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# Advances in hydrotropic solutions: An updated review

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**Abstract**

Approximately a century ago, in 1916, the term 'hydrotropy' was coined by the scientist Carl A. Neuberg to address anionic organic salts which considerably augmented the aqueous solubility of poorly soluble solutes. Currently hydrotropic solutions possess high industrial demand due to their unique features such as easy availability, good recovery, absence of fire hazards, higher separation factors without any solutes emulsification problem and eco-friendly nature. The present review takes the readers through a concise overview, geometrical features of hydrotropic agents, hypothetical mechanisms and their different advances toward drug delivery. Moreover, this review would provide an insight of the future perspectives concerned with the drug delivery and hydrotropism.

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*Keywords:* Hydrotropy; Mesoscale solubilization; Drug carriers and Green chemistry.

## 1. Introduction

The current main problem in the pharmaceutical industry is related to strategies that augment the aqueous solubility of drugs, as almost 70% of the newly discovered drug candidates suffer from poor aqueous solubility [1]. Solubility is one of the prime features to accomplish desired pharmacological response. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately is attributed to solubility of drug moiety [2]. Presently, numerous formulation technologies are available to enhance solubility as well as dissolution profile to enhance oral bioavailability [3]. In addition to these technologies, 'hydrotropy' is one of the recognized techniques available for resolving solubility issues. This review will elaborate various hypothetical and investigational mechanisms, geometrical features and applications of hydrotropic agents in pharmaceutical field which will aid the researchers to explore hydrotropy for progress in drug delivery.

## 2. Hydrotropy and hydrotropic agents

In 1916, 'hydrotropy' term was coined by the scientist Carl A. Neuberg [4]. Hydrotropes with an amphiphilic molecular structure possess the ability to increase the solubility of sparingly soluble organic molecules in water [5]. It is a molecular phenomenon whereby adding a second solute (hydrotrope) helps to increase the aqueous solubility of poorly soluble solutes [6]. Simply the presence of a large quantity of one solute enhances the solubility of another solute [7]. Hydrotropic agents are stated as ionic organic salts which help to increase or decrease the solubility of solute in a given solvent via '*salt in*' or '*salt*

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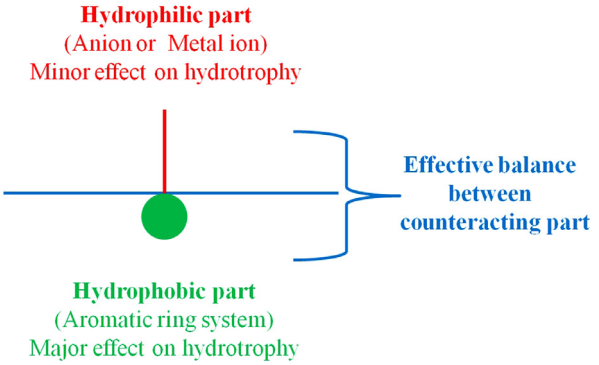


Fig. 1. The structure of a hydrotropic agent.

*out*' effects, respectively. Salts which show '*salt in*' of non-electrolytes are called "hydrotropic salts" and the phenomenon is known as "hydrotropism". They do not exhibit any colloidal properties but they improve solubility by forming weak interaction with solute molecules [8]. A hydrotropic molecule interacts with a less water-soluble molecule via weak van der Waals interactions such as $\pi$–$\pi$ or attractive dipole–dipole interaction [9].

Hydrotropes contain both hydrophobic and hydrophilic fractions in them. In comparison to surfactant, they contain a very small hydrophobic fraction [10]. The efficiency of hydrotrope solubilization depends on the balance between hydrophobic and hydrophilic part of hydrotrope [11]. The larger is the hydrophobic part of an additive, the better is the hydrotropic efficiency; the presence of the charge on the hydrophilic part is less significant [12]. Hydrotropic agents can be anionic, cationic or neutral, organic or inorganic and liquids or solids in nature (Fig. 1). These are freely soluble organic compounds which enhance the aqueous solubility of organic substances by forming stack-type aggregation [13,14]. Few examples of hydrotropic agents are given in Table 1 and Fig. 2 [15,16].

## 3. Mechanism

The enhancement of water-solubility by hydrotrope is based on the molecular self-association of hydrotrope and on the association of hydrotrope molecules with the solute. Although they are widely used in various industrial applications, only sporadic information is available about the mechanisms of hydrotropism. Various hypothetical and investigational efforts are being made to clarify the mechanisms of hydrotrope. The available proposed mechanisms can be abridged according to three designs [17].

(a) Self-aggregation potential
(b) Structure-breaker and structure-maker
(c) Ability to form micelles like structure.

These unique geometrical features and different association patterns of hydrotropes assemblies distinguish them from other solubilizers [18,19].

### *(a) Self-aggregation potential*

Minimum hydrotropic concentration (MHC), is a critical concentration at which hydrotrope molecules start to aggregate, i.e. self-aggregation potential. [6] Solubilization power of hydrotropes is governed by their self-aggregation potential [11]. This potential depends upon their amphiphilic features and the nature of the solute molecule [18,20]. They mainly show the volume fraction dependent solubilization potential [21]. Hydrotropes strongly interact with the solute to generate the complexes and these complexes would then lead to higher aqueous solubility. These outcomes have evolved from fluorescence emissions methods [9], crystallography analysis, molecular dynamics replication and thermodynamic solubility experiments [22–24]. Apart from these, they may act as bridging agents by reducing the Gibbs energy to increase the solubility of solute [23]. Simply, the structure of hydrotrope–water mixture around the drug molecule is the true key toward understanding the origin of self-aggregation potential [25].

### *(b) Structure-breaker and structure-maker*

An electrostatic force of the donor–acceptor molecule plays a vital role in the hydrotropic

Table 1
Examples of hydrotropic agents.

| Type | Example |
|---|---|
| Aromatic anionics | Sodium benzoate, Sodium salicylate, Sodium benzene sulfonate, Sodium benzene di-sulfonate, Sodium cinnamate, Sodium 3-hydroxy-2-naphthoate, Sodium para toluene sulfonate, Sodium cumene sulfonate, nicotinamide, *N*,*N*-diethylnicotinamide and *N*,*N*-dimethyl benzamide (Fig. 2) |
| Aromatic cationics | Paraaminobenzoic acid hydrochloride, Procaine hydrochloride and caffeine (Fig. 2) |
| Aliphatics and linear compounds | Sodium alkanoate, urea and *N*, *N*-dimethyl urea (Fig. 2) |

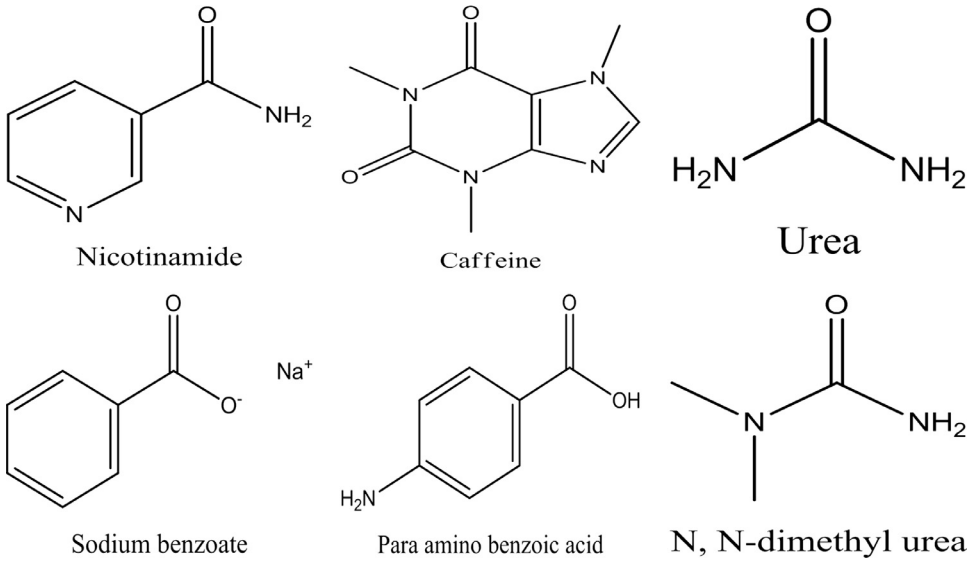


Fig. 2. Commonly used hydrotropic agents.

solubilization; hence, they are also termed as a structure-breaker and a structure-maker [26,27]. Solutes which are capable for both hydrogen donation and acceptance help to increase solubility. Solutropic agents like urea exert their solubilizing effect by changing the nature of the solvent, specifically by altering the solvent's ability to participate in structure formation or its ability of engaging in structure formation via intermolecular hydrogen bonding [28]. Structure-breaker hydrotropes are known as chaotropes while structure maker hydrotropes are known as kosmotrope [29]. Kosmotrope reduces the critical micelle concentration, or CMC by increasing the hydrophobic interaction which decreases the cloud point. Basically kosmotrope influences the cloud point by two ways i.e. (a) helps to form bigger micelles and (b) decrease of hydration. In case of amphiphilic drugs promazine hydrochloride (PMZ) and promethazine, cyclodextrin act as water structure makers and reduce the cloud point [30].

***(c) Ability to form micelles like structure***

This mechanism is based on the self-association of hydrotropes with solutes into a micellar arrangement [31]. Basically they form stable mixed micelles with a solute molecule decreasing electrostatic repulsion between the head groups [32]. Hydrotropes like alkylbenzene sulfonates, lower alkanoates and alkyl sulfates exhibit self-association with solutes and form micelles. Aromatic anionic hydrotrope i.e. nicotinamide, improve solubility of riboflavin via self-association mechanism [33]. In case of PMZ, anionic hydrotropic agents like sodium salicylate forms stable mixed micelles by decreasing electrostatic repulsion between the head groups of PMZ [32].

### *3.1. Fluctuation theory of solutions*

Moreover some researchers also illustrate fluctuation theory of solutions (FTS) to determine the mechanism of hydrotropic solubilization. FTS has recognized two chief factors of hydrotrope-induced solubilization: (i) Hydrotrope–solute interaction and (ii) Water activity depression. The former is conquered by hydrotrope–solute association while the latter is improved by ionic dissociation and hindered by the self-aggregation of the hydrotropes [34].

Apart from the above-mentioned mechanism, the nature and the concentration are the drawing forces for the solubilizing potential of hydrotropes. Aromatic hydrotropic agents with planar structure interact with solute molecules via inducing stacking aggregation mechanisms [35,36]. Caffeine exhibits parallel stacking in aqueous solutions to solubilize the riboflavin [37]. Anionic hydrotropes at low concentrations increase but at higher concentrations decrease the cloud point. Cationic and non-ionic hydrotropes show steep rise in the cloud point of amphiphilic drugs. The extent of cloud-point variation by different hydrotropes is different depending on their nature and structure [38]. Hydrotropes in high concentrations (0.1–0.8 M) form aggregates and decrease the cloud point of amphiphilic drug while in lower concentrations they

Table 2
Examples of solid dispersions for which hydrotropic agents are used.

| Drug | Hydrotropic agent | Key finding | References |
|---|---|---|---|
| Norfloxacin | Sodium benzoate | 9.56 fold enhancement in aqueous solubility | [52] |
| Aceclofenac | Urea 20% and sodium citrate 10% | 1.7 fold improvement *in vitro* dissolution | [53] |
| Theophylline | Urea 5% and sodium citrate 10% | 142.26 times improvement in aqueous solubility | [54] |
| Diclofenac sodium | Urea 20% and sodium citrate 10% | 250 times improvement in aqueous solubility | [55] |
| Lurasidone hydrochloride | Nicotinamide, sodium benzoate and sodium citrate. | Improved drug release | [56] |
| Pizotifen malate | Povidone (Kollidon 12) | Improved aqueous solubility | [57] |

increase the cloud point of amphiphilic drug [39]. The concentration of hydrotropes plays an important role in the solubilization mechanism of drug molecules. Sodium benzoate and sodium salicylate when employed to enhance aqueous solubility of nifedipine illustrated complexation type of interaction at a low concentration and aggregation at high concentration [40]. Hydrotropic solubilization of nimesulide at a lower hydrotrope concentration exhibits weak ionic interactions and at higher hydrotrope concentration exhibits molecular aggregation [41]. Dexibuprofen when combined with hydrotropic agents and subjected to differential scanning calorimetry (DSC) and infrared (IR) spectroscopy studies demonstrated intermolecular interactions between the drug and the hydrotropic agents which increased solubility and dissolution rate of drug [42].

## 4. Applications

Hydrotropes have many realistic applications in both biomedical and engineering fields. The uses involve development of pharmaceutical formulations, food stuffs, detergent solutions, solute separation process, paint industry, coatings, plastic additives, selective separation and alterations in reaction kinetics. In view of these, various applications related to development of pharmaceuticals are discussed.

### *4.1. Hydrotropes as drug carrier*

Hydrotropes have unique potential to act as carriers for active pharmaceutical ingredients. They have ability to generate dynamic, non-covalent assemblies, i.e. clusters in aqueous solutions. In the presence of hydrophobic compounds, these clusters are stabilized by formation of long-lived, highly stable mesoscopic droplets due to a phenomenon known as ‘mesoscale solubilization’. Such materials can help in processing various products ranging from pharmaceuticals, cosmetics and agrochemicals [43]. Subtle changes in surfactant geometry lead to a marked effect on the macroscopic rheological behavior of the system. These micellar solutions act as a template for tissue engineering and as a modifier of the drug delivery [44]. Additionally hydrotropes play various roles like o/w microemulsion stabilizers, viscosity modifiers, cleaning agents, solubilizers in formulation development [45–48]. As they act at the molecular level, hydrotropes provide better efficacy in bottom–up techniques than top–down methods [49]. Considering these functionalities, formulation scientists are fabricating several drug delivery systems based on hydrotropy approach to enhance the therapeutic efficacy of critical drug molecules.

#### *4.1.1. Solid dispersions*

Solid dispersions (SD) are one of the most popular approaches to improving drug release of poorly soluble drugs. It is a molecular mixture of poor water soluble drugs in hydrophilic carriers wherein the drug release profile is driven by the polymer properties. It helps to increase solubility, dissolution profile of poor water soluble drugs. Commonly used polymers in preparation of SD are povidone, cyclodextrin, starch, hydroxy propyl methylcellulose, ethyl cellulose, hydroxy propyl cellulose, polyethylene glycols and silica [50,51]. A single hydrotrope or blend of hydrotropes has been effectively used to formulate the SD. In case of SD, hydrotropes enhance solubility as well as dissolution kinetics due to complete amorphization and intermolecular hydrogen bonding with drug molecules (Table 2).

#### *4.1.2. Transdermal formulations*

Transdermal drug administration provides the benefits of achieving a remedial effect without the risks of impending side effects that may occur after oral administration. The selection of a suitable drug carrier in transdermal formulation is very important since it can affect the percutaneous absorption [58].

5-fluorouracil transdermal formulation was prepared using polyglycerol fatty acid monoesters (PGMC) as hydrotrope. Mean particle size of solution consisting of PGMC was approximately 14 nm.

Hydrotropic transdermal formulation enhanced skin permeation of 5-FU due its ability of hydrotrope to form aggregates [59]. Specifically, in the topical formulation, the distribution coefficient (Log D) value of a compound played a vital role in solubilization. It showed crucial impact on solubility enhancement factor (SEF). Solubility enhancement factor (SEF) is a ratio of solubility of substance in ternary mixture to its solubility in pure solvent under identical temperature conditions. All compounds with log *D* values between 2 and 4.5 showed a SEF > 5 in 40% aqueous solutions of urea while with a log *D* value below 2 or above 5, SEF was < 5. In some cases such as diclofenac and prednicarbate, SEF achieved was > 5 at 5% urea and > 250 at 20% urea [60]. Paraben containing semisolid topical formulations was prepared with nicotinamide which helps to reduce the stratum corneum vehicle partition coefficient. Nicotinamide potentiated the paraben dissolution in aqueous media (solutions, gels) and reduced their partitioning in the oily phase, thereby reducing the toxicological risk also [61].

#### *4.1.3. Parenteral formulations*

Parenteral formulation can be administration via various routes like intravenous, intramuscular, intra-arterial, subcutaneous and intra-dermal. Currently, in hospitalized patients' key element for various therapeutic aliments are parenteral products. Parenteral products provide various advantages like less dosing frequency, rapid onset of action along with good bioavailability. In addition to these conventional parenteral products, novel parenteral delivery systems like liposomes, nanoparticles, implants, patches are also available for controlled, sustained and active targeted drug delivery [62].

Aceclofenac aqueous injection was prepared using mixed hydrotropy (20% urea and 10% sodium citrate) technique via lyophilization. It showed better solubility performance as compared to the pure drug. The enhancement in the solubility of aceclofenac was more than 250 folds and additionally it exhibited better physical and chemical stability also [13]. Aqueous injectable indomethacin formulation was developed using sodium *p*-hydroxy benzoate, sodium benzoate, urea and nicotinamide as hydrotropes. The hydrotropic solubilization of indomethacin at lower hydrotrope concentration was attributed to weak ionic interactions while that at higher hydrotrope concentration was due to molecular aggregation. Indomethacin exhibited highest and lowest solubility in sodium *p*-hydroxy benzoate and urea, respectively. Moreover prepared formulation showed better physical and chemical stability over a period of 6 months [63]. Injectable nifedipine formulation was prepared by mixed hydrotropy technique (30% sodium benzoate and 30% sodium salicylate). It showed better aqueous solubility profile and stability over period of 1 month [64]. Temazepam aqueous injection was prepared using sodium salicylate and nicotinamide as hydrotropes by lyophilization method. Solubilization was enhanced due to an increase in hydrogen bonding between the drug and hydrotrope mixtures [65].

#### *4.1.4. Miscellaneous*

2-hydroxypropyl-beta-cyclodextrin (2-HP-$\beta$-CD) was used to wrap methyl testosterone (MeT) moiety in inclusion complex of MeT-2-HP-beta-CD. The intermolecular hydrogen bonding between MeT and 2-HP-$\beta$-CD helped to enhance solubility of MeT. Also, the prepared MeT-2-HP-beta-CD complex showed 7-fold improvement in oral bioavailability of MeT [66]. Paclitaxel-$\beta$-cyclodextrin functionalized hyperbranched polyglycerol (HPG) micelles were prepared with an objective of solubility enhancement. The prepared micelles showed multi molecular spherical nature with the particle size of 200–300 nm and good dispersity. It showed a burst release followed by continuous extended release. Furthermore, MTT analysis showed good biocompatibility and a promising hydrophobic drug delivery system [67]. Griseofulvin suspensions were prepared using aqueous phase of sodium benzoate. Particle size of the prepared suspension was between 10 μm and 20 μm. It showed 70% drug release at the end of 45 mins [68]. Furosemide floating microspheres were prepared with Eudragit RSPO and niacinamide by solvent evaporation method. The optimized formulation exhibited 98.2% encapsulation efficiency and 145 nm mean particle size. Surface morphology exhibited hollow spherical structure with a smooth outer surface. Enhanced drug solubility was due to complete amorphization and intermolecular hydrogen bonding between the drug and hydrotropes. Moreover it illustrated sustained release in acidic environment and stability up to 1 month [69]. Starch gels were prepared without heat treatment or chemical modification by using sodium salicylate as a gelling agent. Release patterns of the gels were studied using riboflavin as a prototype drug. Riboflavin showed consistent diffusion-controlled kinetics. Pattern of the drug release depended on the initial loading levels and the starch content of the gels. Thus, hydrotrope-gelled starch proved to be a better vehicle for topical drug delivery [70].

Table 3
Examples of titrimetric and spectrophotometric estimations for which hydrotropic agents are used.

| Drug | Dosage form | Hydrotropic agents | Increase in solubility (times) | References |
|---|---|---|---|---|
| **Titrimetric analysis** | | | | |
| Aspirin | Tablets | 0.5 M Ibuprofen sodium | 05 | [71] |
| Aceclofenac | Bulk drug and tablets | 0.5 M Ibuprofen sodium | 120 | [72] |
| | | 2.5 M Sodium salicylate | 400 | [73] |
| Furosemide | | 2 M Sod. benzoate | 90 | [74] |
| Famotidine | Bulk drug | 2 M Sodium salicylate | 25 | [75] |
| Ibuprofen | Bulk drug and tablets | 2 M Sodium benzoate | 80 | [76] |
| Naproxen | Tablets | 0.5 M Ibuprofen sodium | 350 | [77] |
| Salicylic acid | Bulk drug | 0.5 M Ibuprofen sodium | 12 | [78] |
| | | 2.0 M Sodium salicylate | 06 | |
| Salbutamol sulfate | Bulk drug | 2 M Nicotinamide | 17 | [79] |
| Theophylline | Bulk drug | 2 M Sodium | 18 | [80] |
| **Spectrophotometric analysis** | | | | |
| Amlodipine besylate | Bulk drug and Tablets | Urea | 07 | [81] |
| Amlodipine besylate | Bulk drug and tablets | 2 M Sodium acetate | 75 | [82] |
| Atenolol HCl | Tablets | 1 M Metformin hydrochloride | 03 | [83] |
| Aceclofenac | Bulk drug and tablets | 2.5 M sodium salicylate | 400 | [84] |
| Atorvastatin | Tablets | 2 M Urea | 07 | [85] |
| Acetazolamide | Bulk drug | 7.5 M *N*,*N*-dimethyl urea | 02 | [86] |
| | | 5.5 M sodium acetate | 1.8 | |
| Cefadroxil | | 6 M Urea | 10 | [87] |
| Diclofenac sodium | Tablets | 7.5 M *N*, *N* dimethyl urea | 11 | [88] |
| Metronidazole and furazolidone | Tablets | Sodium acetate and 8 M urea solution (50:50% V/V) | 28 | [89] |
| Furazolidone | Tablets | 2 M sodium acetate, 8 M urea, 2 M niacinamide and 2 M sodium benzoate (25:25:25:25% V/V) | 32 | [90] |
| Hydro-chlorothiazide | Tablets | 2 M Nicotinamide | 43 | [91] |
| Indomethacin | Capsule | 2 M niacinamide | 05 | [92] |
| Ketoprofen | Tablets | 2 M Potassium acetate | 210 | [93] |
| Lovastatin | Tablets | 4 M Sodium acetate | 06 | [94] |
| Losartan | Tablets | Sodium chloride | 63 | [95] |
| Metronidazole | Tablets | Sodium benzoate | 05 | [96] |
| Naproxen | Tablets | 2 M sodium benzoate | 120 | [97] |
| Naproxen | Tablets | 0.5 M ibuprofen sodium | 350 | [98] |
| Nalidixic acid | Tablets | Sodium Benzoate | 98 | [96] |
| Ornidazole | Tablets | 0.5 M Ibuprofen sodium | 08 | [99] |
| Ornidazole | Tablets | 10 M Urea | 10 | [100] |
| Rosiglitazone maleate | Bulk drug and tablets | 6 M Urea | 14 | [101] |
| Simvastatin | Bulk drug and tablets | Sodium chloride | 90 | [102] |
| Tinidazole | Tablets | 1 M Lignocaine hydrochloride | 06 | [103] |
| Tenofovir disoproxil fumerate | Tablets | Sodium benzoate | 121 | [104] |
| Tinidazole | Tablets | Sodium benzoate | 06 | [96] |

### *4.2. Titrimetric and spectrophotometric estimations*

The analysis of poorly aqueous soluble drugs is commonly carried out by spectrophotometric method. It involved using various organic solvents like acetone, acetonitrile, benzene, carbon tetrachloride, diethyl ether, ethanol, methanol and toluene. A major drawback related to these organic solvents was their volatile nature, toxicity, flammability and cost. To overcome such difficulties, hydrotropic solutions were used. Hydrotropic agents used in titrimetric and/or spectrophotometric estimations are listed in Table 3.

### *4.3. Green chemistry*

#### *4.3.1. Separation of mixture*

Hydrotropic solutions possess high industrial demand due to their easy availability, good recovery, absence of fire hazards and higher separation factors without any solutes emulsification problem [105–107]. It helps to enhance the solubility of various organic

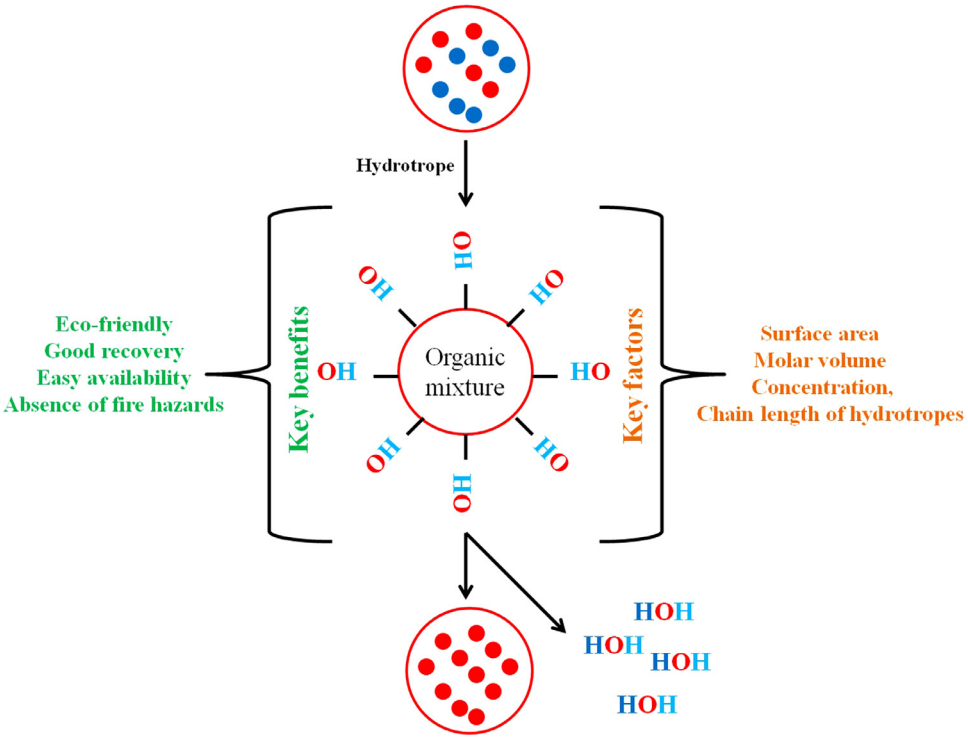


Fig. 3. Hydrotropic mechanism of separation.

Table 4
Examples of mixture separations for which hydrotropic agents are used.

| Mixture | Hydrotropes | Isolated compound | Reference |
|---|---|---|---|
| *Citrus aurantium* L. | Sodium salicylate and sodium cumene sulfonate | Limonoids | [111] |
| Turmeric | Sodium cumene sulfonate | Curcuminoids | [112] |
| Rauwolfia vomitoria | Sodium cumene sulfonate | Reserpine | [113] |
| Black pepper | Butyl benzene sulfonate and sodium dodecyl sulfate | Piperine | [114] |
| Sugar cane bagasse | Alky benzene sulfonates | Ligno-cellulosic fibers (without breaking of the cellulosic material) | [115] |
| 6-aminopenicillanic acid (6-APA) reaction mixture | Sodium butyl monoglycol sulfate | 6-APA | [116] |

solutes such as acids, alcohols, aldehydes, esters, fats, hydrocarbons and ketones [108]. The concentration and hydrophobic parameters (surface area, molar volume of the hydrophobic parts) of hydrotropes appear to be important in solute separations [109]. The influence of a chain length of a hydrotropic agent helps to improve solute recovery (Fig. 3). The addition of the short chain cationic hydrotropes to sodium dodecyl sulfate (SDS) phase helped to enhance oil recovery [110]. Hydrotropes separate the close-boiling isomeric components from their binary mixtures. They are also used to extract various bioactive components from plant material (Table 4).

In addition to extractive separation, hydrotropes are also useful in improving enzymatic hydrolysis efficiency. Hydrotropic pre-treatment helps to augment enzymatic hydrolysis efficiency of common reed and sugar cane bagasse to produce fermentable sugar [117,118]. In case of enzymatic hydrolysis of polysaccharides, it significantly increases the glucose yield [119]. Olefinic compounds like sodium cinnamate (Na-CIN) exhibits the photo switchable recovery of solute under exposure to UV irradiation. Various organic solutes such as cinnamic acid, aspartic acid, curcumin, thymol, benzocaine and natural compounds like forskolin and curcumin are easily recovered

Table 5
Examples of synthesis for which hydrotropic agents are used.

| Reaction media | Hydrotropic solution | Substrate | Reference |
|---|---|---|---|
| Octahydroquinazolinone | 50% aqueous sodium *p*-toluene Sulfonate | Microwave irradiation | [122] |
| b-amino carbonyl compounds | 50% aqueous sodium p-toluene sulfonate | Ultrasound irradiation | [123] |
| Hantzsch esters | Aqueous sodium butyl mono glycol sulfate | Domestic microwave | [124] |
| Aza-Micheal reaction | Glycerol | – | [125] |

under UV irradiation with help of Na-CIN [120]. Hydrotropic solubilization helps to facilitate the aqueous solubility of rapamycin, a poorly water-soluble immunosuppressive drug up to 1000-fold [121]. In extractive isolation process hydrotropes reduce the use of harmful organic solvents and maintains the process environment-friendly.

*4.3.2. Green synthesis*

Hydrotropes provide a simple, efficient and green platform for various industrial organic transformations. Moreover, being economic, non-toxic, non-flammable and eco-friendly, hydrotropic solutions possess surplus physico-chemical features required as alternate green solvents for organic reactions. Within the outline of green chemistry, aqueous hydrotropic method offers several advantages such as trouble-free handling, cleaner reaction profile, high conversions rate and short reaction time making it useful option for the rapid synthesis. Another important characteristic of hydrotropic medium is its simple recovery from the reaction mixture and its recyclability. Furthermore easy recovery of products from hydrotropic solutions makes this protocol an attractive green chemistry approach (Table 5).

## 5. The perspectives for hydrotropy

The progress in hydrotropy has boosted their use in various operational fields. Specifically, the utilization of hydrotropic compounds has been increasingly recognized in formulation development. Various experimental studies have confirmed their solubility potential along with a non-toxic, non-flammable and eco-friendly nature. However, many challenges remain with respect to their structure based mechanism and toxicity profiling since their crucial side effects on normal cells during active targeting are yet to be assessed. When progress in hydrotropy as well as novel drug delivery approaches catch up with contest, hydrotropic mechanisms, stability in biological solutions, biocompatibility and enhanced efficacy along with delivery techniques will be one step closer to reality. This technology is expected to transform the advances toward enhanced therapeutic delivery of poorly aqueous soluble drugs as well as critical moieties with narrow therapeutic index.

## Conflict of interests

Authors have no conflicts of interest to declare.

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