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A REVIEW ON ANALYTICAL METHODS BASED ON HYDROTROPIC PHENOMENON

K R Sreejith*, P L Rajagopal, K P Jyolsna, M K Sharbina

Academy of Pharmaceutical Sciences, Pariyaram Medical College Kannur, Kerala, India. 670503.

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***Correspondence for Author**

Dr. K R Sreejith

Academy of Pharmaceutical Sciences, Pariyaram Medical College Kannur, Kerala, India. 670503.

ABSTRACT

Solubility is one of the important parameter to achieve desired concentration of drug in systemic for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for certain drugs. This is true for parentally, topically and orally administered solutions. Use of the solubility characteristics in bioavailability, pharmacological action and solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Hydrotropy is one of the solubility enhancement techniques 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.

KEYWORDS: Hydrotropy, Solubility, Hydrophobic drugs, Hydrotropes, Solubility enhancement.

INTRODUCTION

Solubility is the phenomenon of dissolution of solute in solvent to give a homogenous system. It is defined in quantitative terms as the concentration of the solute in a saturated solution at certain temperature and qualitative terms as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion.[1, 2] The pharmacopoeia lists

solubility in terms of 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**.[3]

Table 1. Values for estimating solubility of an active ingredient

Descriptive Term	Appropriate Volume of Solvent In Millilitres Per Gram of Solute
Very soluble	Less than 1 part solvent needed to dissolve 1 part solute
Freely soluble	From 1 to 10 parts solvent needed to dissolve 1 part solute
Soluble	From 10 to 30 parts solvent needed to dissolve 1 part solute
Sparingly soluble	From 30 to 100 parts solvent needed to dissolve 1 part solute
Slightly soluble	From 100 to 1000 parts solvent needed to dissolve 1 part solute
Very slightly soluble	From 1000 to 10,000 parts solvent needed to dissolve 1 part solute
Practically insoluble	More than 10,000 parts solvent needed to dissolve 1 part solute

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. Solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.[4-5] A number of methodologies can be adapted to improve solubilization of poor water soluble drug. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. Out of these techniques hydrotropy is acting as a promising tool for solubility enhancement. Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, 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

hydrotrope in water. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.[6]

Hydrotropy is a solubilization phenomenon whereby addition of large amount of second solute results in an increase in the aqueous solubility of another solute. 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. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[7-10]

Hydrotropy is the term originally put forward by Neuberg[11] 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. 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 cosolvency or salting-in. The chemical structure of the conventional Neuberg hydrotropic salts 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. Gaikar et al[6, 11], investigated whether a drug with an amphiphillic structure can exhibit hydrotropic properties. They sought to establish sodium ibuprofen as an effective hydrotrope. On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization.[12] This should imply that hydrotropic agents are molecules having a planar hydrophobic structure brought into solution by a polar group.

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.[13] 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.

Now a day's hydrotropic technique has become simple, cost-effective, safe, accurate, precise and environmental friendly method for the analysis of poorly water-soluble drugs precluding the use of organic solvents. Various organic solvents such as methanol, chloroform, dimethyl formamide and acetonitrile have been employed for solubilization of poorly water soluble drugs to carry out spectroscopic analysis. Drawbacks of these organic solvents include high cost, volatility, pollution and toxicity such as nephrotoxicity or teratogenecity. Organic solvents are harmful if swallowed, inhaled or absorbed through skin. Many analytical methods based on hydrotropic solubilisation are available in literature and this review focus on the application of hydrotropic solubilisation in the analysis of poorly soluble drugs.

ANALYTICAL METHODS

R K Maheshwari., S C Chadurvedi. and N K Jain[14] developed Novel spectrophotometric estimation methods of some poorly water soluble drugs using hydrotropic solubilizing agents. Ultra violet absorption spectroscopic method for the estimation of poorly water soluble drugs like nalidixic acid,norfloxacin,tinidazole,and metronidazole in pharmaceutical formulations has been developed. Aqueous solubilities of these selected model drugs were enhanced to a great extend(5 to 98 fold) in 2.0 M sodium benzoate, and in 2.0 M niacinamide solutions. The selected λmax for nalidixic acid, norfloxacin, tinidazole, and metronidazole, were 330 nm, 318 nm and 320 nm, respectively. The results of analysis have been validated statically, and by recovery studies. The proposed methods are new, simple, economic, accurate, safe, and precise.

R K Maheswari and Ravi sankar shukla[15] developed Quantitative spectrophotometric estimation of famotidine using hydrotropic solubilization technique. In the present investigation, 1.5 M metformin hydrochloride, (an economic drug) solution, was employed as hydrotropic solubilizing agent to solubilize poorly water-soluble drug, famotidine, for its UV analysis. Proposed method is new, simple, environmentally friendly, accurate and reproducible. Accuracy, reproducibility and precision of the proposed method were validated statistically.

R K Maheshwari et al[16] developed a new method for the quantitative estimation of salicylic acid bulk sample using Calcium disodium edetate as hydrotropic solubilizing agent. In the present investigation, hydrotropic solubilization technique has been employed to solubilize the poorly water-soluble, keratolytic drug, salicylic acid (by 1.0 M calcium disodium edetate solution), for its titrimetric analysis. There was more than 45 fold enhancement in aqueous solubility of salicylic acid in 1.0 M calcium disodium edetate solution as compared to the solubility in distilled water. The hydrotropic agent did not interfere in the analysis. The proposed method is new, simple, accurate and reproducible. Statistical data proved the accuracy, reproducibility and precision of the proposed method.

Nilesh jain et al[17] developed a novel, safe, accurate and sensitive spectrophotometric method using sodium acetate solution as hydrotropic solubilizing agent for the quantitative determination of poorly water-soluble drug amlodipine besylate in tablet dosage form. Amlodipine besylate shows maximum absorbance at 365 nm. Sodium acetate did not show any absorbance above 240 nm and thus no interference in the estimation of drug was seen.

Maheshwari R K et al[18]developed an eco-friendly spectrophotometic stimation of atenolol tablets using metformin hydrochloride as hydrotropic solubilizing agent. In the present investigation, 1 M solution of an economic drug, metformin hydrochloride (a hydrotropic solution) was employed as solubilizing agent to extract out the poorly water-soluble, antihypertensive drug, atenolol from fine powder of its tablets. Hydrotropic agent, metformin hydrochloride and commonly used tablet excipients did not interfere in spectrophotometric determination at λ_{max} 275 nm.

R K Maheshwari ., Mithun Singh Rajput and Sampada Sinha[19] developed new quantitative estimation of benzoic acid bulk sample using calcium disodium edetate as hydrotropic solubilizing agent. The hydrotropic agent did not interfere in the analysis. The proposed method is new, simple, accurate and reproducible.

V Pareek., S R Tambe and S B Bhalerao[20] studied the role of different hydrotropic agents in spectrophotometric and Chromatographic estimation of cefixime. Present study deals with two Spectrophotometric methods, Conventional Spectrophotometric Estimation and Area under Curve Method and a chromatographic method for estimation of Cefixime by using five different hydrotropic agents. These include Ammonium acetate (6M), Potassium acetate (5M), Potassium citrate (0.5 M), Sodium citrate (1.25 M) and Urea (8M). Area under curve

method was based on measurement of area under curve (AUC) in the wavelength range 279nm to 298nm. In both spectrophotometric methods, linearity of Cefixime was found in the concentration range 5 to 30µg/ml by using all above hydrotropic agents. For HPTLC method, linearity of Cefixime was found to be in concentration range 100ng to 500ng. Mixture of methanol: ethyl acetate: triethylamine (7:5:0.05v/v) was used as a developing solvent.

R.K. Maheshwari.et al[21] developed quantitative spectrophotometric determination Of cefixime tablet formulation using Sodium tartarate as hydrotropic solubilizing agent. Cefixime exhibits maximum absorbance at 288 nm and follows Beer's law in concentration range of 5-30 mcg/ml. Hydrotropic agent and commonly used tablet additives did not interfere in analysis.

R K Jat ., R C Chhipa and S. Sharma[22] developed a spectrophotometric quantification of etoricoxib in bulk drug and tablets using hydrotropic agent**.** Hydrotropic solubilization technique is used to increase aqueous solubilities of poorly water soluble drugs using hydrotropic agents. In the present investigation hydrotropic solution of sodium benzoate (2M) has been used as a solubilizing agent to solubilize poorly water soluble drug. Etoricoxib shows maximum absorbance at 282 nm. Beer's law was obeyed in the concentration range of 5-20 µg /ml. Results of analysis were validated statistically and by recovery studies. The proposed method is now simple, new, environmentally friendly, and accurate, cost-effictive and successfully employed in routine analysis of etoricoxib bulk drug and tablet dosage forms. Hydrotropic agent sodium benzoate did not interfere in spectrophotometric determination.

R K Jat., R C Chhipa and S Sharma[23] developed a spectrophotometric method for the Estimation of Fluvoxamine Maleate in Tablets Using Hydrotropic Agent urea(10M). Fluvoxamine maleate shows maximum absorbance at 271 nm. Beer's law was obeyed in the concentration range of 5-25 µg /ml. Hydrotropic agent urea did not interfere in spectrophotometric determination.

R K Maheshwari et al[24] applied mixed-hydrotropic solubilization concept in spectrophotometric analysis of frusemide in tablet dosage form**.** In the present investigation, a poorly water-soluble drug, frusemide has been solubilized using hydrotropic blend containing 5 M urea, 1 M sodium acetate and 0.4 M sodium citrate for the spectrophotometric analysis precluding the use of organic solvents.

Nilesh jain et al[25] developed a novel spectrophotometric quantitative estimation method for the determination of hydrochlorothiazide in bulk drug and their dosage forms by using hydrotropic agent . The method was developed using 2 M sodium acetate and 8 M Urea solution as hydrotropic solubilizing agent. Hydrochlorothiazide shows maximum absorbance at 272 nm. Sodium acetate and urea did not show any absorbance above 240 nm, and thus no interference in the estimation was seen. Hydrochlorothiazide is obeyed Beer,s law in the concentration range of 10 t0 50µg/ml in sodium acetate and 5 to 25 µg/ml in urea.

RK Maheshwari et al[26] developed a spectrophotometric determination of Hydrochlorothiazide in tablets Using Mixed Hydrotropic Solubilization Technique.. A novel, safe and sensitive method of spectrophotometric estimation in the ultraviolet region has been developed using a mixed hydrotropic solution containing eight percent each of niacinamide, sodium acetate, sodium benzoate, sodium citrate and urea (total 40% hydrotropic agents), for the quantitative determination of hydrochlorothiazide, a very slightly water soluble diuretic drug in tablet dosage form. Beer's law was obeyed in the concentration range of 20–120 µg/ml.

Merukar S.S et al[27] Applied hydrotropic solubilization phenomenon in spectrophotometric estimation of levofloxacin in tablet dosage. In the present investigation hydrotropic solution of urea (4M) has been employed as solubilizing agent to solubilization poorly water soluble drug Levofloxacin, from fine powder of its tablet dosage form for spectrophotometric determination in ultraviolet region. Levofloxacin shows maximum absorbance at 289 nm. Beer's law was obeyed in the concentration range of 2-12 µg/ml.

R K Maheshwari.et al[28] developed a spectrophotometric determination of naproxen tablets using niacinamide as hydrotropic solubilizing additive. This solution was further diluted to Beer's law range 50-250 µg/ ml for naproxen. Absorbance was noted at 331 nm.

R Revathi et al[29] developed a new spectroscopic determination of nifedipine using hydrotropic Solubilization. A simple, safe and sensitive method of spectroscopic determination of Nifedipine in UV region was developed using 40 % sodium salicylate solution as hydrotropic solubilizing agent. Nifedipine showed λ-max at 350 nm and beer's law was obeyed in the concentration range of 20 – 100 µg/ml.

Gajanand Engla et al[30] developed a simultaneous Spectrophotometric Estimation method of Paracetamol and Aceclofenac in Combined Tablet Formulations using Hydrotropic Solubilization Technique. In the present investigation, the hydrotropic solubilization is employed to enhance the aqueous solubilities of poorly water-soluble drugs, paracetamol and aceclofenac in two-component tablet formulation for simultaneous spectrophotometric determination. Three simple, precise, accurate and economical procedures employed are simultaneous equation method, absorbance ratio method and multicomponent mode of analysis. All the methods utilize the combined hydrotropic blend of 20% urea solution and 20% sodium citrate solution precluding the use of organic solvent. In the mixed hydrotropic solution, paracetamol and aceclofenac shows maximum absorption at 245 nm and 274 nm, respectively and isoabsorptive point observed was 262 nm. The hydrotropic agents show no absorbance above 237 nm. The hydrotropic agents as well as tablet excipients in formulation did not interfere in the analysis.

Rajesh Sharma et al[31] applied hydrotropic solubilization in developing and validating a spectrophotometric method for Simultaneous estimation of paracetamol and diclofenac. In the present investigation, 1.0 M urea solution was employed to solubilize, Paracetamol from fine powder of its tablets to carryout spectrophotometric analysis. Simultaneous estimation was carried out by three methods, Method –A derivative spectrophotometry method, Method-B area under curve method and Method-C multi-component method. The result showed that Beer's law was obeyed in concentration range of 2-40 g/ml with good linearity for both the drugs in all the three methods.

R K Maheshwari et al[32] developed a novel spectrophotometric method for Piroxicam tablet analysis using Ibuprofen Sodium as hydrotropic solubilizing agent. Spectrophotometric analysis was carried out at 358 nm. Ibuprofen sodium does not show any absorbance above 300 nm. Beer' s law was obeyed in the concentration range of 5-35 µg/ml.

Vikas Pareek et al[33] developed spectrophotometric estimation of cefprozil by using different hydrotropic agents. Present study deals with two spectrophotometric methods, Conventional Spectrophotometric Estimation (Method I) and Area Under Curve Method (Method II) for quantitation of Cefprozil by using five different hydrotropic agents. These include Potassium acetate (6.0M), Potassium citrate (1.5M), Sodium acetate (4.0M), Sodium citrate (1.25M) and Urea (10.0M). All these agents do not show absorbance above 245 nm and hence do not interfere with absorbance of Cefprozil (λmax- 280 nm). Area under curve method was based

on measurement of area under curve in the wavelength range 255 nm to 305 nm. Linearity of Cefprozil was found in the concentration range 10 to 60µg/ml by using all hydrotropic agents in both methods.

Deepika singh et al[34] developed a simple ecofriendly titrimetric analytical method to estimate ketoprofen in the bulk drug sample using mixed Hydrotrophy. The enhancement in the solubility of ketoprofen in a mixed hydrotropoic solution containing 30% urea, 11.8% sodium citrate and 13.6% sodium acetate was more than 560 fold (as compared to the solubility in distilled water).

M C Sharma et al[35] studied hydrotropic solubilization phenomenon for spectrophotometric estimation of Tenfovir disoproxil fumerate tablet. 2.0 M sodium benzoate solutions was employed as hydrotropic solubilizing agent. The selected λmax for Tenfovir disoproxil fumerate was 317 nm. The hydrotropic solutions used did not show any absorbance above 233 nm.

S N Anish Vinnakota et al[36] applied mixed hydrotropic solubilization in Spectrophotometric Estimation of Aceclofenac in Tablets. In the present investigation mixed hydrotropic solubilization phenomenon was employed using the solution of 30% urea and 20% of sodium citrate to estimate poorly water-soluble drug aceclofenac from fine powder and its tablet dosage forms. The solubility of aceclofenac in distilled water was found to be 0.225mg/ml, whereas in the mixture of 30% urea and 20% sodium citrate, the solubility was found to be 19.64mg/ml. The increase in solubility of aceclofenac in the mixture was more than 100 folds. Aceclofenac showed maximum absorbance at 274.5nm. Beer's law was obeyed in the concentration range of 5-40 µg/ml.

Shyni Bernard., Molly Mathew and K L Senthilkumar[37] developed a Spectrophotometric method for the estimation of Amlodipine besylate using hydrotropic solubilization using 2M urea solution as hydrotropic solubilizing agent. Amlodipine exhibits absorption maximum at 243 nm. Urea did not show any absorbance above 225 nm and thus no interference in the estimation of drug was seen.Beer's law was found to be obeyed in the concentration range of 5-25µg/mL.

D D Sanap et al[38] developed a Novel and validated spectrophotometric method for the determination of budesonide from bulk and tablets using mixed hydrotropic solubilization

technique using solution containing 45% urea and 5% sodium citrate as hydrotropic solubilizing agent. Budesonide obeyed Lambert Beer's law in the concentration range of 5 to 30µg/ml.

B Thangabalan and P Vijayaraj Kumar[39] developed a spectrophotometric analysis of Cinitapride in tablet dosage form using 2.0 M Sodium Benzoate solution as hydrotropic solubilizing agent. Cinitapride showed λ-max at 395 nm and beer's law was obeyed in the concentration range of 10 – 80 µg/ml.

Gurjer M et al[40] applied hydrotropic Solubilization in Spectrophotometric Determination of Naproxen in Tablet Dosage Form. Urea (4M) has been employed as solubilizing agent and Levofloxacin shows maximum absorbance at 289 nm. Beer's law was obeyed in the concentration range of 2-12 µg/ml.

Nilesh Jain et al[41] applied mixed Hydrotropic Solubilization Phenomenon for Quantitative Analysis of Olmesartan Medoxamil in Tablet. The enhancement of solubility of naproxen drug was more than 65 fold in hydrotropic solution (7.5M N,N-dimethyl urea solution) as compared to solubility in distilled water. Therefore, it was thought worthwhile to solubilize this poorly water soluble drug from fine powder of its tablets by this novel hydrotropic solubilization technique and then carry out its spectrophotometric estimation at 317 nm (N,N-Dimethyl urea does not interfere above 260nm).

Ankit Mangal et al[42] applied hydrotropic solubilization phenomenon in the thin layer chromatrography analysis of omeprazole. This method uses a mixture of 2 M sodium acetate and 8 M Urea solution (50:50% V/V) as hydrotropic solubilizing agent. Olmesartan Medoxomil shows maximum absorbance at 257nm. Sodium acetate, urea, and other tablets excipents did not show any absorbance above 240 nm, and thus no interference in the estimation was seen. Olmesartan medoxomil was obeyed lamberts Beer's law linear in the concentration range of 10 to 50µg/ml.

Engla G et al[43] developed a validated simultaneous spectrophotometric method for estimation of Paracetamol & Diclofenac sodium in tablet Dosage forms using hydrotropic Solubilization technique using 8M urea solution as hydrotropic solubilizing agent. Diclofenac sodium have maximum λmax at 275.6 nm and obeys Beer's law in concentration range of 5-40 µg/ml. Paracetamol have λmax at 243.4 nm and obeys beer's law in concentration range of

5-20 µg/ml. Urea solution does not absorbs above 244 nm and does not show any interference in spectrophotometric estimation.

Mukesh Chandra Sharma and Smita Sharma[44] developed a method for the Quantitative Analysis of Ranitidine Hydrochloride in Pharmaceutical Dosage Form. This Method utilize 10.0 M-urea solution as, hydrotropic solubilizing agent. In the urea solution, Ranitidine hydrochloride show maximum absorbance at a wavelength of about 299 nm. The hydrotropic agent and additives used in the manufacture of tablets did not interfere in the analysis.

Sunitha G et al[45] applied hydrotropic solubilization phenomenon in the spectrophotometric analysis of Valsartan in solid dosage form. In the present investigation, hydrotropic solution of sodium citrate (0.01M) was employed as solubilizing agent to solubilize valsartan (poorly water soluble drug) fine powder and its tablet dosage form for spectrophotometric determination in UV region. Valsartan showed maximum absorbance at 250 nm and followed Beer's law in concentration range of 5-30 mcg/mL.

S N Anish Vinnakota et al[46] developed a method for the Simultaneous Estimation and Validation of Aceclofenac and Paracetamol from bulk and Tablets Using Mixed Hydrotropic Solubilisation. In the present investigation mixed hydrotropic solubilization phenomenon was employed in simultaneous estimation of solubilize poorly water-soluble drugs aceclofenac and paracetamol from bulk powder and its tablet dosage form. Aceclofenac showed maximum absorbance at 274.5 nm, whereas paracetamol showed maximum absorbance at 261.5 nm. The solubility of both aceclofenac and paracetamol was enhanced to greater extent in mixed hydrotropic solution of 30% urea with 20% sodium citrate. Both the drugs showed linearity in the concentration range of 5-40 µg/mL and 4-40 µg/mL.

Archana Mehrotra et al[47] applied mixed hydrotropy in Spectrophotometric analysis of frusemide in Different formulations. There was more than 15-fold enhancement in aqueous solubility of frusemide in a solution of blend of hydrotropic agents which consisted of 30% urea, 13.6% sodium acetate and 11.8% sodium citrate. This solvent mixture was employed to solubilize the drug from the fine powder of tablet formulations of frusemide. The selected λmax for spectrophotometric estimation was 333 nm.

Rounak Shrivastava et al[48] developed a spectrophotometric method for the analysis of gatifloxacin tablets using mixed hydrotrophy. The enhancement of solubility of drug

gatifloxacin was more than 15 fold in mixed hydrotropic solution (20% N,N dimethyl urea and 20% sodium citrate solution) as compared to solubility in distilled water and carried out its spectrophotometric estimation at 333 nm (20% N,N dimethyl urea and 20% sodium citrate being non-interfering in the estimation). The results of the analysis were validated statistically and by recovery studies & its follows Beer's law in concentration range of 10-60 mcg/ml.

M C Sharma and S Sharma[49] developed a spectrophotometric determination of Lamivudine in Bulk and Pharmaceutical Formulation using hydrotropic Solubilization. Aqueous solubility of this selected model drug was to a great extent (21 to 243fold) in 5.0 M sodium benzoate. Lamivudine shows maximum absorbance at 315 nm. Beer's law was obeyed in the concentration 50-300mcg/ml.

S R Kadam et al[50] applied Mixed Hydrotropic Solubilization Technique for Simultaneous Spectrophotometric Estimation of Metronidazole and Miconazole Nitrate from Different Pharmaceutical Dosage Forms. Three novel, simple, accurate, sensitive and economical procedures employed are simultaneous equation method, absorbance ratio method, and dual wavelength method. All methods utilize solution containing 40% urea and 10% sodium benzoates, hydrotropic solubilizing agent. The solubility of drugs increases more than 14 times in mixed hydrotropic solution as compared to solubility in distilled water.In the solution containing 40% urea and 10% sodium benzoate, metronidazole and miconazole nitrate show maximum absorbance at a wavelength of about 325&285 nm respectively and isosbestic point is observed at 296 nm.

Deepak N Patil[51] developed a spectroscopic Determination of Lovastatin By Hydrotropic Solubilization Technique. Lovastatin was found to be poorly water soluble drug and there was more than 6 times increase in the solubility using 4M sodium acetate solution. Sodium acetate did not interfere in the spectroscopic determination of lovastatin (λmax-250).

K Sathish babu et al[52] developed a spectrophotometric method for the determination of diflunisal from its formulation by hydrotropy technique . Sodiun salicilate was used as hydrotropic solubilizing agent.258nm was selected for the study. Beers law was obeyed over the concentration range of 2-8µg/ml.

Baghel U S and Dhiman V[53] applied hydrotropic Solubilization Phenomenon for Estimating Diacerein in Capsule Dosage Form by Spectrophotometry .The aqueous solubility of diacerin was increased by more than 270 folds by using 8M urea solution as hydrotropic agent in comparison solubility in distilled water. Direct spectroscopy and Derivative spectroscopy are the two methods developed and the sample obeys Beer's law in the concentration range of 1-15µg/ml&2-45µg/ml respectively. The wave length of measurement are 257.6 and 280.5 respectively.

R K Jat et al[54] quantitatively estimated of telmisaratn in bulk and tablets by UV spectroscopy. Telmisartan showed maximum absorbance at 216 nm.Beer's law was obeyed in the concentration range of in the range of 5-25µg/ml.10 M urea solution is used as hydrotropic solubilizing agent.

Geet Asnani et al[55] Developed and validated a spectrophotometric method of cefpodoxome proxetil using hydrotropicsolubilizing agents.The present study deals with spectrophotometric analysis of cefpodoxime proxetil by utilizing urea(1M) as hydrotropic solubilizing agent. The linearity was observed in the concenteration range of 10-120µg/ml.

Mahavir Chhajed et al[56] developed a quantitative estimation of acetazolamide bulk sample using hydrotropic solubilising agents . For the same work N,N'-dimethyl urea solution (by 7.5 M), and sodium acetate solution (5.5 M) were used as hydrotropic agent. There was more than 2 fold and 1.8 fold enhancement in aqueous solubility of acetazolamide in 7.5 M N,N'-dimethyl urea solution and 5.5 M sodium acetate solution respectively; compared to the solubility in distilled water.

Gurumurthy Venkatesh et al[57] developed Spectrophotometric estimation of acyclovir using hydrotropic solubilsation phenomenon. It involves the use of hydrotropic solubilization technique to estimate the amount of acyclovir present in tablets by spectrophotometric method using 4M urea and 4M sodium acetate. It was observed that solubility of acyclovir in urea and sodium acetate solutions was increased by six folds as compared with distilled water. The method obeyed Beer's law with maximum absorbance at 255nm.

Ethiraj T et al[58] developed a new spectroscopic estimation of Prulifloxacin using Hydrotropic solubilisation using 30 % sodium salicylate solution as hydrotropic solubilizing

agent. Prulifloxacin showed λmax at 344.4 nm and beer's law was obeyed in the concentration range of 30 – 100 µg/ml.

Yogesh P Agarwal ,M Y Agarwal and A K.Gupta[59] developed a spectrophotometric Estimation of Candesartan Cilexetil by Using Different Hydrotropic Agent. Present study deals with the quantitation of Candesartan cilexetil by using five different hydrotropic agents.They include Potassium acetate (6.0M),Potassium citrate(1.5M),Sodium acetate (4.0M),Sodium citrate(1.25M),and Urea(10.0M).All these agents do not show absorbance above 245nm and hence do not interfere with absorbance of Candesartan(λmax 280nm).Linearityof Candesartan was found in the concenteration range 10 to 50µg/ml by using all hydrotropic agents.

R Jain et al[60] developed a novel ecofriendly spectrophotometric method for estimation of Ziprasidone Hydrochloride Monohydrate using 2 M Citric acid as hydrotropic agent. After solubilizing the Ziprasidone Hydrochloride in selected hydrotropic agent, it was scanned in spectrum mode and the working wavelength for the estimation, considering the reproducibility and variability was found to be 314 nm. The developed method was found to be linear in the range of 20-100 µg/ml.

M Srilakshmi et al[61] developed a spectrophotometric determination of poorly water soluble drug terconazole using hydrotropic solubilization. Terconazole has been solubilized in water using hydrotropic agent of urea and scanned between 200-400nm and the respective reagent blanks in a double beam spectrophotometer.The λmax was found to be 286 nm and Terconazole was found to be linear range of 50-250 µg/ml.

Mastanamma Shaik et al[62] developed a UV-Spectrophotometric Determination of Telmisartan in Bulk and Pharmaceutical Dosage form using Hydrotropic Solubilization technique . Solubility of Telmisartan is increased by using 1M Piperazine as a hydrotropic agent. Telmisartan showed the maximum absorbance at 289 nm. At this wavelength, hydrotropic agent and other tablet excipients did not show any significant interference in the spectrophotometric assay. The developed method was found to be linear in the range of 10-35 µg/ml.

Aditya Narayan Jhariya et al[63] applied Sodium Citrate As Hydrotropic Agent In Spectrophotometric Analysis of Salicylic Acid.

Nikam B Shriram et al[64] developed a novel spectrophotometric method for estimation of Olmesartan Medoxomil from its Tablet Dosage Form Using Hydrotropic Solubilization. This method utilizes 0.05 M Sodium acetate solution as hydrotropic solubilizing agent Where Olmesartan Medoxomil shows maximum absorbance at 256 nm. The 0.05 M Sodium acetate solution does not show any interference with the sampling wavelength. The hydrotropic agent and additives used in the manufacture of tablets did not interfere in the analysis. The drug obeys the Beer's Law in the concentration range 2-14 µg/ml with correlation coefficient value of 0.9987.

Ruchi Jain and Surendra K Jain[65] developed a quantitative estimation of Meloxicam using Hydrotropic Solubilization Technique. Solubility of meloxicam is increased by using 8% phenol and 25% sodium benzoate solution as hydrotropic agent. There was more than 32 fold solubility enhanced in hydrotropic solution as compare with distilled water. The meloxicam shows the maximum absorbance at 362 nm. At this wavelength hydrotropic agent and other tablet excipients do not shows any significant interference in the spectrophotometric assay. The developed method was found to be linear in the range of 15-75 µg/ml.

Nwodo NJ, Nnadi C O and Nnadi K I[66] developed and validated a novel hydrotropic solubilization method for spectrophotometric determination of Halofantrine in pure and solid dosage form using 4 M sodium acetate and 5 M sodium citrate. Solubility of halofantrine was enhanced by a factor of 11 and 18 in 4 M sodium acetate and 5 M sodium citrate respectively. Beer-Lambert's calibration curves were linear at concentration of 2-20 µg/mL.

C Jayakumar et al[67] developed a New Quantitative Estimation of Famotidine Using Hydrotropic Solubilizing Agents citric acid solution (by 7.5 M), and sodium benzoate solution (5.5 M) There was more than 2 fold and 1.3 fold enhancement in aqueous solubility of famoditine in 7.5 M citric acid solution and 5.5 M sodium benzoate solution respectively. The hydrotropic agent did not interfere in the analysis.

Ruchi Jain et al[68] studied a novel approach using hydrotropic solubalization technique for Quantitative Estimation of Entacapone in Bulk Drug and Dosage Form. Solubility of entacapone is increased by using 8M Urea as hydrotropic agent. The entacapone (ENT) shows the maximum absorbance at 378 nm. At this wavelength hydrotropic agent and other tablet excipients do not shows any significant interference in the spectrophotometric assay. The developed method was found to be linear in the range of 4-20 µg/ml.

Jyothi Dahiya et al[69] developed Spectrophotometric Estimation of Dextromethorphan in Bulk Drug Using Hydrotropic Solubilization Technique. Method is based on absorbance at 278nm with hydrotrope Dextromethorphanin double distilled water as solvent.The llinearity was obtained in the concenteration range of 10-120µg/ml.

D Pardha Saradhi et al[70] developed a novel quantitative estimation of poorly water soluble drug atorvastatin by using hydrotropic solubilization technique. The hydrotropic substance is urea. This technique is reliable and simple. In the present study more than 2 folds solubility enhanced when compared to distilled water alone. The urea was used in different concentrations 10,20,30,40,50 and 60mg. The drug and hydrotropic substance ratios were 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6. The hydrotropic substance (urea) did not interfered in the analysis.

Rathore Pooja et al[71] applied hydrotropic solubilization for quantitative estimation and validation of Atenolol and Hydrochlorothiazide in tablet dosage form. In the present investigation, 4M Ammonium acetate solution (Hydrotropic agent) was employed for solubilizing, Atenolol and hydrochlorothiazide (a poorly water soluble drug), from fine powder of its tablets to carryout spectrophotometric analysis. The proposed methods namely simultaneous equation method (Method 1) and absorbance ratio method (Method-2). λmax for Atenolol and hydrochlorothiazide is 224.5 nm and 272.5 nm respectively. Both Atenolol and hydrochlorothiazide obey Beer's law in the concentration range of 10-50 µg/ml (r2=0.9992) and 5-25 µg/ml (r2=0.9994) in 4 M Ammonium acetate (Hydrotropic agent) respectively.

Shyni Bernard et al[72] developed a Simultaneous Estimation of Atorvastatin Calcium and Amlodipine besylate by UV Spectrophotometric method using hydrotropic solubilization. The developed method uses the absorption ratio or Q-value which is based on the measurement of absorptivity at 293 nm (iso-absorptive point, both the drugs were found to have same absorbance at this wave length) and 247 nm (absorption maximum of one of the drugs, Atorvastatin). Both the drugs are insoluble in water and require corrosive organic solvents for solubilization. Therefore an attempt was made to preclude the use of corrosive solvents by the use of 2M Urea by hydrotropic solubilization method. The calibration curves for both drugs were found to be linear in a concentration range of 10-60µg/mL.

V Ruth Beulah and A Shantha Kumar[73] developed Spectrophotometric determination of poorly water soluble drug Lanzoprazole using Hydrotropic solubilization technique. Lanzoprazole showed increased solubility with the increase in the concenteration of sodium benzoate without interference,And thereis no increase in solubility by increase in concenteration of urea and sodium lauryl sulphate.The λmax of drug with sodium benzoate was found to be linear in the range of 5-25µg/ml.

S. Kanolkar and T. Walke [74] developed an analytical method for the for the estimation of Prulifloxacin, from its tablet dosage form. In this method 2.0 M Sodium benzoate solution was employed as hydrotropic solubilizing agentThe λ max was observed at 296nm.The drug follows Beer's law in concentration range of 15-60 mcg/ml with coefficient correlation value of 0.992.

T. Shukla et al[75] developed an analytical method for the Estimation of Lornoxicam in their Marketed Formulation. sodium benzoate was chosen as hydrotrope. The sample solution has shown the λmax at 376 nm and obeys the lambert beer law in the concentration range of 5-25 µg/ml with a correlation coeffi cient of 0.999.

K.Lurdhu Mary and S.Manohar Babu[76] developed an analytical method for estimation of Etraverine by using hydrotropic agents like citric acid, sodium salicylate and sodium benzoate. The maximum absorbance of Etravirine in hydrotropic agent was found at 259, 277,245nm respectively. Etravirine was found to be linear in the concentration range of 1-5µg/ml respectively.

SK.Masthannamma ,K.Sravani, T.Ananta Sridhar and B. Siva Sankar Naik[77] developed UV-Spectrophotometric determination of Metronidazole in bulk and pharmaceutical dosage form using hydrotropic solubilization technique. Solubility of metronidazole is increased by using 8M urea as a hydrotropic agent. Metronidazole showed the maximum absorbance at 318 nm in method A , 314-322 nm in method B and 314 nm in method C. The developed methods were found to be linear in the range of 2-16 µg/ml with correlation coefficients (R) of 0.999, 0.999 and 0.998 respectively.

Aher B.O.,Jain N.P., Jain U.N., Paithankar A.R., Bagul T.P., and Gaikwad S.S[78] developed Novel Spectrophotometric Estimation of Acyclovir Using Hydrotropic Solublizing Agent 5M

Urea solution.The selected wavelength for estimation was 254nm. Linearity was observed in the range of 10-100µg/ml.

S. K. Masthannamma T. Ananta Sridhar, B. Siva Sankar Naik, T. Anil Kumar[79] developed a method for the estimation of tinidazole using 8M urea as hydrotropic agent. tinidazole showed maximum absorbance at 318 nm in method A,314-322 nm in method B and 268 nm in method C. At these wavelengths, hydrotropic agent and other tablet excipients did not show any significant interference in the spectrophotometric assay. The developed methods were found to be linear in the range of 5-25 µg/ml with correlation coefficients (R) of 0.999, 0.991 and 0.999

S.K.Masthannamma,B.Siva Sankar Naik, T.Anil Kumar, T. Ananta Sridhar[80]developed a UV-Spectrophotometric determination of ofloxacin in bulk and pharmaceutical dosage form using hydrotropic solubilization technique using 1M piperacine as hydrotropic agent. ofloxacin showed the maximum absorbance at 288 nm in method A,284-292 nm in method B and 334 nm in method C. At these wavelengths, hydrotropic agent and other tablet excipients didnot show any significant interference in the spectrophotometric assay. The developed methods were found to be linear in the range of 2-12 µg/ml with correlation coefficients (R) of 0.997, 0.998 and 0.999 respectively.

K.Lurdhu Mary and S.Manohar babu[81] developed an an ecofriendly spectroscopic method for estimation of Etraverine by using hydrotropic agents like citric acid, sodium salicylate and sodium benzoate. The maximum absorbance of Etravirine in hydrotropic agent was found at 259, 277,245nm respectively. Etravirine was found to be linear in the concentration range of 1-5µg/ml.

Jesika Rane, Vinod Thakre ,R.L.Bakal, Suraj Patil[82] developed a Novel spectrophotometric estimation of Gliclazide by using mixed hydrotropic solubilization phenomenon using urea and sodium acetate at 225 nm.The method was linear in the range of 2-105µg/ml.

Aher B.O,. Jain N.P, Shinde G.S, Gayke Amol, Jadhav V. K , and Bankar K.A[83] developed a Novel spectrophotometric estimation of atenolol using hydrotropic solublizing agent 5M urea. The selected wavelength was 275 nm.Method was linear in the range of 200-1000 µg/ml.

V.Niraimathi, A.Jerad Suresh, A.Alageswaran[84]developed a UV Spectrophotometric Determination of Fenofibric Acid by Using mixed Hydrotropy. 2M urea, and 1M sodium citrate solution was used as hydrotropic solubilizing agents. Method A involves the determination of fenofibric acid by standard absorbance method at 299 nm. Method B and Method C involves the determination of fenofibric acid by first derivative spectrophotometry and second derivative spectrophotometry respectively. The normal spectrum was derivatized to first and second order derivative spectrum. The Beer's concentration was found to be taken 5-30 µg/mL; Method D involves the determination of fenofibric acid by area under curve in the range of 275-316 nm

CONCLUSION

The survey reveals that the UV-spectrophotometric estimation of poorly water soluble drugs were conducted successfully by using the approach of hydrotropic solubilization technique. The aqueous solubility of many drugs like nalidixic acid, norfloxacin ,tinidazole, metronidazole, metformin hydrochloride, salicylic acid, amlodipine besylate, atenolol, benzoic acid, cefexime, etoricoxib, Fluvoxaminemaleate, frusemide, hydrochlorthiazide, levofloxacin, naproxen, nifedipine, paracetamol, diclofenacsodium ibuprofen sodium,cefprozil,etc were found to be enhanced by the incorporation of sodiumbenzoate,niacinamide,sodiumacetate,sodiumtartarate,urea,sodiumcitrate,sodiumsalicylate,sodium ascorbate, potassium acetate as hydrotropic solubilizers respectively.The method was new ,simple and safe. In present scenario this method is getting lot of values and may be proved the best method in future.

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