International Research Journal of Pharmaceutical and Applied Sciences
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2012; 2(1):63-74

IRJPAS **ISSN-2277-4149**

Review Article

EXTRACTION OF HERBAL DRUGS BY USING HYDROTROPY SOLUBLIZATION PHENOMENON

Ankit Mangal[1]*, Sandeep Singh Bhadoriya[1], Sorabh Joshi[2], Gaurav Agrawal[3], Amit Gupta[3], Narendra Mandoria[4]

[1]Vikrant Institute of Pharmacy, Indore, [2]Cipla Pvt.Ltd. Indore, [3]R.M.S. College of Pharmacy, Bhanpura, [4]Vikram University, Ujjain, (M.P), India

(Received: 16 Feb, 2012; Accepted: 20 Feb, 2012; Published: 29 Feb, 2012)

*Corresponding author's email: ankitmangal@vitmindore.com

ABSTRACT

Extraction of the herbal drugs has always been a challenging task for the researchers. In this present review, an attempt has been made to give an overview of extraction of herbal drugs by using hydrotropy solublization phenomenon. A hydrotrope is an organic substance that increases the solubility of surfactants and water insoluble phyto-constituents of herbal drugs such as esters, acids, alcohols, aldehydes, ketones, hydrocarbons, and fats in an aqueous solution. Hydrotropes, such as sodium alkyl benzene sulfonates and sodium butyl monoglycol sulfate, were used for the selective extraction of water insoluble phyto-constituents by cell permeabilization.

KEY WORDS: Extraction, Hydrotropy, Herbal drugs.

INTRODUCTION

Plant-derived substances have recently become of great interest owing to their versatile applications. Medicinal plants are the richest bio-resource of drugs of traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates and chemical entities for synthetic drugs [1].

Extraction (as the term is pharmaceutically used) is the separation of medicinally active portions of plant (and animal) tissues using selective solvents through standard procedures. The products so obtained from plants are relatively complex mixtures of metabolites, in liquid or semisolid state or (after removing the solvent) in dry powder form, and are intended for oral or external use. These include classes of preparations known as decoctions, infusions, fluid extracts, tinctures, pilular (semisolid) extracts or powdered extracts. Such preparations have been popularly called galenicals, named after Galen, the second century Greek physician [2].

Extraction of phytoconstituents from the plant material is the first step in the phytochemical process. Extraction of phytoconstituents is dependent on the solubility as well as the surface permeability of the solvent. Many times certain phytoconstituents are not extracted in the normal extraction process due to solubility factor. As a result 100% extraction is not achieved. To counter this problem various techniques have been used time and again. Super critical fluid extraction is one such process which helps to counter many of the problems, but it has certain drawbacks as automation, feasibility and cost factor. A novel approach to overcome all these problems is the use of Hydrotropes [3]

The term hydrotropic agent was first introduced by Neuberg (1916) to designate anionic organic salts which, at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes[4]. However, the term has been used in the literature to designate nonmicelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Hydrotropic solubilization process involves cooperative intermolecular interaction with several balancing molecular forces, rather than either a specific complexation event or a process dominated by a medium effect, such as co-solvency or salting-in. Hydrotropic agents have been observed to enhance the aqueous solubility of poorly water-soluble drugs. [5-24]

Hydrotropes, such as sodium alkyl benzene sulfonates and sodium butyl monoglycol sulfate, were used for the selective extraction of water insoluble or non polar phyto-constituents by cell permeabilization. Some other hydrotropes are sodium benzene sulfonate, sodium toluene sulfonate, sodium xylene sulfonate (SXS), sodium cumene sulfonate, sodium cymene sulfonate.

The self aggregation of the hydrotropes has been considered to be a pre-requisite for a number of applications in various fields such as drug solubilization [25], chemical reactions [26], separation of organic compounds[27], extraction of curcuminoids from turmeric [28] extraction of embelin from *Embelica ribes* [29], Piperine from *Piper nigrum* [30, 31] and Boswellic acids from *Boswellia serrata* resins [32], Diosgenin from *Dioscorea* Rhizomes [33].

Mechanism of Action

1. The plant cell wall is made up of phospholipid bilayer. The hydrotrope destroys the phospholipid bilayer and penetrates through the cell wall into the inner structures. The water soaking shows very less effect on cork cells. The cellulose and suberin lamella are the cell wall component of cork cells. The suberin lamella makes the cork cell impermeable to water. But, the hydrotrope solutions break open the water impermeable suberin lamella and then the mature cork cells. The cork cell layers are disturbed by the hydrotrope and the aqueous solution penetrates through the cell wall. When the inner part is exposed to the hydrotrope 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 [34].

2. 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 hydrotrope-solubilization action [35, 36]

3. 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' [37].

Choice of solvents for conventional Methods

Successful determination of biologically active compounds from plant material is largely dependent on the type of solvent used in the extraction procedure. Properties of a good solvent in plant extractions includes, low toxicity, ease of evaporation at low heat, promotion of rapid physiologic absorption of the extract, preservative action, inability to cause the extract to complex or dissociate. The factors affecting the choice of solvent are quantity of phyto-chemicals to be extracted, rate of extraction, diversity of different compounds extracted, diversity of inhibitory compounds extracted, ease of subsequent handling of the extracts, toxicity of the solvent in the bioassay process, potential health hazard of the extractants [38]. The choice of solvent is influenced by what is intended with the extract. Since the end product will contain traces of residual solvent, the solvent should be non-toxic and should not interfere with the bioassay. The choice will also depend on the targeted compounds to be extracted[39].

The various solvents that are used in the extraction procedures are [40]:

1. Water
2. Acetone
3. Alcohol
4. Chloroform
5. Ether
6. Dichloromethanol

Problems with conventional Methods of Extraction:

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[41].

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 [42].

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 sulfonate (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. The process was further optimized with respect to concentration of hydrotropes and temperature of extraction[43].

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 hydrotrope solutions. Hydrotrope molecules, after adsorption on a cell wall, cause disorder in its structure and in the bilayered cell membrane to facilitate the rapid extraction of piperine. The hydrotrope solution showed selective and rapid extraction of piperine from black pepper. The recovered piperine was ~ 90% pure and substantially free from oleoresins. The type and nature of the hydrotrope, the hydrotrope concentration, the temperature, and the particle size all had significant effects on the extraction process[44].

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. The extracted dioscin was further hydrolyzed in the same hydrotropic solutions to diosgenin without significant decomposition to 3,5-diene, unlike in the conventional process. The parameters affecting the extraction of dioscin, such as the nature and concentration of the hydrotrope, the temperature, and the particle size, was optimized. Sodium cumene sulfonate was the most efficient hydrotrope for the extraction of dioscin and also for its hydrolysis to diosgenin at 353 K. Diosgenin precipitates from aqueous NaCS solutions with >95% purity at 293 K because of its poor solubility in aqueous solutions[45].

4. Extraction of Curcumin by Hydrotropes: Curcuminoids are present in the oleoresin cells, which are present in the cortex. The cork cells covering cortex are composed of inner and outer cellulose layers and a median suberin lamella. The mature cork cell is dead and impermeable to water. In the hydrotropic extraction of turmeric, rhizomes were pulverized to obtain certain mesh size powder. In the process the outer covering of epidermis, hypodermis and cork cells gets disturbed and the oleoresin cells containing curcuminoids can be directly exposed to hydrotrope solution. The hydrotrope action on cork cells need to be monitored by microscopic studies of several sections of rhizomes. The inner part was also exposed directly to aqueous hydrotrope solutions to monitor the hydrotrope effect on the oleoresin cells. Na+ salt of following hydrotropes have greater ability for extraction of curcuminoids from *Curcuma longa*; Butyl mono glycol sulfate>Salicylate>cumene sulfoante[46].

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. Limonoids are present in citrus fruits in the form of aglycones and glucosides. At present, limonoid aglycones and limonoid glucosides are extracted in multiple steps using different solvents. In order to understand their potential bioactivity, it may be beneficial to isolate and purify these compounds using environment friendly methods. A new method of extraction and purification of limonoids was established using a hydrotrope polystyrene adsorbent resin. Extraction of aglycones and glucosides was achieved in

a single step, using an aqueous solution of sodium cumene sulphonate (Na-CuS). Sour orange (Citrus aurantium L.) seed powder was extracted with 2 M Na-CuS solution at 45 degrees C for 6 h. The filtered extract was diluted with water and loaded on an SP 700 adsorbent column. The column was washed with distilled water to remove the hydrotrope and then eluted using water and methanol in different compositions to obtain three compounds. The structures of the isolated compounds were confirmed by NMR spectroscopy as deacetyl nomilinic acid glucoside (DNAG), deacetyl nomilin (DAN) and limonin (LIM).

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 forskohlii* 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. The purity of the recovered forskolin decreased from 85% to 70% on decreasing particle size of the roots. Nearly 80% of the forskolin having 50% purity was recovered from the coleus roots using 2.0 mol/dm^3 aqueous sodium cumene sulfonate (Na−CS) solutions at 363 K. Na−CS showed the most efficient solubilization of forskolin from the *Coleus* roots among all the other hydrotropes.

7. Hydrotropic extraction of bioactive limonin from sour orange (*Citrusaurantium* L.) seeds: Limonoids 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. The extraction efficiency was dependent on hydrotrope concentration, extraction temperature and percent of raw material loaded. 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. Prominent limonoid aglycone such as limonin was extracted and quantified for process optimization. Both hydrotropes gave maximum limonin yield at 2 M

concentration, extraction temperature of 45 °C and 10% solid loading. A maximum limonin yield of 0.65 mg/g seeds was obtained using Na-CuS whereas only 0.46 mg/g seed was obtained using Na-Sal. Using this process, the use of organic solvents can be reduced dramatically to keep the process environmental friendly for the extraction of bioactive compounds.

DISCUSSION

Hydrotropes are promising agents which have the ability to facilitate extraction process by enhancement the solublity. 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.

CONCLUSION

Hydrotropic extraction shows tremendous potential to (a) undergo specific interactions with amphiphile, (b) modify mixing behavior of oil and water, (c) self-associate in water (d) 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 hydrotrope solution in aqueous solutions. Because the solubility enhancement is insignificant at lower hydrotrope 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.

ACKNOWLEDGEMENT

Authors are grateful to Vikrant Institute of Pharmacy, Indore, Cipla Pvt.Ltd. Indore, Vikram University, Ujjain. R.M.S College of Pharmacy, Bhanpura.

REFERENCES

1. Ncube NS, Afolayan AJ, Okoh AI. Assessment techniques of antimicrobial properties of natural compounds of plant origin: current methods and future trends. African

Journal of Biotechnology **2008**; 7 (12): 1797-1806.

2. Remington JP. Remington: The science and practice of pharmacy, 21st edition, Lippincott Williams & Wilkins, 773-774.
3. P. P. Dongre, D. M. Kannur, V. Kosambiya, B. D. Desai. Significant Role of Hydrotropes in Extraction of Phytoconstituents- A Review, *IJPSR*, **2011**; 2(4): 730-734.
4. Neuberg, C. Hydrotropy. *Biochem. Z* **1916**; 76: 107-109.
5. Maheshwari RK. New application of hydrotropic solublization in the spectrophotometric estimation of ketoprofen in tablet dosage form. *Pharma Review* **2005**; 3: 123-5.
6. Maheshwari RK. A novel application of hydrotropic solublization in the analysis of bulksamples of ketoprofen and salicylic acid. *Asian J. Chem*. **2006**;18: 393-6.
7. Maheshwari RK. Novel application of hydrotropic solubilization in the spectrophotometric analysis of tinidazole in dosage form. *Asian J. Chem.* **2006**; 18: 640-4.
8. Maheshwari RK. Application of hydrotropic solubilization in the analysis of aceclofenac. *Asian J. Chem.* **2006**; 18: 1572-4.
9. Maheshwari RK. Novel application of hydrotropic solubilization in the spectrophotometric analysis of piroxicam in solid dosage form. *Indian Drugs* **2006**; 8: 683-5.
10. Maheshwari RK. A novel application of hydrotropic solubilization in the spectrophotometric estimation of frusemide in tablets. *Pharma Review* **2006**; 4: 148-9.
11. Maheshwari RK. Application of hydrotropic solubilization phenomenon in spectrophotometric estimation of norfloxacin in tablets. *Indian J. Pharm. Edu. Res.* **2006**; 40: 237-240.
12. Maheshwari RK, Chaturvedi SC and Jain NK. Application of hydrotropic solubilization phenomenon in spectrophotometric analysis of hydrochlorothiazide tablets. *Indian drugs* **2005**; 42: 541-4.
13. Maheshwari RK, Chaturvedi SC and Jain NK. Titrimetric analysis of aceclofenac in tablets using hydrotropic solubilization technique. *Indian Drugs* **2006**; 43: 516-8.
14. Maheshwari RK and Bisnoi SR. Spectrophotometric analysis of hydrochlorothiazide tablets using chlorpheniramine maleate as hydrotropic solubilizing agent. *Asian J. Chem.* **2008**; 8: 6594-6.

15. Maheshwari RK, Deswal S, Tiwari D, Ali N and Jain S. Quantitative analysis of hydrochlorothiazide tablets using lignocaine hydrochloride as hydrotropic agent. *Asian J. Chem.* **2009**; 2: 1642-4.
16. Maheshwari RK, Arif D, Mittal P, Manchandani P, Indurkhya A and Jawade S. A novel method for quantitative determination of aceclofenac in bulk drug and tablets using ibuprofen sodium as a hydrotropic solubilizing agent. *J. Appl. Chem. Res.* **2008**; 5: 63-8.
17. Poochikian GK and Cradock JC. Enhanced chartreusin solubility by hydroxybenzoate hydrotropy. *J. Pharm. Sci.* **1979**; 68: 728-32.
18. Darwish A, Florence AT and Saleh AM. Effects of hydrotropic agents on the solubility, precipitation and protein binding of etoposide. *J. Pharm. Sci.* **1989**; 78: 577-81.
19. Etman MA, Salama RO, Shamsedeen MA and El-Kamel A. Solubilization of etodolac for parenteral administration. *Indian J. Pharm. Sci.* **2001**; 63: 459-67.
20. Rasool AA, Hussain AA and Dittert LW. Solubility enhancement of some waterinsoluble drugs in the presence of nicotinamide and related compounds. *J. Pharm. Sci.* **1991**; 80: 387- 93.
21. Jain NK, Agrawal RK and Singhai AK. Formulation of aqueous injection of carbamazepine. *Pharmazie* **1990**; 45: 221-5.
22. Shah SP and Flanagan DR. Solubilization of salicylamide and acetaminophen by antihistamines in aqueous solution. *J. Pharm. Sci*. **1990**; 79: 889-92.
23. Suzki H and Sunada H. Mechanistic studies on hydrotropic solubilization of nifedipine in nicotinamide solution. *Chem. Pharm. Bull*. **1998**;46: 125-30.
24. Maheshwari RK. Mixed hydrotropy in spectrophotometric analysis of poorly watersoluble drug. *Indian Pharmacist* **2007**; 6: 66-7.
25. Meghal Desai and Jigisha Parikh: Thermodynamic Study for Aggregation Behavior of Hydrotropic Solution. World Academy of Science, Engineering and Technology 57: **2009**; 227-229.
26. Lee, J., Lee, S. C., Acharya, G., Chang, C. and Park, K: Hydrotropic solubilization of paclitaxel analysis of chemical structures for hydrotropic property. *Pharm. Res.*, **2003** 20(7):; 1022-1030.
27. B. M. Khadilkar, V. G. Gaikar and A. A. Chitnavis: Aqueous hydrotrope solution as a safer medium for microwave enhanced hantzsch

dihydropyridine ester synthesis. *H Tetrahedron Lett.* **1995** 36(44):; 8083-8086.

28. D. V. Dandekar and V. G. Gaikar: Hydrotropic extraction of curcuminoids from turmeric. Sep. *Sci. Technol.*, **2003**; 38(5):185-1215.
29. C. Latha: Selective Extraction of Embelin from *Embelia ribes* by Hydrotropes. Separation *Science and Technology* **2006** 41(16); 3721 – 3729.
30. G. Raman and V. G. Gaikar: Extraction of piperine from *Piper nigrum* (black pepper) by hydrotropic solubilization. *Ind. Eng.Chem. Res.*, **2002**; 41(12): 2966-2976.
31. “Extraction of organic constituents from solids” **1987**; German Patent DE 3, 706594.
32. Raman Girija, Gaikar Vilas: Hydrotropic solubilization of boswellic acids from *Boswellia serrata* resin. *American Chemical Society* **2003**; 19: 8026-8032.
33. Sanjay P. Mishra and Vilas G. Gaikar: Recovery of Diosgenin from Dioscorea Rhizomes Using Aqueous Hydrotropic Solutions of Sodium Cumene Sulfonate. *Ind. Eng. Chem. Res*, **2004**; 43 (17): 5339-5346.
34. Trease and Evanse: Pharmacognosy. Rajkamal Electric press Delhi 526 15th edition **2005.**
35. Rong Guo, Qiqing Zhang, Junhong Qian, Aihua Zou “Hydrotrope and hydrotrope-solubilization action of penicillin-K in CTAB/n-C5H11OH/H2O system. *Physicochemical and Engineering Aspects*; **2002** 196: 223–234.
36. Lachman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy, 3, Verghese Publishing, New Delhi, 462-426 Indian edition **1987**.
37. Stig E Friberg: Hydrotropes. *Current Opinion in Colloid & Interface Science*, **1997** 2:490-494.
38. Eloff JN. Which extractant should be used for the screening and isolation of antimicrobial components from plants. *Journal of Ethnopharmacology* **1998**; 60: 1–8.
39. Das K, Tiwari RKS, Shrivastava DK. Techniques for evaluation of medicinal plant products as antimicrobial agent: Current methods and future trends. *Journal of Medicinal Plants Research* **2010**; 4(2): 104-111.
40. Prashant Tiwari, Bimlesh Kumar, Mandeep Kaur, Gurpreet Kaur, Harleen Kaur. Phytochemical screening and Extraction: A Review. *International Pharmaceutica Sciencia*, **2011**,1(1);96-106.
41. S.S.Agrawal M. Paridhavi: Herbal Drug technology. Universities press Hyderabad; 327. Fist Edition **2007**.

42. Girija Raman and Vilas G. Gaikar : Microwave-Assisted Extraction of Piperine from *Piper nigrum*. *Ind. Eng. Chem. Res.* **2002**, 41 (10): 2521–2528.
43. Qin, W., Tao, Z., Younhui, Y. Youyuan, D. Intensification of Curcumin Leaching with Ultrasound. Value Adding, Solvent **1996** Extr. 1679-1684.
44. Dandekar DV, Jayaprakasha GK, Patil BS. Simultaneous extraction of bioactive limonoid aglycones and glucoside from Citrus aurantium L. using hydrotropy. *Z Naturforsch C.* **2008** Mar-Apr; 63(3-4):176-80.
45. Sanjay P. Mishra and Vilas G. Gaikar., Hydrotropic Extraction Process for Recovery of Forskolin from *Coleus Forskohlii* Roots., *Ind. Eng. Chem. Res.*, **2009**, *48* (17);8083–8090.
46. Deepak V. Dandekar, G.K. Jayaprakasha, Bhimanagouda S. Patil.,Hydrotropic extraction of bioactive limonin from sour orange (*Citrusaurantium* L.) seeds, *Food Chemistry* **2008**, 109(3); 515-520.