Enhance the Solvent Potential of Water

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Water is considered the greenest solvent. Nonetheless, the water solubility of natural products is still an incredibly challenging issue. Indeed, it is nearly impossible to solubilize or to extract many natural products properly using solely water due to their low solubility in this solvent.

green extraction water solvents water extraction green solvent water solubilisation low water solubility natural products solubilisation natural products solubilization

1. pH Range and Salts

The use of salts or pH adjustment is largely implemented together with other methods. Hereinafter, the specific effects of these two methods to enhance the solvent potential of water was described.

pH control is of major importance in understanding and monitoring water solubility and the extractability of multiple natural products. As can be seen in the case of anthocyanin delphinidin, the flavylium cation—which is dominant at a pH lower than 5—is the most soluble form of delphinidin and reaches a solubility of 71 mg/L in acidic water [1]. Therefore, a suitable way to extract such a compound from a plant resource such as berries is to use acidic water (e.g., pH = 2.3) to increase anthocyanin solubility and diffusion through the matrix [2]. pH adjustment may be performed with acids (e.g., hydrochloric acid) and bases (e.g., sodium or potassium hydroxide), as well as with salts (e.g., sodium carbonate to increase the pH or ammonium chloride to reduce it).

Salts can not only alter the pH but also monitor other water solvent properties. When added to water, salts split into ions that modify water behaviour. In particular, specific ion effects act on the surface charge and tension, electrostatic interactions and charge density [3]. When applied to solubilisation or extraction, useful salts such as kosmotropic and in particular chaotropic ones can be employed to alter interactions between water and NPs as well as their organisation. The direct consequence of these changes may be the increased solubility of NPs. Indeed, when a chaotropic salt is added to water, it weakens the interactions between each water molecule and each NP, thereby strengthening water-NP interactions to facilitate their solubilisation. This is called the salting-in effect [4]. Salts can also destabilise biological structures such as oil bodies or membranes, which could lead to coalescence and the release of protected NPs [5]. Finally, the use of salts could assist the mass transfer of NPs from the biological matrix to the water solvent [3].

The use of salts is very common in pharmaceutical industries dealing with natural products, as it is a very affordable and simple method to apply even at a very large scale for extraction and purification purposes.

Nevertheless, this method could raise sustainability and cost-effectiveness questions if the salts used in the process have to be removed from the final product. Indeed, such removal could imply additional costly and energy-consuming downstream processing steps such as membrane filtrations [6]. In an ideal situation, salts should remain in the final product not only to simplify the process but also to potentially stabilise the extracted NP or even to enhance its properties (compared to those of the free NP solubilised in water) [7].

2. Cosolvents

The use of cosolvents has to be the most obvious and common way to tune water solvent properties for green extraction purposes due to its ease of implementation, which consists of mixing water with one or more miscible solvents. Ethanol is one particularly notable cosolvent used with water.

Pharmaceutical industries are heavy users of cosolvents. For sure, this method is employed a lot for both extraction and purification steps. Before starting the process development and in particular its upscaling, the cosolvent has to be chosen wisely considering many parameters, including cost, availability, toxicity, efficacy and processing ability, recyclability and of course the amount added to water [8]. Once the appropriate cosolvent and its proportion are chosen, this method is quite easy to implement on an industrial scale. The environmental impacts of the corresponding process strongly depend on the target NP and the matrix extracted, as well as the nature of the retained cosolvent and its amount and also the galenic desired for the final product. As a matter of fact, if the cosolvent could remain in the final product, the process would be all the more sustainable.

3. Surfactants

The use of surfactants is becoming a well-renowned technique in solubilisation and extraction of NPs. It involves the addition of surfactants, which are amphiphilic organic molecules of variable size, to water. Surfactants are surface-active molecules capable of forming micelles once their concentration is high enough (i.e., when C > critical micellar concentration—CMC). Micelles are colloidal-form clusters composed of surfactant molecules oriented in a way that separates hydrophobic moieties from water and exposes hydrophilic moieties to water [9]. Each surfactant has a given CMC.

The surfactant principle of action is to reduce surface tension. Different shapes of micelles are described: (classic) micelles, cylindric, layers and reverse [10]. These objects are able to solubilise non-polar NPs within their core, thus making those NPs more soluble in water (within micelles). The obtention and stabilisation of micelles are ensured by means of hydrophobic and hydration forces, π–π stacking interactions (in the case of aromatic-ring-containing surfactants) and hydrogen bonding [11][12]. Some examples of commonly used surfactants for NP solubilisation or extraction include non-ionic surfactants such as Triton X-100, Tween 20 or Tween 80, anionic surfactants such as docusate, cationic surfactants such as trimethyltetradecylammonium bromide, or even zwitterionic surfactants such as lecithin (glycerophospholipid mixtures) [13]. The extraction step must be performed using a concentration of surfactants higher than the CMC (typically around 1 to 10 mM) so that micelles are obtained and are able to

solubilise the NPs within their core. Another useful property of micelles to exploit in green extraction processes is their cloud point. This consists of a temperature above which micelles are disorganised and therefore no longer water-soluble, which leads to dephasing. To purify the NPs after the extraction step, the user should bring these elements up to cloud point temperature and then add a centrifugation step to concentrate both the NPs and surfactants in the upper layer [10]. This extraction technique is called Cloud Point Extraction (CPE).

4. Complexing Ligands

Contrary to the previous methods, which are quite common in studies of solubilisation and extraction of NP, the use of complexing ligands is still rather unusual in this field. This method consists of adding a complexing agent readily soluble in water to create a complex with the target compound [13]. The target compounds are typically metallic ions rather than NPs per se, which is why this method is uncommon in green extraction. One particular case of complexing ligands dissolved in water would be phytosomes. Phytosomes are phyto-phospholipid complexes composed of NPs and phospholipids [14]. They have a particle shape of variable diameter ranging from 50 nm up to 100 µm on average. Once complexed, NPs are far more soluble in water.

5. Inclusion Complexes

The use of inclusion complexes in the solubilisation and extraction of NPs has increased notably since 2010. In this method, an inclusion ligand is added to water. Inclusion ligands are amphiphilic molecules composed of a hydrophilic outer surface, which interacts with water and leads to its solubilisation, and an inner hydrophobic cavity able to host a hydrophobic moiety or an entire molecule [15]. An inclusion complex containing an NP will greatly increase its solubility in water. For instance, hesperetin formed as a complex with 2-hydroxypropyl-beta-cyclodextrin (HP-β-CD) is 400 times more soluble in water compared to its free form [16].

Inclusion complexes and in particular CDs were extensively used by many pharmaceutical companies in a wide variety of treatments since the 1970s [17]. More or less one hundred pharmaceutical products involving CDs were approved up to now, according to a supplier of these inclusion agents [18]. From a practical industrial point of view, processes based on the use of inclusion complexes are simple to implement, whatever the production scale. Additionally, the corresponding method is globally sustainable as it does not imply additional treatment steps. Moreover, these bio-based solubilisers will remain on the final product to improve their bioavailability and are initially introduced by simple stirring in water at room temperature [19].

6. Stacking Complexes

Stacking complexes have barely been used in extraction, instead constituting a solubilisation technique [13]. Nevertheless, this could serve as a powerful method to extract NPs in a sustainable way that could favour the extract's bioactivity. A stacking agent is generally a small, organic and amphiphilic molecule, with at least a decent water solubility. These agents are able to create aggregates (different from micelles) with hydrophobic molecules.

The obtained stacking complexes are therefore much more soluble in water than the isolated hydrophobic compound ever was. Stacking is the major stabilising force involved in these complexes. More precisely, π–π interactions occur and enable the stacking phenomenon. Such complexes appear with a given molar ratio. The ideal target NPs for this method are π-electron donors such as compounds containing double bonds. Different geometric configurations of π–π stacking interactions have been described: edge-to-face stacking, offset stacking and face-to-face stacking. Given the weakness of their stabilising interactions, stacking complexes consist of drug delivery systems with huge potential [20].

Stacking complexes are naturally occurring in vivo systems in many bioresources, especially in plant cell walls. Indeed, these complexes are of major importance in plant cell wall organisation and stabilisation. For instance, polysaccharides such as pectin and phenolic compounds such as anthocyanidins rely on these interactions [21]. In addition, stacking complexes are responsible for the coloured appearance of many flower pigments, which are NPs of interest such as anthocyanidins [22]. This is why this method could be relevant for implementation in green extraction, using actual NPs as stacking agents.

These complexes have been studied for pharmaceutical purposes as a way to enhance the water solubility of existing and recognised APIs since the 1950s. Although, the π–π stacking interactions involved in the solubility enhancement of the studied drugs started to be well described and understood in the 1970s [23]. As mentioned above, stacking complexes appear to be theoretically suitable drug-delivery systems, nonetheless, they are still at the research stage, and it seems that there is still no real industrial use for this method. This is mostly due to safety concerns about the complexing agents used for pharmaceutical goals [20]. If consider the perspectives for industrial developments, the researchers could forecast that the corresponding process would not be that difficult to implement. Indeed, no extra energy-consuming steps would be involved, especially if the agent were to be kept in the final products.

7. Hydrotropes

Hydrotropes are small, amphiphilic surface-active molecules similar to stacking agents. However, contrary to stacking complexes, this method has been increasingly used in green extraction since 2000. A critical concentration similar to the CMC (established for surfactants) has been defined for hydrotropes and is known as the Minimum Hydrotropic Concentration (MHC). Above the MHC, hydrotropes form aggregates and begin to efficiently solubilise the target NP. A common order of magnitude for this MHC is 1 M. Even so, it is still unclear whether this aggregate occurs solely in the presence of the hydrophobic NP or with the hydrotrope alone [24].

The application of hydrotropes in the pharmaceutical field is still limited to the research stage and it seems that there is still no approved drug involving such solubiliser, as in the case of stacking agents. Yet, it is suggested that the use of hydrotropes would be suitable for the extraction of NPs at an industrial scale. As a matter of fact, some hydrotropes with high-temperature stability appear to be easily reusable, thus giving way to a promising and sustainable method [25]. In the case of hydrotropes which could not be removed from the final product, the main concern about their use in the pharmaceutical field is their high concentration which is needed to reach satisfying

extraction yields. This concentration range typically raises problems of toxicity and thus limits the potential applications of this method [26].

8. NADES

Natural deep eutectic solvents (NADES) are fully organised liquids composed of naturally occurring metabolites found in most living cells [27]. They were introduced in 2011 and were then quickly and increasingly applied in green extraction [28]. Whilst water sometimes forms an intrinsic part of NADES as an actual component, it can also be used to dissolve initially dry NADES to reduce their viscosity for instance. In this sense, the researchers can consider NADES as being an aqueous solvent whereby water represents at least half of the total composition. NADES are obtained by mixing different compounds at very specific molar concentrations.

The molecular structure and stability of NADES are based on the extensive hydrogen bonding that occurs between compounds. There are five categories of NADES according to their composition: acid and base, neutral, neutral with acids, neutral with bases, and amino acids containing NADES. Most NADES exhibit very low toxicity and are sometimes even edible [27].

Aqueous NADES are extremely well suited to use in green extraction both in a laboratory and on an industrial scale. As a matter of fact, their components are remarkably low-cost, NADES are relatively easy to formulate, and they are non-toxic and highly biodegradable. Amongst the most renowned NADES, the researchers can count choline chloride:urea, choline chloride:lactic acid, choline chloride:ethylene glycol, glucose:fructose:sucrose, and malic acid:glucose [29]. Each of these NADES could easily be dissolved in at least 50% water to make it an aqueous solvent with practical advantages such as viscosity and cost reductions.

Regarding applications in the health industry, certain compositions of aqueous NADES were patented by Givaudan in 2015 [30]. This method was used by the company to produce at least two cosmetic active ingredients [31]. In 2017, another company named Gattefossé launched its cosmetic active ingredient made from an aqueous NADES composed of glycerin and fructose [32]. If the researchers now consider strictly speaking the pharmaceutical industrial application of this method, it might not exist yet. Nevertheless, as this method was successively used in a related health industrial sector, it seems feasible to apply it in pharmaceutical processes. In fact, the corresponding process is globally sustainable even if NADES tend to be viscous. If viscosity is a problem for given applications, the water dilution can be simply increased. Again, to remain sustainable, the process should not include NADES removal. This purification is hard to achieve because of many NADES properties including their generally very low vapor pressure [28].

9. Reactive Extraction

Reactive extraction is a novel concept and the researchers first coined the term in this entry. It covers the extraction methods involving the chemical modification of the target NP(s) by means of a reactive extractant. After the reaction, the NP becomes much more water-soluble. The NP may be transformed back into its initial form in the

final extract or could also remain chemically modified, depending on the applied process. Very few papers describe this kind of transformation and of course, they do so without employing the expression *reactive extraction*. Most of the reactive extractants the researchers have identified are either salts [33] or surfactants [34].

Reactive extraction is based on the use of chaotropic salts, surfactants, or even pH adjustments, as well as physical modification such as a change in temperature or a processing step inducing phase separation. All these techniques can lead to one or more modifications of the target NP to make it more water-soluble so that extraction yields are increased.

10. Enzymes

Enzymes are natural active proteins (macromolecules of a least roughly 50 amino acids) synthetised by organisms and which act as biocatalysts. These active proteins are highly specific and can perform the same reactions millions of times at an exceedingly high pace (high turnover rate). The water extraction of NPs may be greatly increased by the use of enzymes [10].

Hydrolases and lyases are the most useful enzyme categories in green extraction. Indeed, they catalyse the hydrolysis and other kinds of bond cleavage of many molecules such as structural polysaccharides, proteins and lignin, thus enabling the disassembly of plant cell walls [35]. Such plant cell wall degradation may lead to easier access of NPs for water solvents. Moreover, the degradation itself can release phenolic compounds from the cell wall [36].

Most of the enzymes used in green extraction are obtained from fungus and bacteria strains. The following enzymes have been successfully used for NP extraction from plant sources: cellulases, pectinesterase, polygalacturonase, rhamnogalacturonan hydrolase, alpha-amylase, peptidase, trypsin, papain and more [36]. Typically, one or more of these enzyme categories are added into water and the plant matrix is extracted through stirred maceration, with pH and temperature adjustments to fit enzyme needs. Even more complicated NPs to extract such as some polyunsaturated fatty acids can be isolated using this method by adding a cold-pressing step to the process [37].

No application was identified in pharmaceuticals using enzymes during the extraction step. Nevertheless, there were many promising lab-scale results related to the extraction of NP as explained above. Furthermore, active ingredients for dietary supplements and cosmetics are currently produced by at least one company. Indeed, Biolie which is specialised in enzymatic extraction already launched three active ingredients for dietary supplements and more or less a dozen for cosmetics using this method [38]. Even if this method is not the easiest to optimise nor to scale up, it would be possible to produce pharmaceuticals using enzymes which are efficient green biocatalysts.

11. ISPWE

In situ plant water extraction involves physical treatments capable of extracting plant water in situ, along with NPs. This extraction method does not require the addition of any solvents, as the water contained in the plant is sufficient. The two main technologies required to achieve this solvent-free extraction were identified as microwaves and Pulsed Electric Fields (PEF). The mass transfer of NPs from the wet matrix to the exterior is greatly enhanced by these treatments.

In the case of Solvent-Free Microwave Extraction (SFME), both heat and mass transfers occur in the same direction so that NPs are efficiently extracted by water in situ. Contrary to most processes that involve conventional heating (i.e., surface heating), microwaves ensure that selective volume heating is applied to the matrix (from its core to the exterior) [38]. As for PEF, which is a non-thermal process, the in situ water extraction relies on the irreversible electroporation of the matrix cells. This kind of extensive cell membrane or wall destruction happens if the potential difference between the two electrodes is high enough ($E >> E_{critical}$) [39].

In green extraction, this method could efficiently be applied to any matrix with a high-water content (wet sample) for it to serve as a solvent. Such physical treatments are exceptionally fast and typically last just a few minutes. These processes are also low energy-consuming [40].

12. Switchable Solvents

Switchable solvents are green solvents that are readily tuneable in a reversible way using the appropriate trigger, for instance, through reactions with CO_2. Other acids such as hydrochloric acid could serve as a trigger, but generally, CO_2 is preferred because of its advantages (ease of handling related to its gaseous state, generally non-toxic, available and inexpensive). Amongst the developed switchable solvents, switchable water appears to be an excellent water-based solubilisation and extraction method to target non-polar NPs. Switchable water is obtained by adding a base soluble into the water, such as N,N,N’,N’-tetramethylbutane-1,4-diamine [41]. This base enables ‘the switch,’ which consists of the addition or depletion of CO_2 to monitor the ionic strength of the aqueous solution. At the end of the process, it is possible to remove the base from the water solution to make it clean and safe once again.

Bases such as amines or polyamines may be used to obtain switchable water. In the absence of CO_2, the aqueous solution has a low ionic strength because of the amine. If CO_2 is added to the solution, the base is protonated once or more depending on its protonatable sites, giving the aqueous solvent a sudden, strong ionic strength [42]. In a typical green extraction protocol involving switchable water, a base is introduced into the water before adding the matrix containing the NPs. Depending on the solubility of the target compounds, that switchable water is either carbonated or uncarbonated. CO_2 bubbling can be used to achieve the classic 1 atm loading capacity of interest for switchable water. Depending on the process, once the NPs have been extracted, CO_2 pressure may be adjusted to monitor their solubility. Finally, the base can easily be recovered from the water after the complete removal of CO_2.

It would appear that there is currently no industrial application of switchable water in the pharmaceutical field. This method is still at a research level, nonetheless, promising results of NPs extraction were obtained thanks to it. In particular, it was shown that the base involved in obtaining 'the switch' is highly recyclable at the end of lab-scale processes [43]. This suggests that the corresponding potential industrial process could be sustainable.

13. SWE

Subcritical water extraction is a particular physical state of water approaching its critical point. More precisely, SWE is typically obtained and used at a temperature between 100 to 200 °C and maintained at a pressure of up to 22.1 MPa, enabling it to stay in liquid form rather than becoming a gas [44]. Compared to water used at an ambient temperature and pressure, SWE is a less polar solvent that behaves more like methanol and is, therefore, able to solubilise and extract less polar NPs that ambient water could not.

In terms of physicochemical properties, SWE shows a reduced dielectric constant approaching those of acetonitrile or methanol. Its viscosity and surface tension are also decreased, which enables a deeper penetration of the liquid into the matrix used for extraction. Finally, the density and the diffusion rate of SWE are lower than in the case of ambient water, which leads to an enhanced mass transfer of the dissolved ions and molecules [45].

SWE is generally far more efficient and convenient than extraction with water at ambient temperatures or hot water without pressure control, especially because of the speed of the corresponding process [36]. Moreover, after the extraction step, SWE once again becomes ambient water and the non-polar compounds may spontaneously form a separate phase in which they are easy to recover since the compounds that were once soluble in SWE are no more.

There has not been an application of SWE in pharmaceuticals to date. Nevertheless, this technique is actually used by at least two major industries to produce active ingredients for the nutraceutical and cosmetic markets. These are Lubrizol [46] and Sensient [47][48]. The corresponding extracts are rich in bioactive NPs and have complex compositions. That is why the researchers can hypothesise that it rather meets the needs of nutraceutical and cosmetics industries, more than pharmaceutical ones which are generally looking for high-purity molecules. In any case, SWE appears to be a green and sustainable technique efficient for the extraction of NP and is already mature enough for some markets of the health industry.

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