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A REVIEW ON EXTRACTION OF HERBAL DRUGS AND THE ENHANCEMENT OF SOLUBILITY BY HYDROTROPY TECHNIQUE

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ABSTRACT

Aqueous solubility of a therapeutically active substance is a key property as it governs dissolution, absorption and thus the therapeutic effects *in-vivo.* Recently more than 40% APIs (Active Pharmaceutical Ingredients) developed in Pharmaceutical Industry are practically insoluble in water. Formulation of poorly soluble compounds for oral delivery now presents one of the interesting challenges to formulation scientists in the pharmaceutical industry. Solubility can be enhanced by many techniques among them hydrotropy is of very much importance which enhance solubility to many folds with use of Hydrotropes like sodium benzoate, sodium citrate, urea, Niacinamide etc. and have many advantages like; it does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system etc. Hydrotropes are promising agents which have the ability to facilitate extraction process by enhancement the solubility. This review focuses the application hydrotropic agent that solubilises hydrophobic drugs especially in case of oral formulation solubility remains a critical factor and their use in extraction of herbal drugs by using hydrotropy Solubilization phenomenon. The main objective of the present review is to explore the possibility of employing a new inexpensive hydrotropic agent, to replace the use of an organic solvent and Hydrotropes such as sodium alkyl benzene sulfonates and sodium butyl monoglycol sulphate were used for the selective extraction of water insoluble phyto-constituents by cell permeabilization. Hence Hydrotropy is new, simple, economic, safe method, can be used in analysis and extraction of herbal drug.

KEYWORDS: *Hydrotropy, Urea, Extraction, Solubility enhancement.*

INTRODUCTON

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Due to advanced research & development, there are varieties of new drugs & their Derivatives are available. But more than 40% of lipophilic drug candidates fail to reach market due to poor bioavailability, even though these drugs might exhibit potential pharmacodynamics activities. Several techniques have been used to solubilize the poorly water-soluble drugs. Hydrotropic solubilization technique is one of them.[1] Hydrotropy is the term originally put forward by Neuberg to describe the increase in the solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids. However, the term has been used in the literature to designate non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Sodium benzoate, sodium salicylate, sodium acetate, sodium ascorbate, Niacinamide, sodium citrate, urea are the most popular examples of hydrotropic agents which have been used to solubilize a large number of poorly water-soluble compounds.[2, 8] The use of sodium benzoate solution (2 M) in place of organic solvents for the purpose of Solubilization to facilitate the titrimetric analysis of the poorly water- soluble NSAIDs, ibuprofen, Flurbiprofen and naproxen.[3, 9]

This technique can be applied for the selective extraction of water insoluble phyto-constituents by cell permeabilization of herbal drugs which have low solubility in aqueous medium without affecting the physicochemical properties of the constituents. These Hydrotropes can prove efficient in the extraction of various resins as well as certain low permeability agents enhance aqueous solubility of different solutes and selective extraction of bioactive compounds on a commercial scale. Product yield achieved with the supercritical fluid extraction can be achieved by using the hydrotropic solution in aqueous solutions. Because the solubility enhancement is insignificant at lower hydrotropic concentrations, simple dilution by water provides an easy recovery method, just as does the release of pressure in supercritical fluid extraction. In future hydrotropy will be the promising way to extract herbal drug without using excess heat and temperature.[4]

Mixed hydrotropy Solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents, which may give miraculous synergistic enhancement effect on solubility of poorly water soluble drugs, utilization of it in the formulation of dosage forms of water insoluble drugs and to reduce concentration of

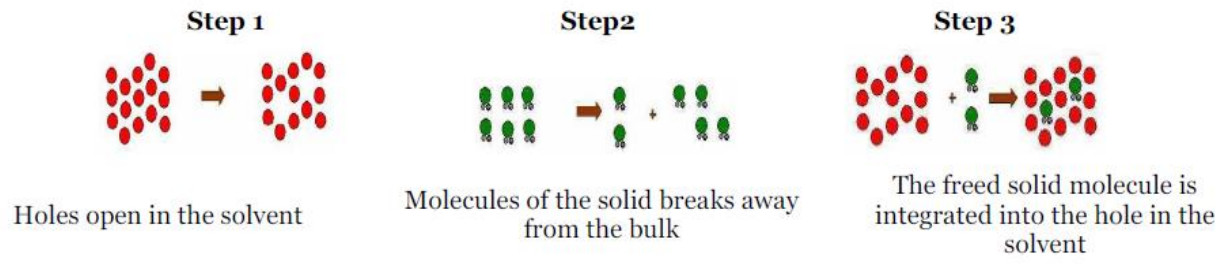
individual hydrotropic agent to minimize the side effects (in place of using a large concentration of one Hydrotropes a blend of, say, 5 Hydrotropes can be employed in 1/5th concentrations reducing their individual toxicities. Veena Nair, Mithun S Rajput were developed a novel, safe and sensitive method of spectrophotometric estimation in the ultraviolet region using a mixed hydrotropic solution, containing a blend of 30% w/v urea, 13.6% w/v sodium acetate and 11.8% w/v sodium citrate for the quantitative determination of ketoprofen, a poorly water soluble drug, in tablet dosage form. Beer's law was obeyed in the concentration range of 4–20 µg/ml. There was more than 570-fold enhancement in aqueous solubility of ketoprofen in mixed hydrotropic solution as compared with the solubility in distilled water precluding the use of organic solvents. Nilesh Jain, Ruchi Jain, Navneet Thakur, Brahm Prakash Gupta, Jitendra Banweer and Surendra Jain were developed Spectrophotometric method using 2 M sodium acetate and 8 M Urea solution as hydrotropic solubilizing agent for the quantitative determination of poorly water-soluble hydrochlorothiazide in tablet dosage form. There were more than 55 and 70 fold enhancements in the solubility of hydrochlorothiazide increases in 2 M sodium acetate and 8 M Urea solution as compared to solubilities in distilled water.

MECHANISM OF HYDROTROPE ACTION

1. A hydrotrope is a compound that solubilize hydrophobic compounds in aqueous

Solutions. Typically, Hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. Hydrotropes do not have a critical concentration above which self aggregation 'suddenly' start to occur.

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.



Instead, some Hydrotropes aggregate in a step-wise self-aggregation process, gradually increasing aggregation size. However, many Hydrotropes do not seem to self-aggregate at all, unless a solubilization has been added.[10, 12]

2. The plant cell wall is made up of phospholipid bilayer. The Hydrotropes destroys the phospholipids bilayer and penetrates through the cell wall into the inner structures. The water soaking shows very less effect on cork cells. The suberin lamella makes the cork cell impermeable to water. But, the Hydrotropes solutions break open the water impermeable suberin lamella and then the mature cork cells. The cork cell layers are disturbed by the Hydrotropes and the aqueous solution penetrates through the cell wall. When the inner part is exposed to the Hydrotropes solution, the cell swells, and frees the cells from closely bound structures. Hydrotropic solutions precipitated the solutes; out of the solution on dilution with water thus enable the ready recovery of the dissolved solutes.[5]

3. Hydrotropic agents can make the O/W and W/O microemulsion and the lamellar liquid crystal destabilized, which results in the „phase transition from lamellar liquid crystal phase to bi-continuous structure this is called as Hydrotrope- solubilization action. Vitamin C shows Hydrotropes-solubilization action.[6]

4. Hydrotropes are known as 'coupling agents'. When Hydrotropes are added to a turbid liquid with relatively high water content causes the liquid to become transparent because of phase transition.[7]

COMMONLY USED HYDROTROPES[8]

The Hydrotropes are known to self-assemble in solution. The classification of Hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, *a*- and *b*naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene. The aromatic Hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective Hydrotropes action may be due to the availability of interactive pi-orbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilisation of compounds. **[13, 14]**

ADVANTAGES OF HYDROTROPIC SOLUBILIZATION TECHNIQUE[15]

1. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, and cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification, It only requires mixing the drug with the Hydrotropes in water.
2. It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs titrimetric and spectrophotometric precluding the use of organic solvents.
3. It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc.
4. It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.
5. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

ADVANTAGES OF MIXED HYDROTROPIC SOLUBILIZATION [16]

1. It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.
2. It is new, simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs titrimetric and spectrophotometric precluding the use of organic solvents.
3. It precludes the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc.
4. Preparation of dry syrups (for reconstitution) of poorly water-soluble drugs.
5. Preparation of topical solutions of poorly water-soluble drugs, precluding the use of organic solvents. Such as tinidazole, metronidazole and salicylic acid using sodium benzoate and sodium citrate.
6. Preparation of injection of poorly water soluble drugs.
7. The use of hydrotropic solubilizers as permeation enhancers.
8. The use of hydrotropy to give fast release of poorly water-soluble drugs from the suppositories.
9. Application of mixed- hydrotropy to develop injection dosage forms of poorly water-soluble drugs.
10. Application of hydrotropic solubilization in nanotechnology (by controlled precipitation).

11. Application of hydrotropic solubilization in extraction of active constituents from crude drugs (in pharmacognosy field).
12. Hydrotropic solutions can also be tried to develop the dissolution fluids to carry out the dissolution studies of dosage forms of poorly water-soluble drugs.

PROBLEMS WITH CONVENTIONAL METHODS OF EXTRACTION [18,19]

1. Continuous hot extraction (Soxhlet Extraction): Continuous solvent extraction of raw material results in the extraction of active as well as other components, such as carbohydrates, gums, and oils. As a result, the solvent extraction processes usually gives complex extract. This has to be then purified by multi step techniques such as chromatography or crystallization. Apart from the poor extract quality, difficulties in handling large volumes of inflammable volatile organic solvents and residual solvent traces remaining in the final product limit the use of organic solvents for extraction.
2. High-pressure steam treatment and supercritical fluid extraction can also enhance extraction rates by using an osmotic shock and carbon dioxide respectively; however, these techniques can be used only for high-value and low-volume materials due to involvement of high cost.
3. Ultrasound treatment ruptures the cell walls through strong dynamic stressing, which results to increase the yield and mass-transfer rate in several solid-liquid extraction processes. The effect of ultrasound is, however, localized, and its application to a large volume of raw material might be inefficient.
4. There are two problems to overcome in the extraction from solid plant materials, releasing the essential oil from solid matrix and letting it diffuse out successfully in a manner that can be scaled-up to industrial volumes. Specifically in the essential oil extraction, microwave mediated processes are highly desirable due to their small equipment size (portability) and controllability through mild increments of heating. However, so far the microwave technology has found a purity of 85% of piperine from black pepper. Hydrotropes were used for the selective extraction of piperine by cell permeabilization of *Piper nigrum* fruits, the recovered piperine was approx.90% pure and substantially free from oleoresins.

USE OF HYDROTROPIC AGENT FOR EXTRACTION OF HERBAL DRUGS

1. Extraction of Embelin from Embelia ribes by Hydrotropes: The research work proposes an alternate strategy of the extraction of Embelin (2,

5-dihydroxy-3-undecyl-p-benzoquinone) from *Embelia ribes*. The aromatic Hydrotropes such as sodium n butyl benzene sulfonates (NaNBBS), and sodium cumene sulfonate (NaCS) were found to be effective for the selective extraction of embelin with a recovery of 95% Embelin from the aqueous solution of hydrotropes with high purity.[16]

2. Extraction of Piperine from *Piper nigrum* (Black Pepper) by Hydrotropic Solubilization: Hydrotropes, such as sodium alkyl benzene sulfonates and sodium butyl monoglycol sulfate, were used for the selective extraction of piperine by cell permeabilization of *Piper nigrum*fruits. Penetration of the hydrotrope molecules into the cellular structures and subsequent cell permeabilization were hypothesized to explain the enhanced extraction rates of aqueous Hydrotropes solutions.[17]
3. Extraction of dioscin from dioscorea rhizomes by Hydrotropes: Aqueous solutions of aromatic Hydrotropes were investigated for cell permeabilization and extraction of dioscin from dioscorea rhizomes. Sodium cumene sulfonate was the most efficient Hydrotropes for the extraction of dioscin, also for its hydrolysis to diosgenin at 353 K.
4. Extraction of Curcumin by Hydrotropes: Curcuminoids are present in the oleoresin cells, which are present in the cortex. Na+ salt of following hydrotropes have greater ability for extraction of curcuminoids from *Curcuma longa*; Butyl mono glycol sulfate>Salicylate>cumene sulfoante.[20]
5. Extraction of bioactive limonoid aglycones and glucoside from Citrus aurantium L. using hydrotropy: Citrus limonoids were demonstrated to possess potential biological activities in reducing the risk of certain diseases.[21]
6. Hydrotropic Extraction Process for Recovery of Forskolin from *ColeusForskohlii* Roots: A simple and rapid method based on hydrotropic solubilization is developed for isolation of forskolin from *coleus forskolin* roots. The plant cells are permeabilized by aqueous hydrotrope solutions followed by extraction and solubilization of forskolin into the hydrotrope solutions of alkyl benzene sulfonates and carboxylates. The solubility of forskolin is increased by 350 times in the hydrotropic solutions and it is possible to recover 85% pure forskolin from the hydrotropic solutions by simple dilution with water.
7. Hydrotropic extraction of bioactive limonin from sour orange (*Citrusaurantium* L.) seeds: Limonoid are potential bioactive compounds present only in citrus among fruits and vegetables. A new process for extraction of limonoid aglycones from sour orange (*Citrus aurantium* L.) seeds was investigated using aqueous hydrotropic solutions; two hydrotropes such as sodium salicylate (Na-Sal) and sodium cumene sulphonate (Na-CuS)

were studied using Box-Behnken experiment design. Response surface analysis (RSA) of data was performed to study the effect of parameters on extraction efficiency.[21]

The above cited examples have shown that they can be used in the extraction of various herbal drugs. This technique can be applied in the extraction of such herbal drugs which have low solubility in aqueous medium. Such extracts can be prepared by addition of Hydrotropes without affecting the physicochemical properties of the constituents. These Hydrotropes can prove efficient in the extraction of various resins as well as certain low permeability agents. This review focuses the application hydrotropic agent in herbal drug extraction technology and its scope in pharmaceutical research and development. The main objective of the present review is to explore the possibility of employing a new inexpensive hydrotropic agent, to replace the use of an organic solvent.

Novel Pharmaceutical Applications of Hydrotropic Solubilization in various fields of Pharmacy [22]

1. Preparation of dry syrups (for reconstitution) of poorly water-soluble drugs.
2. Quantitative estimations of poorly water soluble drugs by UV-Visible spectrophotometric analysis precluding the use of organic solvents.
3. Quantitative estimations of poorly water soluble drugs by titrimetric analysis. Such as ibuprofen, Flurbiprofen and naproxen using sodium benzoate.
4. The use of hydrotropy to give fast release of poorly water-soluble drugs from the suppositories.
5. Preparation of hydrotropic solid dispersions of poorly water-soluble drugs precluding the use of organic solvents. Such as felodipine using polyethylene glycol 6000 and poly-vinyl alcohol.
6. Preparation of topical solutions of poorly water-soluble drugs, precluding the use of organic solvents. Such as tinidazole, metronidazole and salicylic acid using sodium benzoate and sodium citrate. The use of hydrotropy to give fast release of poorly water-soluble drugs from the suppositories.
7. Application of mixed- hydrotropy to develop injection dosage forms of poorly water-soluble drugs.
8. Hydrotropic solutions can also be tried to develop the dissolution fluids to carry out the dissolution studies of dosage forms of poorly water-soluble drugs.
9. The use of hydrotropic solubilizers as permeation enhancers.
10. Preparation of injection of poorly water soluble drugs.

11. Application of hydrotropic solubilisation in nanotechnology (by controlled precipitation).
12. Application of hydrotropic solubilisation in extraction of active constituents from crude drugs (in pharmacognosy field).

CONCLUSION

Hydrotropes are amphiphilic in nature i.e. composed of hydrophilic as well as lipophilic portions. These molecules are generally used as solubility enhancer (solubilizes). By this article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. This technique described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility.

Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of hydrotropy technique as mentioned above.

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