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ADVANCES IN HYDROTROPIC SOLUTIONS: AN UPDATED REVIEW

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, high 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 towards drug delivery. Moreover, this review would provide an insight into the future perspectives concerned with drug delivery and hydrotropism.

HYDROTROPY, MESOSCALE SOLUBILIZATION, DRUG CARRIER, 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 substance features to accomplish the desired pharmacological response. The therapeutic effectiveness of a drug depends upon the bioavailability and ultimately is attributed to the 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 the pharmaceutical field, which will aid the researchers in exploring hydrotropy for progress in drug delivery.

2. Hydrotropy and hydrotropic agents

In 1916, the term 'hydrotropy' 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]. Hydrotropes 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 out' effects, respectively.

Salts which show a '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 interactions with solute molecules [8]. A hydrotropic molecule interacts with a less water-soluble molecule via a weak Van der Waals interaction, such as a π-π or attractive dipole-dipole interaction [9].

Hydrotropes contain both hydrophobic and hydrophilic fractions. In comparison to surfactant, they contain a very small hydrophobic fraction [10]. The efficiency of hydrotropic solubilization depends on the balance between hydrophobic and hydrophilic parts of the 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 important [12]. Hydrotropes can be anionic, cationic

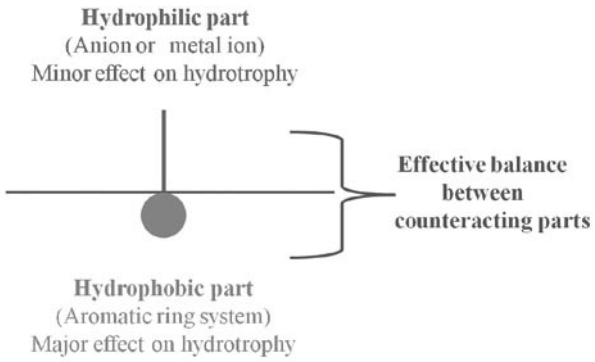

Fig. 1. The internal effective structure of a hydrotrope

Table 1

Examples of hydrotropic agents

Type	Example
Aromatic anionic	Sodium benzoate, sodium salicylate, sodium benzene sulphonate, sodium benzene di-sulphonate, sodium cinnamate, sodium3-hydroxy-2-naphthoate, Sodium para- toluene sulphonate, sodium cumene sulphonate, nicotinamide, N,N-diethylnicotinamide, N,N-dimethyl benzamide (see Fig. 2)
Aromatic cationic	Paraaminobenzoic acid hydrochloride, procaine hydrochloride and caffeine (see Fig. 2).
Aliphatic and linear compound	Sodium alkanoate, urea and N,N-dimethyl urea (see Fig. 2).

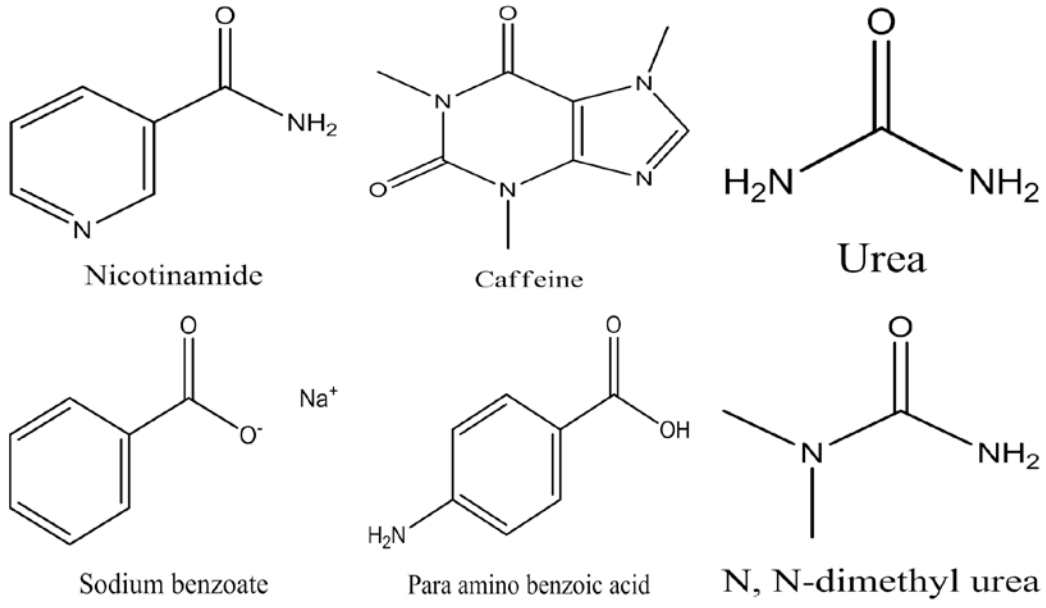

Fig. 2. Chemical formulae of the commonly used hydrotropic agents

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]. A few examples of hydrotropic agents are given in Table 1 and in Fig. 2 [15, 16].

3. Mechanism of hydrotropism

The enhancement of water-solubility by the hydrotrope is based on the molecular self-association of the hydrotrope and on the association of hydrotrope molecules with the solute. Although they are widely used in various industrial applications, only sporadic information on the mechanisms of hydrotropism is available. Various hypotheses and research efforts are being made to clarify the mechanisms of hydrotropism. 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 micelle-like structures.

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

Self-aggregation potential. Minimum hydrotropic concentration (MHC) is a critical concentration at which hydrotrope molecules start to aggregate, i.e., self-aggregation potential [6]. The solubilization power of hydrotropes is governed by their self-aggregation potential [11]. This potential depends upon their amphiphilic features and the nature of a 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 could then lead to higher aqueous solubility. These outcomes have evolved from the 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 a solute [23]. Simply, the structure of the hydrotrope-water mixture around the drug molecule is the true key toward understanding the origin of the self-aggregation potential [25].

Structure-breaker and structure-maker. An electrostatic force of the donor-acceptor molecule plays a vital role in the hydrotropic solubilization; hence, they are also termed as a structure-breaker and a structure-maker [26, 27]. Solutes which are capable both of hydrogen donation and acceptance help to increase solubility. Solutropic agents, such as 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 ones are known as kosmotropes [29]. Kosmotropes reduce the critical micelle concentration (CMC) by increasing the hydrophobic interaction which decreases the cloud point. Basically, a kosmotrope influences the cloud point in two ways, i.e., helps (*i*) to form bigger micelles and (*ii*) to decrease hydration. In case of amphiphilic drugs, promazine hydrochloride (PMZ) and promethazine, cyclodextrin act as water structure-makers and reduce the cloud point [30].

Ability to form micelle-like structures. 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 the electrostatic repulsion between the head groups [32]. Hydrotropes, such as alkyl-benzene sulfonates, lower alkanoates and alkyl sulphates, exhibit self-association with solutes and form micelles. Aromatic anionic hydrotrope agents, i.e. nicotinamide, improve the solubility of riboflavin via a self-association mechanism [33]. In case of PMZ, anionic hydrotropic agents, such as sodium salicylate, form stable mixed micelles by decreasing the electrostatic repulsion between the head groups of PMZ [32].

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;

(*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 above-mentioned mechanism, the nature and the concentration are the drawing forces for the solubilizing potential of hydrotropes. An aromatic hydrotropic agent with a planar structure interacts with solute molecules via inducing stacking aggregation mechanisms [35, 36]. Caffeine exhibits parallel stacking in aqueous solutions to solubilize the riboflavin [37]. Anionic hydrotropic agents at low concentrations increase but, at higher concentrations, decrease the cloud point. Cationic and non-ionic hydrotropes show a steep rise in the cloud point of amphiphilic drugs. The extent of the cloud-point variation for using different hydrotropes does variously depend on their nature and structure [38]. Hydrotropes in high concentrations (0.1 – 0.8 M) form aggregates and decrease the cloud point of amphiphilic drugs while in lower concentrations they increase the cloud point of amphiphilic drugs [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 the aqueous solubility of nifedipine, illustrated the complexation type of interaction at a low concentration and aggregation at a high one [40]. The hydrotropic solubilization of nimesulide exhibits weak ionic interactions at a lower hydrotrope concentration and molecular aggregation at a higher one [41]. Dexibuprofen, when combined with hydrotropic agents and investigated by the differential scanning calorimetry (DSC) and the infrared (IR) spectroscopy, demonstrated intermolecular interactions between the drug and the hydrotropic agents, which increased solubility and dissolution rate of the drug [42].

4. Application of hydrotropes

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

Hydrotropes as drug carriers. These have a unique potential to act as carriers for active pharmaceutical ingredients. They have the ability to generate dynamic, non-covalent assemblies, i.e. clusters in aqueous solutions. In the presence of hydrophobic compounds, these clusters are stabilized by the 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 behaviour of the system. These micellar solutions act as a template for tissue engineering and as a modifier of the drug delivery [44]. Additionally, hydrotropes are of considerable importance in various applications, such as oil/water (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 the 'bottom-up' techniques than the 'top-down' ones [49]. Considering these functionalities, formulation scientists are fabricating several drug delivery systems based on the hydrotropic approach in order to enhance the therapeutic efficacy of critical drug molecules.

Solid dispersions (*SD*) are the most popular ways of improving the 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 and dissolution profile of poor water-soluble drugs. Commonly used polymers in preparation of SD are povidone, cyclodextrin, starch, hydroxy propyl methylcellulose, ethyl cellulose, hydroxypropylcellulose, polyethyleneglycols and silica [50, 51]. A single hydrotrope or a blend of them has been effectively used to formulate the SDs. In case of SDs, hydrotropes enhance solubility as well as dissolution kinetics due to complete amorphization and intermolecular hydrogen bonding with drug molecules (see Table 2).

Table 2

Examples of solid dispersions using hydrotropic agents

Drug	Hydrotropic agent	Key finding	Reference
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	Improvement of drug release	[56]
Pizotifen malate	Povidone (Kollidon 12)	Improvement in aqueous solubility	[57]

Transdermal formulations. Transdermal administration of drugs 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 percutaneous absorption [58].

A 5-Fluorouracil transdermal formulation was prepared using polyglycerol fatty acid monoesters (PGMC) as a hydrotrope. Mean particle size of the solution consisting of PGMC was approximately 14 nm. The hydrotropic transdermal formulation enhanced skin permeation of 5-FU due to the ability of the hydrotrope to form aggregates [59]. Specifically, in the topical formulation, the value of the distribution coefficient ($\log D$) of a compound played a vital role in solubilization. It showed a crucial impact on the solubility enhancement factor (SEF). This factor is a ratio of the solubility of a substance in ternary mixture to its solubility in pure solvent under identical temperature conditions. All compounds with $\log D$ values between 2.0 and 4.5 showed a SEF more than 5 in 40 % aqueous solutions of urea while with a $\log D$ value below 2 or above 5, SEF was less than 5. In some cases such as diclofenac and prednicarbate, SEF achieved a value that was more than 5 at 5 % urea and more than 250 at 20 % urea [60]. Paraben-containing semisolid topical formulations were prepared with nicotinamide which helped 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 also reducing the toxicological risk [61].

Parenteral formulation can be the administration via various routes, such as intravenous, intramuscular, intra-arterial, subcutaneous and intradermal. Currently, parenteral products are the key element for therapeutic aliments in hospitalized patients. These products provide various advantages, such as a lower dosing frequency, and a 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].

An aceclofenac aqueous injection was prepared using a 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 also exhibited better physical and chemical stability [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 a 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, the prepared formulation showed better physical and chemical stability over a period of six months [63]. An injectable nifedipine formulation was prepared by a mixed hydrotrope technique (30 % sodium benzoate and 30 % sodium salicylate). It showed a better aqueous solubility profile and stability over a period of one month [64]. A temazepam aqueous injection was prepared using sodium salicyate and nicotinamide as hydrotropes by the lyophilization method. Solubilization was enhanced due to an increase in hydrogen bonding between the drug and hydrotrope mixtures [65].

Miscellaneous. 2-Hydroxypropyl-beta-cyclodextrin (2-HP-beta-CD) was used to wrap methyltestosterone (MeT) moiety in the inclusion complex of MeT-2-HP-beta-CD. The intermolecular hydrogen bonding between MeT and 2-HP-beta-CD helped to enhance the solubility of MeT. The prepared MeT-2-HP-beta-CD complex also showed 7-fold improvement in the 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 a multimolecular spherical nature with the particle size of 200 to 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]. Greseofulvin suspensions were prepared using the aqueous phase of sodium benzoate. The particles of the prepared suspension ranged in size from 10 to 20 μm. It showed a 70 % drug release at the end of 45 min [68]. Furosemide floating microspheres were prepared with Eudragit RSPO and niacinamide by the solvent evaporation method. The optimized formulation exhibited a 98.2 % encapsulation efficiency and 145 nm particle size in the average. Surface morphology displayed a hollow spherical structure with a smooth outer surface. Enhanced drug solubility was due to complete amorphization and intermolecular hydrogen bonding between the drug and the hydrotropes. Moreover, it illustrated sustained release in acidic environment and stability up to one 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].

Titrimetric and spectrophotometric estimations. The analysis of poorly aqueous soluble drugs is commonly carried out by the spectrophotometric method. It involved the use of various organic solvents, like acetone, acetonitrile, benzene, carbon tetrachloride, diethylether, ethanol, methanol and toluene. The main shortcomings related to these organic solvents were 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.

Green chemistry. This is a scientific field that has arisen in the 1990s. It studies enhancements of chemical processes that can have a beneficial impact on the environment.

Separation of mixture. Hydrotropic solutions possess high industrial demand due to their easy availability, good recovery, absence of fire hazards and high separation factors without any solutes emulsification problem [105–107]. It helps to enhance the solubility of various organic solutes such as acids, alcohols, aldehydes, esters, fats, hydrocarbons and ketones [108]. The concentration and hydrophobic parameters (the surface area, the molar volume of the

Table 3

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

Drug	Dosage form	Hydrotropic agent	Increase in solubility, times	Reference
Titrimetric analysis				
Aspirin	Tablets	0.5M ibuprofen sodium	05	[71]
Aceclofenac	Bulk drug and tablets	0.5M ibuprofen sodium	120	[72]
		2.5 M sodium salicylate	400	[73]
Furosemide		2 M sodium benzoate	90	[74]
Famotidine	Bulk drug	2M sodium salicylate	25	[75]
Ibuprofen	Bulk drug and tablets	2 M sodium benzoate	80	[76]
Naproxen	Tablets	0.5M ibuprofen sodium	350	[77]
Salicylic acid	Bulk drug	0.5 M ibuprofen sodium	12	[78]
		2.0 M sodium salicylate	06	
Salbutamol sulphate	Bulk drug	2M nicotinamide	17	[79]
Theophylline	Bulk drug	2M sodium	18	[80]
Spectrophotometric analysis				
Amlodipine besylate	Bulk drug and tablets	Urea	07	[81]
Amlodipine besylate	Bulk drug and tablets	2M sodium acetate	75	[82]
Atenolol HCl	Tablets	1M metformin hydrochloride	03	[83]
Aceclofenac	Bulk drug and tablets	2.5 M sodium salicylate	400	[84]
Atorvastatin	Tablets	2M Urea	07	[85]
Acetazolamide	Bulk drug	7.5 M N,N-dimethyl urea	02	[86]
		5.5 M sodium acetate	1.8	
Cefadroxil		6M urea	10	[87]
Diclofenac sodium	Tablets	7.5M 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	2M Nicotinamide	43	[91]
Indomethacin	Capsule	2 M niacinamide	05	[92]
Ketoprofen	Tablets	2M potassium acetate	210	[93]
Lovastatin	Tablets	4M sodium acetate	06	[94]
Losarton	Tablets	Sodium chloride	63	[95]

to be continued

The end of Table 3

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	0.5M ibuprofen sodium	08	[99]
Ornidazole	Tablets	10 M urea	10	[100]
Rosiglitazone maleate	Bulk drug and tablets	6M urea	14	[101]
Simvastatin	Bulk drug and tablets	Sodium chloride	90	[102]
Tinidazole	Tablets	1 M lignocaine hydrochloride	06	[103]
Tenfovir disoproxil fumerate	Tablets	Sodium benzoate	121	[104]
Tinidazole	Tablets	Sodium benzoate	06	[96]

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 of cationic hydrotropic agents 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 the plant material (see Table 4).

In addition to extractive separation, hydrotropes are also useful in improving enzymatic hydrolysis efficiency. Hydrotropic pre-treatment helps to augment enzymatic

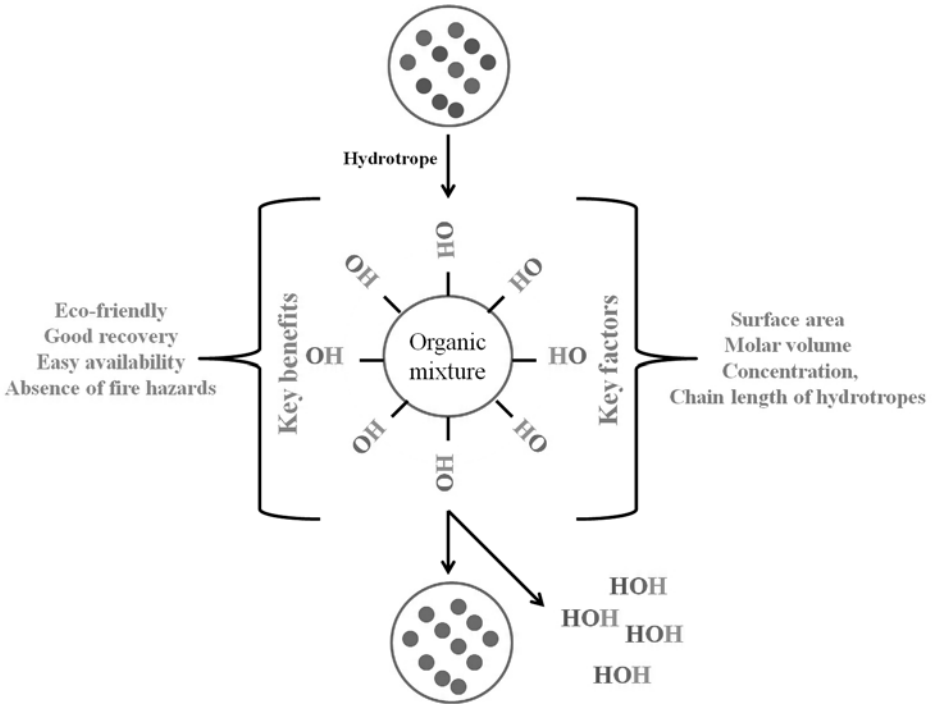

Fig. 3. Hydrotropic mechanism of separation

Table 4

Examples of mixture separations for which hydrotropic agents are used

Mixture	Hydrotrope	Isolated compound	Reference
Citrus aurantium L.	Sodium salicylate and sodium cumene sulphonate	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]
Sugarcane bagasse	Alky benzene sulfonates	Ligno-cellulosic fibers (without breaking of the cellulosic material)	[115]
6-aminopenicillanic acid (6-APA) reaction mixture	Sodium butyl monoglycol sulphate	6-APA	[116]

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

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 physical and chemical features required as alternate green solvents for organic reactions. Within the outline of green chemistry, the aqueous hydrotropic method offers several advantages, such as trouble-free handling, cleaner reaction profile, high conversion rate and short reaction time, making it a useful option for rapid synthesis. Another important characteristic of the hydrotropic medium is its simple recovery from the reaction mixture and its recyclability. Furthermore, easy recovery of

Table 5

Examples of synthesis for which hydrotropic agents are used

Reaction media	Hydrotropic solution	Substrate	Reference
Octahydro-quinazolinone	50% aqueous sodium *p*-toluene sulfonate	Microwave irradiation	[122]
B-amino carbonyl compounds	50% aqueous sodium *p*-toluene sulphonate	Ultrasound irradiation	[123]
Hautzsch esters	Aqueous sodium butylmono-glycolsulphate	Domestic microwave	[124]
Aza-Micheal reaction	Glycerol	–	[125]

products from hydrotropic solutions makes this protocol an attractive green chemistry approach (see Table 5).

5. The perspectives for hydrotropy

The progress in the studies of hydrotropes has boosted their use in various practical implementations. 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 the challenge, 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 towards enhanced therapeutic delivery of poorly aqueous soluble drugs as well as critical moieties with narrow therapeutic index.

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Дхапте В.В., Мехта П.П. ОБЗОР СОВРЕМЕННЫХ ДОСТИЖЕНИЙ В ИССЛЕДОВАНИИ ГИДРОТРОПНЫХ РАСТВОРОВ.

Около столетия тому назад, в 1916 году, термин «гидротропия» был введен ученым Карлом Нойбергом для наименования солей с органическими анионами, которые значительно повышают растворимость в воде слаборастворимых веществ. В настоящее время гидротропные растворы пользуются большим спросом со стороны промышленности благодаря их уникальным свойствам, таким как доступность, простота утилизации, отсутствие пожароопасности, высокий коэффициент разделения без каких-либо веществ с проблемами эмульгирования, а также экологичность. Настоящий обзор знакомит читателей с кратким описанием, структурными свойствами гидротропных веществ, предположительными механизмами доставки лекарственных средств в организме, а также с подтверждениями этих механизмов. Данный обзор должен создать правильное представление о перспективах лекарственной доставки и гидротропизма.

ГИДРОТРОПИЯ, МЕЗОМАСШТАБНАЯ СОЛЮБИЛИЗАЦИЯ, НОСИТЕЛЬ ЛЕКАРСТВЕННЫХ СРЕДСТВ, «ЗЕЛЕНАЯ ХИМИЯ».

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