of ibuprofen from the pharmaceutical solid wastes using aqueous solutions of $[N_{4444}]Cl$ (at a concentration of 45 wt%) [step (1)]; followed by step (2), the elimination of the insoluble excipients by filtration; and then the process of the recovery of ibuprofen using water as the anti-solvent [step (3)], and the recycling and reuse of the aqueous solution and the anti-solvent [step (4)]. This work is focused on the optimization of steps (1) and (3) evaluating the best ionic liquid and optimal concentrations to maximize the extraction and recovery. The results reported here show that it is possible to achieve up to 97.92 ± 2.65% and 97.07 ± 0.14% of ibuprofen extraction and recovery efficiency from the pills, respectively. Knowing the optimization result scenario, the most adequate integrated process was selected on the basis of a balance between the performance of extraction, the purity achievable and the operational simplicity. From both economic and environmental points of view, the promising and

competitive status of the integrated process developed can be predicted. The possibility of valorising a valueless feedstock together with the transversal nature of the integrated process proposed here supports its industrial relevance.

Acknowledgements

This work was developed in the scope of the project CICECO-Aveiro Institute of Materials (Ref. FCT UID/CTM/50011/2013), financed by national funds through the FCT/MEC and when applicable co-financed by FEDER under the PT2020 Partnership Agreement. The authors acknowledge FCT for the financial support from the post-doctoral and doctoral scholarships SFRH/BPD/79263/2011 and SFRH/BD/94901/2013 granted to S. P. M. Ventura and F. A. e Silva, respectively. This publication is also financed from the European Social Fund as a part of the project "Educators for the elite – integrated training program for PhD students, post-docs and professors as academic teachers at the University of Gdansk" within the framework of the Human Capital Operational Programme, Action IV. This work was supported by a STSM Grant (Ref. COST-STSM-CM1206-27298) from COST Action CM1206 (EXIL – Exchange on Ionic Liquids). This publication reflects the views only of the authors, and the funder cannot be held responsible for any use which may be made of the information contained therein.

References

1 P. T. Anastas and J. C. Warner, *Green chemistry: theory and practice*, Oxford University Press, 2000.
2 P. Glavič and R. Lukman, *J. Cleaner Prod.*, 2007, **15**, 1875–1885.
3 F. Kerton and R. Marriott, *Alternative Solvents for Green Chemistry*, RSC Publishing, 2013.
4 N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123–150.
5 M. Maase, K. Massonne and U. Vagt, Chemfiles, 5, https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Aldrich/Brochure/al_chemfile_v5_n6.pdf (accessed on 3rd March 2016).
6 Z. C. Liu, R. Zhang, C. M. Xu and R. G. Xia, *Oil Gas J.*, 2006, **104**, 52–56.
7 Linde ionic compressor, http://www.lindeus.com/en/innovations/hydrogen_energy/fuelling_technologies/ionic_compressor.html (accessed on 3rd March 2016).
8 Innovative 1-drop sample preparation by ionic liquid HILEM IL1000, http://www.monocomp.e.telefonica.net/eqprep/IL%201000.pdf (accessed on 3rd March 2016).
9 R. D. Rogers and K. R. Seddon, *Science*, 2003, **302**, 792–793.
10 J. S. Wilkes, *J. Mol. Catal. A: Chem.*, 2004, **214**, 11–17.
11 H. Olivier-Bourbigou, L. Magna and D. Morvan, *Appl. Catal., A*, 2010, **373**, 1–56.
12 C. Chiappe and D. Pieraccini, *J. Phys. Org. Chem.*, 2005, **18**, 275–297.
13 M. Freemantle, *Chem. Eng. News*, 1998, **76**, 32–37.
14 D. Zhao, M. Wu, Y. Kou and E. Min, *Catal. Today*, 2002, **74**, 157–189.
15 M. Armand, F. Endres, D. R. MacFarlane, H. Ohno and B. Scrosati, *Nat. Mater.*, 2009, **8**, 621–629.
16 C. Liao, B. Guo, X.-G. Sun and S. Dai, *ChemSusChem*, 2015, **8**, 353–360.
17 G. Quijano, A. Couvert and A. Amrane, *Bioresour. Technol.*, 2010, **101**, 8923–8930.
18 M. G. Freire, A. F. M. Claudio, J. M. M. Araujo, J. A. P. Coutinho, I. M. Marrucho, J. N. C. Lopes and L. P. N. Rebelo, *Chem. Soc. Rev.*, 2012, **41**, 4966–4995.
19 H. Passos, M. G. Freire and J. A. P. Coutinho, *Green Chem.*, 2014, **16**, 4786–4815.
20 F. Pena-Pereira and J. Namieśnik, *ChemSusChem*, 2014, **7**, 1784–1800.
21 R. A. D. Arancon, C. S. K. Lin, K. M. Chan, T. H. Kwan and R. Luque, *Energy Sci. Eng.*, 2013, **1**, 53–71.
22 C. M. Galanakis, *Trends Food Sci. Technol.*, 2012, **26**, 68–87.
23 I. A. O. Reis, S. B. Santos, L. A. Santos, N. Oliveira, M. G. Freire, J. F. B. Pereira, S. P. M. Ventura, J. A. P. Coutinho, C. M. F. Soares and Á. S. Lima, *Food Chem.*, 2012, **135**, 2453–2461.
24 I. A. O. Reis, S. B. Santos, F. D. S. Pereira, C. R. S. Sobral, M. G. Freire, L. S. Freitas, C. M. F. Soares and Á. S. Lima, *Sep. Sci. Technol.*, 2013, **49**, 656–663.
25 F. Federici, F. Fava, N. Kalogerakis and D. Mantzavinos, *J. Chem. Technol. Biotechnol.*, 2009, **84**, 895–900.
26 R. Devesa-Rey, X. Vecino, J. L. Varela-Alende, M. T. Barral, J. M. Cruz and A. B. Moldes, *Waste Manage.*, 2011, **31**, 2327–2335.
27 F. A. e Silva, T. Sintra, S. P. M. Ventura and J. A. P. Coutinho, *Sep. Purif. Technol.*, 2014, **122**, 315–322.
28 I. A. O. Reis, A. F. Campos, P. H. S. Santos, S. B. Santos, C. M. F. Soares and Á. S. Lima, *Sep. Sci. Technol.*, 2014, **50**, 520–528.
29 W. Bi, M. Tian, J. Zhou and K. H. Row, *J. Chromatogr. B: Biomed. Sci. Appl.*, 2010, **878**, 2243–2248.
30 K. Bica, P. Gaertner and R. D. Rogers, *Green Chem.*, 2011, **13**, 1997–1999.
31 T. Baysal, S. Ersus and D. A. J. Starmans, *J. Agric. Food Chem.*, 2000, **48**, 5507–5511.
32 Z. Mendes, S. Crisóstomo, F. B. Marques, A. P. Martins, V. Rodrigues and C. F. Ribeiro, *Rev. Port. Clin. Geral*, 2010, **26**, 12–20.
33 P. Trueman, K. Lowson, A. Blighe, A. Meszaros, D. Wright, J. Glanville, D. Taylor, J. Newbould, M. Bury, N. Barber and Y. Jani, Report of DH funded national project. York Health Economics Consortium and The School of Pharmacy, University of London, York and London, 2010.
34 J. Natarajan and S. Altan, *Drug Inf. J.*, 1997, **31**, 589–595.
35 S. Castensson, in *Pharmaceuticals in the Environment*, Springer, Berlin, Heidelberg, 2008, pp. 489–499.

36 C. F. Poole and S. K. Poole, *J. Chromatogr. A*, 2010, **1217**, 2268–2286.
37 Q. Yang, H. Xing, B. Su, Z. Bao, J. Wang, Y. Yang and Q. Ren, *AIChE J.*, 2013, **59**, 1657–1667.
38 B. Burghoff, E. L. V. Goetheer and A. B. D. Haan, *Ind. Eng. Chem. Res.*, 2008, **47**, 4263–4269.
39 K. B. Smith, R. H. Bridson and G. A. Leeke, *J. Chem. Eng. Data*, 2011, **56**, 2039–2043.
40 R. A. Faria and E. Bogel-Łukasik, *Fluid Phase Equilib.*, 2015, **397**, 18–25.
41 A. Forte, C. I. Melo, R. Bogel-Łukasik and E. Bogel-Łukasik, *Fluid Phase Equilib.*, 2012, **318**, 89–95.
42 C. C. Weber, A. J. Kunov-Kruse, R. D. Rogers and A. S. Myerson, *Chem. Commun.*, 2015, **51**, 4294–4297.
43 P. D. McCrary, P. A. Beasley, G. Gurau, A. Narita, P. S. Barber, O. A. Cojocaru and R. D. Rogers, *New J. Chem.*, 2013, **37**, 2196–2202.
44 A. F. M. Cláudio, M. C. Neves, K. Shimizu, J. N. Canongia Lopes, M. G. Freire and J. A. P. Coutinho, *Green Chem.*, 2015, **17**, 3948–3963.
45 V. Pareek, S. Tambe and S. Bhalerao, *Int. J. Pharm. Biol. Sci.*, 2010, **1**, 1–10.
46 M. Dharmendira Kumar and N. Nagendra Gandhi, *J. Chem. Eng. Data*, 2000, **45**, 419–423.
47 M. Dhinakaran, A. B. Morais and N. N. Gandhi, *Asian J. Chem.*, 2013, **25**, 231–236.
48 M. T. Zafarani-Moattar and S. Hamzehzadeh, *Fluid Phase Equilib.*, 2011, **304**, 110–120.
49 H. Passos, M. P. Trindade, T. S. M. Vaz, L. P. da Costa, M. G. Freire and J. A. P. Coutinho, *Sep. Purif. Technol.*, 2013, **108**, 174–180.
50 T. E. Sintra, R. Cruz, S. P. M. Ventura and J. A. P. Coutinho, *J. Chem. Thermodyn.*, 2014, **77**, 206–213.
51 A. F. M. Cláudio, A. M. Ferreira, M. G. Freire and J. A. P. Coutinho, *Green Chem.*, 2013, **15**, 2002–2010.
52 T. Scheytt, P. Mersmann, R. Lindstädt and T. Heberer, *Water, Air, Soil Pollut.*, 2005, **165**, 3–11.
53 Y. Pei, J. Zhang, X. Song, M. Zhao and J. Wang, *Sep. Sci. Technol.*, 2015, **50**, 1641–1646.
54 The free chemical database at http://www.chemspider.com (accessed on 3rd March 2016).
55 M. Munoz, C. M. Domínguez, Z. M. de Pedro, A. Quintanilla, J. A. Casas, S. P. M. Ventura and J. A. P. Coutinho, *Sep. Purif. Technol.*, 2015, **150**, 252–256.
56 M. Poliakoff and P. Licence, *Nature*, 2007, **450**, 810–812.
57 M. B. Lakin, T. H. Shockley and E. G. Zey, *US Patent No*, US5300301A, 1994.
58 E. G. Zey, T. H. Shockley, D. A. Ryan and G. L. Moss, *US Patent No*, US5151551A, 1992.