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Hydrotropic Solubilization: Tool for Eco-Friendly Analysis

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Deepak Ghogare*, Sheetal Patil

Department of Quality Assurance Technique, Alard College of pharmacy, Pune (MH), India 411057

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ABSTRACT

In an analysis of drug by various methods solvent play major in every step. Solvent selection effect on the accuracy, sensitivity, cost, result of the method. Selection of solvent governing by the solubility of the drug. Many of the drug listed in pharmacopeia and new chemical entity are poorly water soluble. Analysis of poorly water-soluble drugs most frequently used the organic solvent like methanol, ethanol, chloroform, acetonitrile, hexane. Most of them toxic in nature. They may also source pollution and costlier. Volatile nature major source of inaccuracy. Hydrotropic solubilization technique is the best approach to increase the water solubility of poorly water-soluble drugs and overcome problem-related with organic solvents. This review investigates feature of hydrotropy and hydrotropic agent and their different advance toward pharmaceutical analysis. This review also provides the future prospective concerned with the green pharmaceutical analysis.

INTRODUCTION:

When we see the Indian Pharmacopeia and US Pharmacopeia more than one-third of the drugs listed that fall into the poorly water-soluble or water-insoluble categories. It was also reported that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility. Most of the newly developed drug molecules are lipophilic in nature and poor solubility is one of the most difficult problems of these drugs. Drug analysis in pure or final product also important step. Various organic solvents such as methanol, chloroform, dimethylformamide and acetonitrile have been employed for solubilization of poorly water-soluble drugs to carry out analysis of poorly water-soluble drugs. The drawback of these organic solvents includes high cost, volatility, pollution and toxicity such as nephrotoxicity or teratogenicity, organic solvents are harmful if swallowed, inhaled or absorbed through the skin. also, as per I.C.H guideline Q_3 CR_3 (impurities guideline for residual solvents), these solvents come under the category of Class 2 solvent i.e solvents which are in limited use. So, there is an urgent need to replace organic solvent with safe eco-friendly, cost-effective solvent for spectrophotometric analysis. Hydrotropic solubilization concept may be a proper choice to preclude the use of organic solvents. Many analytical methods based on hydrotropic solubilization are available in literature and this review focus on the application of hydrotropic solubilization in the analysis of poorly soluble drug.

SOLUBILITY

The solubility, in quantitative terms, is defined as the concentration of the solute in a saturated solution at a certain temperature, and in qualitative terms is defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. The solubility of the drug may be expressed as parts, percentage, molarity, molality, volume fraction and mole fraction. A poorly water-soluble drug (poorly soluble drug) refers to a practically insoluble drug in the U.S. Pharmacopoeia & is defined as a drug having a water solubility of less than 0.1 mg/ml, its oral absorption is usually poor or at least inconsistent. [1, 2]

The pharmacopeia lists solubility in terms of a number of milliliters of solvent required to dissolve 1g of solute. If exact solubilities are not known, the Pharmacopoeia provides general terms to describe a given range. These descriptive terms are listed in Table 1.

Table 1: Expression for approximate solubility[3]

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

METHODS TO ENHANCE THE SOLUBILITY OF DRUG

In pharmaceutical field, it is often required to prepare aqueous solutions of a variety of insoluble drugs. Special techniques are required to solubilize poorly water soluble and water insoluble drugs. Following approaches can be employed to enhance the aqueous solubility of a drug solute.[4,5]

1. Micronization
2. Nanonization
3. Supercritical fluid recrystallization
4. Spray freezing into liquid and lyophilization
5. Evaporative precipitation into aqueous solution
6. Use of surfactants
7. Use of salt forms
8. Use of precipitation inhibitors
9. Alteration of PH of drug
10. Solvent deposition
11. Solid dispersion

12. Eutectic mixture

13. Hydrotropic solubilization

The approaches mentioned in points 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 have been used widely in various fields of pharmacy. However, applications of hydrotropic solubilization have not been explored to appreciable extent in various fields of pharmacy.

HYDROTROPY SOLUBILIZATION

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. Hydrotropy is a solubilization phenomenon whereby addition of a large amount of the second solute results in an increase in the aqueous solubility of another solute. 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. The chemical structure of the conventional Neuberg's hydrotropic salts (proto-type, sodium benzoate) consists generally of two essential parts, an anionic group and a hydrophobic aromatic ring or ring system. The anionic group is obviously involved in bringing about high aqueous solubility, which is a prerequisite for a hydrotropic substance. The type of anion or metal ion appeared to have a minor effect on the phenomenon. On the other hand, the planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to **"salt in"** the solute and those salts that decrease solubility **"salt out"** the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called **"hydrotropic salts"** a phenomenon known as "hydrotropism". Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute.[5]

COMMONLY USED HYDROTROPES

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 behavior. 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 sulfate) 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 the cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of compounds.[6]

MECHANISM OF HYDROTROPE ACTION

The mechanism by which the hydrotropic effect occurs is not clear. Some workers have speculated that hydrotropy is simply another type of solubilization, with the solute dissolved in oriented clusters of the hydrotropic agents. Hydrotropic solutions do not show colloidal properties. however, others feel that this phenomenon is more closely related to complexation involving a weak interaction between the hydrotropic agent and the solute. Still other reason that the phenomenon must be due to a change in solvent character because of a large amount of additive needed to bring about the increase in solubility.

A hydrotrope is a compound that solubilizes 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' starts to occur. 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 solubilisate has been added.[5]

CHARACTERISTICS OF HYDROTROPES

1. Completely soluble in water and practically insoluble in the system.

2. Hydrotropes are surface active and aggregate in aqueous solution because of their amphiphilic structure.

3. Should not produce any temperature when dissolved in water.

4. Cheap and easy availability.

5. Nontoxic and non-reactive.

6. Insensitive to temperature effects, when dissolved in water.

7. The solvent character being independent of pH, high selectivity, and the absence of emulsification are the other unique advantages of the hydrotrope.

FEATURES OF HYDROTROPES

1. Unprecedented solubilization increase

2. Very high selectivity

3. Easy recovery of solute from a solution.

4. Economical and cost effective.

5. The absence of emulsion.

6. The absence of hazards present in other solvents used in extractive separation.

ADVANTAGES OF HYDROTROPIC SOLUBILIZATION

1. Hydrotropy is suggested to be superior to other solubilization methods, such as miscibility, micellar solubilization, co-solvency and salting in, because the solvent character is independent of PH, has high selectivity and does not require emulsification.

2. It only requires mixing the drug with the hydrotrope in water.

3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

MIXED HYDROTROPIC SOLUBILIZATION

Mixed hydrotropic 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 hydrotrope a blend of, say, 5 hydrotropes can be employed in 1/5th concentrations reducing their individual toxicities.[5]

ADVANTAGES OF MIXED HYDROTROPIC SOLUBILIZATION

1. It may reduce the large total concentration of hydrotropic agents necessary to produce the modest increase in solubility by employing a combination of agents in lower concentration.

2. It is new, simple, cost-effective, safe, accurate, precise and environmentally friendly method for the analysis (titrimetric, spectrophotometric, chromatographic) 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.

Each hydrotropic agent is effective in increasing the water solubility of selected hydrophobic drugs. No universal hydrotropic agent has been found effective to solubilize all hydrophobic drugs. Thus, finding the right hydrotropic agent for a poorly water-soluble drug requires screening of a large number of candidate hydrotropes.However, once the effective hydrotropic agent is identified for a series of structurally different drugs, the structure-activity relationship can be established.[5]

Agrawal et al. investigated the effect of various hydrotropes such as sodium benzoate, sodium salicylate and Piperazine on the solubility of Nimesulide. The solubility enhancement of Nimesulide by the hydrotropes observed in decreasing order as piperazine>sodium ascorbate> sodium salicylate> sodium benzoate> nicotinamide. Parenteral formulations using piperazine as a hydrotrope were developed and studied for physical and chemical stability.[10]

PHARMACEUTICAL APPLICATION OF HYDROTROPY SOLUBILIZATION

Table 2: Application of hydrotropy in the various pharmacy field

Sr. No.	Pharmacy field	Hydrotropy application in
1	Pharmaceutics	formulation of Solid Dispersion
		formulation of Topical preparation
		formulation of Transdermal patch
		formulation of Parenteral preparation
		formulation of Suppositories
		Preparation of Nanotechnology
2	Pharmaceutical analysis	Spectrophotometric analysis
		Titrimetric analysis
		Thin layer chromatography
3	Pharmacognosy	Extraction of an active constituent
4	Pharmaceutical chemistry	Separation of mixture
		Green synthesis

APPLICATION OF HYDROTROPIC SOLUBILIZATION IN PHARMACEUTICAL ANALYSIS

Analytical method development and validation are the continuous and interdependent task associated with the research and development, quality control and quality assurance department. In the development of analytical method selection of solvent is critical step. Selected solvent should not be interfering in the analysis of drug. Most frequently organic solvents are used to solubilize drug. In the different analytical method, we can use hydrotropic solubilization technique for increase water solubility of poorly water-soluble drug to rule out the use of organic solvent due to their side effects.[9]

TITRIMETRIC ANALYSIS

IP and BP titrimetric analysis for bulk drug basically carried out using ethanol, methanol, propylene, chloroform, etc. To rule out the use of organic solvents we can employ titrimetric analysis using hydrotropic aqueous solution for bulk drug analysis. The hydrotropic agent used in the titrimetric analysis are listed in following table 3,

Table 3: Examples of titrimetric analysis for which hydrotropic agents are used

SR NO	TOPIC NAME	JOURNAL NAME	YEAR OF PUBLICATION
1	Quantitative analysis of salbutamol bulk sample using nicotinamide hydrotrope. (11)	International Journal Pharmaceutical Science Research	2012
2	Quantitative analysis of famotidine bulk sample using sodium salicylate hydrotrope. (12)	International Journal of Pharmaceutical and Life Science	2012
3	Titrimetric analysis of ketoprofen in the bulk drug sample using sodium citrate as a hydrotropic agent. (13)	International Journal of Pharma and Biosciences	2013
4	Titrimetric analysis of ibuprofen bulk drug sample by using urea as a hydrotropic solubilizing agent. (14)	International Journal of Current Pharmaceutical Journal	2015
5	Quantitative analysis of salicylic acid bulk sample using hydrotropic solubilizing agent. (15)	Asian Journal of Pharmaceutical Clinical Research	2016

SPECTROPHOTOMETRIC ANALYSIS

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. Some of them toxic. Volatile nature is major problem cause error in result. To rule out such difficulties, hydrotropic solutions were used. Spectrophotometric estimations using hydrotropic agent are listed in following Table 4.

Table 4: Examples of spectrophotometric estimations for which hydrotropic agents are used

Sr. No.	Topic name	Journal name	Year of publication
1	Novel spectrophotometric estimation of some poorly water-soluble drugs using hydrotropic solubilizing agents. (16)	Indian Journal of Pharmaceutical Science.	2006
2	Eco-friendly spectrophotometric estimation of atenolol tablets using metformin hydrochloride as hydrotropic solubilizing agent. (17)	Indian J Pharm Sci.	2010
3	Role of different hydrotropic agents in spectrophotometric and Chromatographic estimation of cefixime. (18)	Asian Journal of Pharmaceutical and Clinical Research.	2010
4	Quantitative spectrophotometric determination of cefixime tablet formulation using Sodium tartrate as hydrotropic solubilizing agent. (19)	International Journal of Pharmacy & Technology.	2010
5	Spectrophotometric quantification of Etoricoxib in bulk drug and tablets using hydrotropic agent. (20)	Pharmacophore.	2010
6	Spectrophotometric Estimation of Fluvoxamine Maleate in Tablets Using Hydrotropic Agent. (21)	International Journal of Pharmaceutical Quality Assurance.	2010
7	Application of mixed hydrotropic solubilization concept in spectrophotometric analysis of frusemide in tablet dosage form. (22)	The Pharma Research.	2010
8	Novel spectrophotometric quantitative estimation of hydrochlorothiazide in bulk drug and their dosage forms by using hydrotropic agent. (23)	International Journal of Applied Pharmaceutics.	2010
9	New spectrophotometric determination of Hydrochlorothiazide in tablets Using Mixed Hydrotropic Solubilization Technique. (24)	India Der Pharmacia Lettre.	2010
10	Application of hydrotropic solubilization phenomenon in spectrophotometric estimation of levofloxacin in tablet dosage. (25)	International Journal of ChemTech Research.	2010
11	Spectrophotometric determination of naproxen tablets using niacinamide as hydrotropic solubilizing additive. (26)	Journal of Current Pharmaceutical Research.	2010
12	New spectroscopic determination of	International Journal of	

	nifedipine using hydrotropic Solubilization. [27]	Pharmacy and Pharmaceutical Sciences.	2010
13	Simultaneous Spectrophotometric Estimation of Paracetamol and Aceclofenac in Combined Tablet Formulations using Hydrotropic Solubilization Technique. [28]	International Journal of Chemical and Analytical Science.	2010
14	A novel application of hydrotropic solubilization in Development and validation of spectrophotometric method for Simultaneous estimation of paracetamol and diclofenac. [29]	International Journal of Pharma and BioSciences.	2010
15	Novel Spectrophotometric Analysis of Piroxicam Tablets Using Ibuprofen Sodium as Hydrotropic Solubilizing Agents. [30]	International Journal of Pharmaceutical Sciences and Drug Research.	2010
16	Spectrophotometric estimation of cefprozil by using Different hydrotropic agents. [31]	International Journal of Pharmacy and Pharmaceutical Sciences.	2010
17	a quantitative estimation and validation of atorvastatin calcium and pioglitazone in tablet dosage form by hydrotropic solubilization phenomenon. [32]	International Journal of Pharmatech Research.	2010
18	Hydrotropic solubilization phenomenon spectrophotometric estimation of Tenofovir disoproxil fumarate tablet. [33]	Journal Chemistry Pharm. Research	2010
19	Application of Mixed Hydrotropic Solubilization in Spectrophotometric Estimation of Aceclofenac in Tablets. [34]	Current Pharma Research.	2011
20	The spectrophotometric method of estimation of Amlodipine besylate using hydrotropic solubilization. [35]	Journal of Applied Pharmaceutical Science.	2011
21	Novel and validated spectrophotometric determination of budesonide from bulk and tablets using mixed hydrotropic solubilization technique. [36]	International Journal of Pharmaceutical Science Research.	2011
22	Spectrophotometric analysis of Cinitapride in tablet dosage form using 2.0 M Sodium Benzoate solution as hydrotropic solubilizing agent. [37]	Journal of Analytical Chemistry.	2011
23	Analytical Application of Hydrotropic Solubilization in Spectrophotometric Determination of Naproxen in Tablet Dosage Form. [38]	International Journal of Pharmaceutical & Biological Archives	2011
24	Application of Mixed Hydrotropic Solubilization Phenomenon for	The Pharma Review	2011

	Quantitative Analysis of Olmesartan Medoxamil in Tablet. [39]		
25	Validated simultaneous spectrophotometric method for estimation of Paracetamol & diclofenac sodium in tablet Dosage forms using hydrotropic Solubilization technique. [40]	Pharmacia.	2011
26	Spectrophotometric Determination and Application of Hydrotropic Solubilization in the Quantitative Analysis of Ranitidine Hydrochloride in Pharmaceutical Dosage Form. [41]	International Journal of Pharm Tech Research.	2011
27	Spectrophotometric analysis of gatifloxacin tablets using mixed hydrotropy. [42]	International Journal of Pharmaceutical Science and Research.	2011
28	Simultaneous Estimation and Validation of Aceclofenac and Paracetamol from bulk and Tablets Using Mixed Hydrotropic Solubilisation. [43]	Asian Journal of Biochemical and Pharmaceutical Research.	2011
29	Application of mixed hydrotropy in Spectrophotometric analysis of frusemide in Different formulations. [44]	Bulletin of Pharmaceutical Research.	2011
30	Novel application of hydrotropic solubilization phenomenon in the spectrophotometric analysis of Valsartan in solid dosage form. [45]	Journal of Pharmacy Research.	2011
31	Mixed Hydrotropy Solubilization Approach for Quantitative Estimation of Eprosartan Mesylate and Hydrochlorothiazide by UV Spectrophotometer. [46]	Pharmaceutica Analytica Acta	2011
32	Eco-friendly spectrophotometric method development and their validation for quantitative estimation of Pramipexole Dihydrochloride using mixed hydrotropic agent. [47]	Journal Chemical Pharmaceutical Research	2011
33	Spectrophotometric determination of Lamivudine in Bulk and Pharmaceutical Formulation using hydrotropic Solubilization. [48]	International Journal of Chem Tech Research.	2011
34	Application of Mixed Hydrotropic Solubilization Technique for Simultaneous Spectrophotometric Estimation of Metronidazole and Miconazole Nitrate from Different Pharmaceutical Dosage Forms. [49]	International Journal of Pharmaceutical & Biological Archives.	2012
35	Spectroscopic Determination of	International Journal of	2012

	Lovastatin by Hydrotropic Solubilization Technique. [50]	Pharmaceutical and Chemical Sciences	
36	Spectrophotometric determination of diflunisal from its formulation by hydrotropy technique. [51]	International Journal of Medicinal Chemistry & Analysis.	2012
37	Exploring the Application of Hydrotropic Solubilization Phenomenon for Estimating Diacerein in Capsule Dosage Form by Spectrophotometry. [52]	Asian Pacific Journal of Tropical Biomedicine	2012
38	Quantitative estimation of telmisartan in bulk and tablets by UV spectroscopy. [53]	International Journal of Drug Research and Technology	2012
39	New quantitative estimation of acetazolamide bulk sample using hydrotropic solubilizing agents. [54]	World Journal of Pharmaceutical research.,	2012
40	Spectrophotometric estimation of acyclovir using hydrotropic solubilisation phenomenon. [55]	Journal of Pharmacy Research.	2012
41	New spectroscopic estimation of Prulifloxacin using Hydrotropic solubilization. [56]	Novel Science International Journal of Pharmaceutical Science.	2012
42	Spectrophotometric Estimation of Candesartan Cilexetil by Using Different Hydrotropic Agent. [57]	International Journal of Pharmaceutical Sciences Letters.	2013
43	Novel Eco-friendly Spectrophotometric Method for Estimation of Ziprasidone Hydrochloride Monohydrate using Hydrotropic Solubilization Technique. [58]	American journal of Pharm Tech Research.	2013
44	Spectrophotometric determination of poorly water-soluble drug terconazole using hydrotropic solubilization. [59]	Indo American Journal of Pharmaceutical Research.	2013
45	UV Spectrophotometric Determination of Telmisartan in Bulk and Pharmaceutical Dosage form using Hydrotropic Solubilization technique. [60]	Journal of Scientific Research in Pharmacy.	2013
46	Application of Sodium Citrate as Hydrotropic Agent in Spectrophotometric Analysis of Salicylic Acid. [61]	Journal of Recent Advances in Pharmaceutical Research.	2013
47	Novel Spectrophotometric Method for Estimation of Olmesartan Medoxomil from its Tablet Dosage Form Using Hydrotropic Solubilization. [62]	Ars Pharmaceutica	2013
48	A novel approach using Hydrotropic Solubilization Technique: Quantitative estimation of meloxicam. [63]	Asian Journal of Pharmaceutical and Clinical Research.	2013

49	Development and Validation of Novel Hydrotropic Solubilization Method for Spectrophotometric Determination of Halofantrine in Pure and Solid Dosage Form. [64]	Scholars Academic Journal of Pharmacy.	2013
50	New Quantitative Estimation of Famotidine Using Hydrotropic Solubilizing Agents. [65]	International Journal of Pharmacy and Pharmaceutical Science Research	2013
51	A Novel Approach using Hydrotropic Solubilization Technique for Quantitative Estimation of Entacapone in Bulk Drug and Dosage Form. [66]	Advanced Pharmaceutical Bulletin	2013
52	Spectrophotometric Estimation of Dextromethorphan in Bulk Drug Using Hydrotropic Solubilization Technique. [67]	Asian Journal of Pharmaceutical Analysis.	2013
53	A novel quantitative estimation of poorly water-soluble drug atorvastatin by using hydrotropic solubilization technique. World journal of Pharmaceutical Research. [68]	World journal of Pharmaceutical Research.	2013
54	A novel application of hydrotropic solubilization for quantitative estimation and validation of Atenolol and Hydrochlorothiazide in tablet dosage form. [69]	Journal of Medical Pharmaceutical and Allied Sciences.	2013
55	Simultaneous Estimation of Atorvastatin Calcium and Amlodipine besylate by UV Spectrophotometric method using hydrotropic solubilization. [70]	Hygenia: Journal of drug and medicine	2013
56	Spectrophotometric determination of poorly water-soluble drug Lanzoprazole using hydrotropic solubilization technique. [71]	Indo American Journal of Pharmaceutical Research	2014
57	New spectrophotometric estimation of Prulifloxacin using Neuberg's hydrotropic salt. [72]	International journal of pharmaceutical, chemical, and biological sciences	2014
58	Exploring the use of sodium benzoate as hydrotrope for the estimation of Lornoxicam in their marketed formulation. [73]	Pharmaceutical Methods.	2014
59	Spectroscopic determination of poorly water-soluble drug rosiglitazone using hydrotropy solubilization technique. [74]	Indian journal of pharmaceutical science	2014
60	An eco-friendly spectroscopic method for estimation of Etravirine by using hydrotropic agents. [75]	World journal of Pharmacy and Pharmaceutical Sciences.	2014

61	Development and validation of UV spectrophotometric method for chlorthalidone in bulk and pharmaceutical dosage forms. (76)	World Journal of Pharmaceutical Research	2014
62	Uv spectrometric method development and validation for estimation of simvastion in bulk and tablet dosage form using mixed hydrotropy solubilization technique. (77)	An international journal of advances in pharmaceutical science	2014
63	UV Spectrophotometric determination of Metronidazole in bulk and pharmaceutical dosage form using hydrotropic solubilization technique. (78)	Journal of Global Trends in Pharmaceutical Sciences.	2015
64	Novel Spectrophotometric Estimation of Acyclovir Using Hydrotropic Solubilizing Agent. (79)	Innovational Journal of Chemistry.	2015
65	UV Spectrophotometric determination of tinidazole in bulk and pharmaceutical dosage form using hydrotropic solubilization technique. (80)	International Journal of Research and Development in Pharmacy and Life Sciences.	2015
66	UV Spectrophotometric determination of Ofloxacin in bulk and pharmaceutical dosage form using hydrotropic solubilization technique. (81)	International Journal of Pharmacy & Technology.	2015
67	An eco-friendly Spectroscopic method for estimation of Etravirine by using hydrotropic agents. (82)	World journal of pharmacy and pharmaceutical sciences.	2015
68	spectrophotometric estimation of Gliclazide by using mixed hydrotropic solubilization phenomenon.(83)	Journal of Drug Discovery and Therapeutics.	2015
69	UV Spectrophotometric Determination of Fenofibric Acid by Using Hydrotropy. (84)	International Journal of Pharma Sciences and Research	2015
70	Novel spectrophotometric estimation of atenolol using hydrotropic solubilizing agent. (85)	International Journal of AdvancedResearch in Biological Sciences.	2015
71	New Spectrophotometric Method for the Estimation of Lomefloxacin in Tablets using Sodium benzoate as Hydrotropic Agent. (86)	Asian Journal of Pharmaceutical Education and Research	2016
72	Development and validation of mixed hydrotropic solubilization method for spectrophotometric determination of Ornidazole in bulk drug and tablet. (87)	Journal of Pharmacy Research.	2017

THIN LAYER CHROMATOGRAPHY

In quantitative and qualitative analysis thin layer chromatography play vital role. Its observed that the rate of migration of a substance on a given adsorbent depends upon solvent used. to perform TLC of poorly water-soluble drugs organic solvent used. Using hydrotropic solvent, we can preclude use of organic solvent.

Table 5: Examples of TLC for which hydrotropic agents are used

1	Novel application of hydrotropy in thin layer chromatography. [88]	The Indian pharmacist	2010
2	Novel application hydrotropic solubilization phenomenon in the thin layer chromatography analysis of omeprazole. [89]	Journal of Current Pharmaceutical Research	2011

MIXED SOLVENCY CONCEPT

Due to toxicity, volatility and high cost of organic solvent various method used to increase the aqueous solubility of insoluble drugs. Maheshwari RK has developed mixed-solvency concept. On the basis of a large experiment on solubilization of poorly water-soluble drug Maheshwari says water-soluble substances whether liquids, solids or gas may act as a solubilizer for poorly water-soluble drugs. He states that 'A weaker solvent may act as strong solvent for a particular solute in the presence of other solid (in solution form).' His study was found that additive and synergistic solvent action on the solubility of salicylic acid could be obtained by using aqueous solutions containing different excipients (liquids and solids both).By application of this concept, innumerable solvent system can be developed. Following table enlisted some work done by using mixed solvency concept for roll out use of organic solvent.[90]

Table 5: Examples of use of mixed solvency concept in drug analysis

1	"Solid as solvent"- Novel spectrophotometric analysis of satranidazole tablets using phenol as solvent. [91]	Indian Pharmacist	2014
2	"Solid as solvent"- Novel spectrophotometric analysis of norfloxacin tablets using phenol as solvent. [92]	International Journal Current Pharmaceutical Research	2014
3	"Solid as solvent"-Novel spectrophotometric analysis of tinidazole tablets using melted phenol as solvent. [93]	Asian Journal of Pharmaceutical Research.	2015
4	Utilization of mixed solvency technique in spectrophotometric analysis of cefixime trihydrate tablets. [94]	International Journal of Pharmaceutical Research and Analysis.	2015
5	Development and validation of simple UV spectrophotometric method of quantization of Nifedipine in solid dosage formulation using mixed solvency concept. [95]	World Journal of Pharmaceutical Research	2017
6	Development and validation of simple UV spectrophotometric method of quantization of Ondansetron hydrochloride in solid dosage formulation using mixed solvency concept. [96]	International Journal of Pharmaceutical science and drug research	2017
7	Development and validation of simple UV spectrophotometric method of quantization of Diazepam in solid dosage formulation using mixed solvency concept. [97]	International Journal of Current Pharmaceutical Research	2017
8	Development and validation of simple UV spectrophotometric method of quantization of Domperidone in solid dosage formulation using mixed solvency concept. [98]	A Journal of Drug Design and Discovery	2017
9	Development and validation of simple UV spectrophotometric method of quantization of Domperidone in solid dosage formulation using mixed solvency concept. [99]	European Journal of Biomedical and Pharmaceutical Sciences	2017
10	Development and validation of simple UV Spectrophotometric method of quantization of indomethacin in solid dosage formulation using mixed solvency concept. [100]	The Pharma Innovation Journal	2017
11	Development and validation of simple UV spectrophotometric method of quantization of ornidazole in solid dosage formulation using mixed solvency concept. [101]	World Journal of Pharmaceutical Research	2017
12	Simultaneous estimation of ofloxacin and tinidazole in solid dosage form by UV Spectrophotometry using mixed solvency concept. [102]	European Journal of pharmaceutical and Medical Research	2017

FUTURE PERSPECTIVE

While advances in the application of hydrotropic solubilization to the drug analysis have been progressing rapidly. As the research in analytical chemistry concern with development of different method hydrotropy successfully applied on titrimetric, spectrophotometric analysis. Without a doubt, in the near future more studies on another technique like HPTLC, HPLC method to preclude the use of organic solvent due to their toxicity, cost and record maintain. Similarly, use of hydrotropic solubilization in pharmaceutical field like pharmaceutics, pharmacognosy and pharmaceutical chemistry.

CONCLUSION:

From above study, conclude that Solubility is one of the important parameters to select accurate solvent for analysis of drug. Many of the drug listed in pharmacopeia are poorly water soluble. Analysis of poorly water-soluble drugs most frequently used organic solvents which are toxic, costly and required maintain record. There are many techniques to increase aqueous solubility of poorly water-soluble drugs. Hydrotropy solubilization technique and mixed solvency concept are the best approaches to increase water solubility of poorly water-soluble drugs and use successfully in analysis of drug. These methods are safe, simple and eco-friendly. Day to day use of hydrotropy and mixed solvency are increasing in pharmaceutical analysis, in future we can explore use of hydrotropy and mixed solvency concept in estimation of drug by HPLC, HPTLC methods to avoid use of organic solvents.

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