IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# "A REVIEW ARTICLE- ECOFRIENDLY AND ECONOMIC APPLICATIONS OF MIXED HYDROTROPIC SOLUBILIZATION IN THE PHARMACEUTICAL FIELDS OF ANALYSIS AND FORMULATIONS"

**YASHI THAKUR, KHUSHBOO NAGWANSHI, SIMRAN LUDHIANI, R.K. MAHESHWARI**

Shri G.S. Institute of Technology and Science, 23, Park Road, Indore 452003 (M.P.), India

**ABSTRACT**

Solubility of poorly water-soluble drugs has been a really vital issue in screening studies of new chemical entities as well as formulation research. Drug efficacy can be restricted by poor aqueous solubility. Therefore, solubilization of poorly water-soluble drug is encountered on challenging factor. Poor solubility of any drug or chemical entity directly affects its bioavailability, as bioavailability is dependent on several factors like drug solubility and permeation across biological membranes. Various methodologies have been employed to enhance the aqueous solubility of poorly water-soluble drug. Hydrotropic solubilization is one of them. Hydrotropic solubilization is the process of enhancement in aqueous solubility of poorly water-soluble drugs in presence of large concentration of a hydrotropic agent or hydrotropes. Hydrotropes possess the ability to increase the solubility of drug. Various hydrotropic agents such as sodium benzoate, sodium citrate, niacinamide, sodium caprylate, sodium acetate, sodium ascorbate, sodium gluconate, urea etc., have been employed to increase the solubility of poorly water-soluble drugs. Mixed hydrotropic solubilization is a novel and advance way for enhancement in solubility of poorly water-soluble drugs by using different hydrotropic agents in small and safe concentrations to reduce the toxicities.

**Keywords: Solubility, Hydrotropy, Mixed hydrotropy, Hydrotropic agents, Poorly water-soluble drugs.**

## INTRODUCTION

Hydrotropes are a class of chemical compounds that cause a several fold increase in the aqueous solubility for sparingly soluble solute under normal conditions. This phenomenon is termed hydrotropy. Hydrotropy is considered as a unique and unprecedented solubilization technique because of the easy recovery of dissolved solute and possible re-use of hydrotropic solutions. This technique also facilitates the separation of close boiling isomeric components from their binary mixtures forming simple eutectics and non-isomers in mixtures besides increasing the rate of heterogeneous reactions. Neuberg (1916) identified this pioneering technique. The only drawback of hydrotropic solubilization is the use of large concentration of hydrotropic agents which lead to limit its application. Thus, to overcome this problem and to increase the application of hydrotropic solubilization Dr. R.K. Maheshwari proposed the mixed hydrotropic solubilization technique in 2008. It is novel and more advance way for increasing the solubility of poorly water-soluble drugs. Mixed hydrotropic solubilization involves the addition of small concentration of different hydrotropic agents to increase the solubility of poorly water-soluble drugs by several folds. The increase in solubility can be measured by solubility enhancement ratio which is, the solubility of drug in hydrotropic solution upon the solubility of drug in water.[1]

$$\textbf{Solubility Enhancement Ratio} = \frac{\text{Solubility of drug in mixed hydrotropic solution}}{\text{Solubility of drug in water}}$$

## ADVANTAGES OF MIXED HYDROTROPIC SOLUBILIZATION

1. It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of solubilizing agents in lower concentration.
2. It is new, simple, cost-effective, safe, accurate, precise and environmentally friendly method for the analysis (trimetric, spectrophotometric and TLC analysis) of poorly water-soluble drugs 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.

## APPLICATION OF MIXED HYDROTROPY

### 1.TITRIMETRIC ANALYSIS –

Maheshwari R.K. *et al.* estimated solubility of ketoprofen through titrimetric and found the enhancement in the solubility of ketoprofen in a mixed hydrotropic solution containing 30% Urea and 30% Sodium citrate was more than 700-fold. Mixed hydrotropic solution was employed to solubilize a poorly water-soluble drug ketoprofen, in bulk to carry out titrimetric analysis precluding the use of organic solvents. The bulk containing ketoprofen was analyzed successfully. Statistical data proved accuracy, reproducibility and the precision of the proposed method.[2]

Maheshwari R.K. *et al.* found a miraculous synergistic effect on enhancement in solubility of very sparingly water-soluble drug by mixing more than one hydrotropic agent. The enhancement in the solubility of frusemide in a mixed hydrotropic solution containing 5 M Urea, 1 M Sodium acetate and 0.4 M Sodium citrate was more than 15-fold (as compared to the solubility in distilled 1water). This proved a synergistic enhancement in solubility of very sparingly water-soluble drug due to mixed hydrotropy. Mixed hydrotropic solution was employed to solubilize frusemide, in bulk to carry out titrimetric analysis precluding the use of organic solvents. The bulk containing frusemide as well as the tablets containing frusemide were analyzed successfully. Statistical data proved accuracy, reproducibility and the precision of the proposed method. The presence of hydrotropic agents did not interfere in the analysis of frusemide.[3]

Shrivastav R. *et al.* performed titrimetric estimation of aceclofenac using mixed hydrotropic solubilization. Miraculous synergistic effect on enhancement in solubility of poorly water-soluble drug was observed by mixing two hydrotropic agents. The enhancement of solubility of drug aceclofenac was more than 700-fold in (22.5% Urea + 22.5% Sodium citrate) solution as compared to solubility in distilled water. Mixed hydrotropic solution was employed to solubilize a poorly water-soluble drug, aceclofenac, from fine powder of its tablets to carry out

titrimetric estimation precluding the use of organic solvents. The tablet containing aceclofenac were analyzed. Recovery studies and statistical data proved accuracy, reproducibility and precision of the proposed method. The presence of hydrotropic agents (urea and sodium citrate) did not interfere in the analysis.[4]

Maheshwari R.K. *et al.* studied that the mixed hydrotropy blend (MHB) containing 15% Sodium salicylate, 5%w/v Niacinamide, 5%w/v Sodium acetate and 5%w/v Sodium citrate have been employed to solubilize a poorly water soluble drug, ibuprofen for its titrimetric analysis in tablets and found the enhancement in solubility more than 40 folds as compared to the solubility in water. Results of analysis by proposed methods were comparable with those of standard Indian pharmacopeial method. Results of analysis have been validated statistically. The proposed method is quicker than pharmacopeial method with its novelty, simplicity, accuracy and reproducibility.[5]

**Table: -1 Application of mixed hydrotropy in titrimetric analysis**

| S.NO. | DRUGS | MIXED HYDROTROPY SOLUTION | SOLUBILITY ENHANCEMENT RATIO | REFERENCE NO. |
|---|---|---|---|---|
| **1.** | Ketoprofen | 30% Urea and 30% Sodium citrate | >700 Folds | 2 |
| **2.** | Frusemide | 5 M Urea, 1 M Sodium acetate, 0.4 M Sodium citrate | >15 Folds | 3 |
| **3.** | Aceclofenac | 22.5% Urea and 22.5% Sodium citrate | >700 Folds | 4 |
| **4.** | Ibupofen | 15% Sodium salicylate,5%w/v Niacinamide, 5%w/v Sodium acetate and 5% Sodium citrate | >40 Folds | 5 |

## 2. IN SPECTROPHOTOMETRIC ANALYSIS –

Nair, V and Rajput, M.S. found novel, safe and sensitive method of UV spectrophotometric analysis by using a mixed hydrotropic solution, containing a blend of 30% w/v Urea, 13.6% w/v Sodium acetate and 11.8% w/v Sodium citrate for the quantitative determination of ketoprofen, a poorly water-soluble drug, in tablet dosage form. Beer's law was obeyed in the concentration range of 4–20 µg/ml. There was more than 570-fold enhancement in aqueous solubility of ketoprofen in mixed hydrotropic solution as compared with the solubility in distilled water precluding the use of organic solvents. Hydrotropic agents and commonly used tablet excipients did not interfere in spectrophotometric estimation.[6]

Maheshwari R.K. *et al.* described that in this investigation, a blend consisting of 30% Urea and 30% Sodium citrate solution has been used as hydrotropic solubilizing agent for ketoprofen to carry out its spectrophotometric analysis. Ketoprofen shows tremendous increase in solubility of more than 700 folds in this blend. Thus, it was thought worthwhile to solubilize ketoprofen by this blend of solubilizing agents to carry out spectrophotometric analysis. Ketoprofen showed maximum absorbance at 260 nm and Beer's law was obeyed in concentration range of 4-20 µg/ml. The mean percent label claims estimated were very close to 100 with low values of standard deviation, percent coefficient of variation and standard error indicating the accuracy of the proposed analytical method. The results of recovery studies showed that the mean percent recoveries ranged from 99.49 to 101.37, which further proved the validity and reproducibility of the proposed method. Thus, it may be concluded that the proposed method of analysis is new, simple, cost-effective, environmentally friendly, safe, accurate, and reproducible.[7]

Maheshwari R.K. *et al.* described new method of UV spectrophotometric estimation by using a mixed hydrotropic solution containing 8 % 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. There was more than 25-fold enhancement in aqueous solubility of hydrochlorothiazide in mixed hydrotropic solution as compared with the solubility in distilled water precluding the use of organic solvents. Hydrotropic agents and commonly used tablet excipients did not interfere in spectrophotometric estimation. Results of the analysis were validated statistically and by recovery studies.[8]

Sherja A.P. *et al.* found that there was a significant synergistic effect on enhancement in solubility of a poorly water-soluble drug by mixing two hydrotropic agents. The enhancement in solubility of nitazoxanide was more than 10 and 12 folds in 1 M Sodium benzoate solution (SB) and 1 M Sodium salicylate (SS) solution, respectively as compared to its solubility in distilled water. The enhancement in the solubility of nitazoxanide in a mixed hydrotropic solution (SB-SS) containing 1 M Sodium benzoate and 1 M Sodium salicylate was more than 17 folds. Thus, a mixed hydrotropic solution of sodium benzoate and sodium salicylate was employed to carry out spectrophotometric analysis precluding use of organic solvents. The tablets containing nitazoxanide were analyzed successfully.[9]

Sanap D.D. *et al.* used mixed hydrotropic solution containing 45% Urea and 5% Sodium citrate as hydrotropic solubilizing agent for the quantitative determination of poorly water-soluble budesonide from bulk and tablet dosage form. The solubility of budesonide increases more than 20 times in mixed hydrotropic solution as compared to solubility in distilled water, thus, a mixed hydrotropic solution containing 45% Urea and 5% Sodium citrate was employed to carry out spectrophotometric analysis precluding use of organic solvents.[10]

Shrivastav R. *et al.* found a new, simple, safe, accurate and reproducible spectrophotometric analytical method for the quantitative estimation of gatifloxacin in solid dosage form by mixed hydrotropic agents. 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. Therefore, it was thought worthwhile to solubilize this poorly water-soluble drug from fine powder of its tablets by this novel mixed hydrotropic solubilization technique and then carryout its spectrophotometric estimation at 333 nm (20% N, N dimethyl urea and 20% Sodium citrate). The results of the analysis were validated statistically and by recovery studies & it follows Beer's law in concentration range of 10-60 µg/ml. The percent label claims and percent recoveries estimated were close to 100 with low values of standard deviation, percent coefficient of variation and standard error.[11]

Kadam S.R. *et al.* studied 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. The results of analysis have been validated statistically and by recovery studies. Parameters such as linearity, precision, accuracy, specificity and robustness were studied as reported in the International Conference on Harmonization guidelines. So, this method can be successfully employed in the routine analysis of metronidazole and miconazole nitrate in bulk drug and dosage forms like ovules and gel.[12]

Jain R. *et al.* found methods developed for the simultaneous estimation of poorly water-soluble drugs levofloxacin and ornidazole in tablet dosage form using 2 M Sodium acetate and 8 M Urea solution (50:50% w/w) as mixed hydrotropic solution. Sodium acetate and urea solution did not show any absorbance above 240 nm and thus no interference in the estimation of drugs were seen. Levofloxacin and ornidazole follows the Beer's law in the concentration range of 5-25 µg/ml (r2= 0.9997 and 0.9998). Method-A simultaneous equation method employs 287 and 320 nm as two analytical wavelengths, method-B is absorption ratio method, which uses 301 and 320 nm as two analytical wavelengths were used for estimation of levofloxacin and ornidazole. The mean percent label claims of tablet dosage were found to be 98.528±0.431 and 97.916±0.732 in method A, 97.586±0.821 and 98.642±0.293 in method B for levofloxacin and ornidazole respectively. The standard deviation, coefficient of variance and standard error were obtained for levofloxacin and ornidazole was satisfactorily low. The developed methods were validated according to ICH guidelines and values of accuracy, precision and other statistical

analysis were found to be in good accordance with the prescribed values therefore the both methods can be used for routine monitoring of LEVO and OZ in industry in the assay of bulk drug and tablets.[13]

Jain N. *et al.* explored hydrotropic solubilization methods which were developed for the simultaneous estimation of poorly water-soluble drugs metronidazole (MTR) and furazolidone (FZ) in a tablet dosage form using 2 M Sodium acetate and 8 M Urea solution (50:50% v/v) as a mixed hydrotropic solution. MTR and FZ show maximum absorbance at 319 and 364 nm, respectively. Sodium acetate and urea solution did not show any absorbance above 240 nm and thus no interference in the estimation of drugs was seen. MTR and FZ follow Beer's law in the concentration range of 10–50 lg/ml and 5–25 lg/ml (r2 = 0.9992 and 0.9996). The developed methods were validated according to ICH guidelines and values of accuracy, precision and other statistical analysis were found to be in good accordance with the prescribed values therefore both methods can be used for routine monitoring of MTR and FZ in industry in the assay of bulk drug and tablets.[14]

Remi S. and Varkey J. worked on UV spectrophotometric method using a hydrotropic blend of 20% Sodium benzoate and 20% Niacinamide for the estimation of poorly water-soluble drug paliperidone in bulk and pharmaceutical dosage form. There were more than 87-fold solubility enhanced in hydrotropic blend as compared with distilled water. The paliperidone shows the maximum absorbance at 286 nm. At this wavelength hydrotropic agents 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 10-50 µg/ml with correlation coefficient ($r^2$) of 0.9990. The mean percent label claims of tablets of paliperidone in two marketed formulation I and formulation II estimated by the proposed method was found to be 99.48 + 0.292 and 98.01 + 0.326 respectively. The developed method was validated according to ICH guidelines and values of accuracy, precision and other statistical analysis were found to be in good accordance with the prescribed values.[15]

Soni K. and Sharma K. worked on an eco-friendly method to estimate spectrophotometrically, the nimesulide drug in tablet formulations without the help of organic solvent. Mixed hydrotropic tends to decrease the concentration of individual solubilizers and toxicity. Organic solvents are most frequently employed in spectrophotometric analyses. They may be sources of pollution. Some of them may be toxic while others may be costlier. In the present investigation, it was proposed to solubilize nimesulide by use of the mixed hydrotropic concept. Nimesulide shows maximum absorbance in the concentration range of 10-50 µg/ml at 390 nm. The method of analysis has been validated for different parameters like linearity, accuracy, and precision. The percent drug estimated in tablet formulation of tablet-I and of tablet-II were 102.61± 0.669 and 102.10± 0.461 respectively. The range of percent recoveries varied from 102.24±0.508 to 102.83±0.442. Sodium citrate and phenol do not interfere above 300 nm. The analytical method was found to be simple, free from toxicity, economic and eco-friendly.[16]

Mishra G.P. *et al.* worked to enhance the solubility of poorly water-soluble drug and performed simultaneous estimation of aeclofenac and paracetamol using mixed hydrotropy. In the present investigation, mixture of 20 mL (2 M) Urea, 30 mL of (5 M) Sodium acetate (hydrotropic solubilizing agent) was used to solubilize aceclofenac and paracetamol and carried out spectrophotometric analysis. The methods employed were absorbance ratio method (method I), derivative method (method II). The result showed that Beer's law was obeyed in concentration range of 5-50 g/mL with good linearity (r2 0.99) for both the drugs in both methods. The recoveries were within 99.67-101.33% for aceclofenac and 99.46-101.92% for paracetamol. Precision was good with acceptable limits of detection (LOD) and quantitation (LOQ) for both compounds. The optimized methods showed good reproducibility and recovery with standard deviation of < 1.0% and percent relative standard deviation less than 2.0%.[17]

Jain N. *et al.* developed novel, safe, accurate and sensitive method for spectrophotometric quantitative determination of poorly water-soluble drug torsemide by using mixture of 2 M Sodium acetate and 8 M Urea in the ration of 50:50% v/v solution as hydrotropic solubilizing agent. Toresemide a very slightly water-soluble diuretic drug in tablet dosage form. There were more than 86-fold enhancements in the solubility of torsemide increases in mixed hydrotropic solution as compared to solubility in distilled water precluding the use of organic solvents. Toresemide shows maximum absorbance at 288 nm. Sodium acetate, urea and other commonly used tablet excipients did not show any absorbance above 240 nm, and thus no interference in the estimation was seen. Torsemide is obeyed Beer's law in the concentration range of 10 to 50 µg/ml (r 2 = 0.9996) in mixed hydrotropic solution with mean recovery ranging from 99.23 to 99.64%. The present investigation is new, simple, economic,

safe, rapid, accurate and reproducible. The developed methods were validated according to ICH guidelines and result of accuracy, precision and other statistical analysis were found to be in good accordance with the prescribed values.[18]

Rathod S. *et al*. concluded mixed hydrotropy as a new, simple and rapid method indicating UV spectroscopy was developed and validated for the estimation of indomethacin in pure form, and in formulation. Mixed hydrotropic solution was used as a solvent. The adequate drug solubility and maximum assay sensitivity (320 nm) in the wavelength range of (200–400 nm), the linear calibration curve was obeyed in the con(Y=0.015X-0.002), and correlation Coefficient (R2=0.998). This determination of indomethacin capsules form, no interference was found from capsule excipients at the selected wavelength and analysis conditions. It was concluded that the developed method is accurate, sensitive, precise, and reproducible and indirectly for the estimation of indomethacin content in pharmaceutical formulation.[19]

Patil S. *et al*. applied mixed hydrotropy technology and concluded it as the ability to increase the aqueous solubility can be a valuable aid for increasing the efficacy and/or reducing adverse effects for certain drugs. In the given study the aqueous solubility of acyclovir was found to be 2 mg/ml that give the satisfactory result with regression coefficient of about 0.991. The present study was performed on UV spectrophotometer with selected wavelength of 339 nm. Linearity range was 10-50 µg/ml) and assay results was found to be 101.48%. The proposed method was new, simple, cost effective, accurate, sensitive, free from pollution and precise and can be adopted for routine analysis of acyclovir in tablet dosage form. Presence of hydrotropic agent do not show any significant interference in the spectrophotometric assay thus further confirming the applicability and reproducibility of the developed method.[20]

Salunke. P. *et al*. employed mixed hydrotropy concept in method development of ornidazole. The present work was made to obstruct the use of toxic organic solvents by preparing mixed blend of 10% Sodium acetate, 10% Urea, 10% Niacinamide, and 10% Sodium tri-citrate. Wavelength 319.20 nm was selected for the developed spectrophotometric method of ornidazole. The solubility enhancement for ornidazole in the mixed hydrotropic solution was found to be more than 40-fold as compared to the distilled water. The linearity was found to be 5-25 µg/ml with correlation coefficient 0.999. The inter- and intraday precision was found 0.9166% and 0.6066% relative standard deviation (RSD), respectively. The repeatability was found 0.23 in % RSD. The limit of detection and limit of quantitation were found to be 0.1264 and 0.38, respectively. Ruggedness study for external parameters was found within limits. The percent recovery was found to be 101.48 (for n = 9). The % purity was found 101.41. Results of method for analysis of tablet were found 99.905%. All validation parameters were found within limits.[21]

**Table: - 2 Application of mixed hydrotropy in spectrophotometric analysis**

| S.NO. | DRUGS | MIXED HYDROTROPIC SOLUTIONS USED | SOLUBILITY ENHANCEMENT RATIO | REFERENCE NO. |
|---|---|---|---|---|
| **1.** | Ketoprofen | 30% Urea, 13.6% Sodium acetate, 11.8% Sodium citrate | >570 Folds | 6 |
| **2.** | Ketoprofen | 30% Urea, 30% Sodium citrate | >700 folds | 7 |
| **3.** | Hydrochlorothiazide | 8% Niacinamide, 8% Sodium acetate, 8% Sodium benzoate, 8% Sodium citrate | >25 Folds | 8 |
| **4.** | Nitazoxanide | 1 M Sodium benzoate, 1 M Sodium salicylate | >17 Folds | 9 |
| **5.** | Budesonide | 45% Urea and 5% Sodium citrate | >20 Folds | 10 |
| **6.** | Gatifloxain | 20% N, N-dimethyl urea and 20% Sodium citrate | >15 Folds | 11 |
| **7.** | Metronidazole | 40% Urea and 10% Sodium benzoate | >14 Folds | 12 |
| **8.** | Miconazole | 40% Urea and 10% Sodium benzoate | >14 Folds | |
| **9.** | Levofloxacin | 50% 2 M Sodium acetate and 50% 8 M Urea | >49 Folds | 13 |
| **10.** | Ornidazole | 50% 2 M Sodium acetate and 50% 8 M Urea | >45 Folds | |
| **11.** | Metronidazole | 50% 2 M Sodium acetate and 50% 8 M Urea | >36 Folds | 14 |
| **12.** | Furazolidone | 50% 2 M Sodium acetae and 50% 8 M Urea | >28 Folds | |
| **13.** | Paliperidone | 20% Sodium benzoate and 20% Niacinamide | >87 Folds | 15 |
| **14.** | Nimesulide | 25% Sodium citrate and 30% Phenol | >900 Folds | 16 |
| **15.** | Aceclofenac | 2% Sodium acetate and 2% Urea | >3 Folds | 17 |
| **16.** | Paraetamol | | | |
| **17.** | Torsemide | 50% 2 M sodium Acetate and 50% 8 M Urea | >86 Folds | 18 |

**3. IN FORMULATION AND DEVELOPMENT-**

Maheshwari R.K. and Indurkhya A. studied the effect of hydrotropes such as urea and sodium citrate and blends (Urea + Sodium citrate) on the solubility of aceclofenac and prepared a formulation. The enhancement in the solubility of aceclofenac was more than 5 and 25 folds in 30% Sodium citrate solution and 30% Urea solution, respectively, as compared to its solubility in distilled water. The enhancement in the solubility of aceclofenac in a mixed hydrotropic solution containing ≥ 20% urea and 10% sodium citrate solution was more than 250 folds (compared to its solubility in distilled water). This proved a synergistic enhancement in solubility of a poorly water- soluble drug due to mixed hydrotropy. Synergistic combination of hydrotropic agents can minimize the number of hydrotropic agents employed, minimizing the chances of their toxicities. Aqueous injection of aceclofenac, using the mixed hydrotropic solubilization technique, was developed and by using the lyophilization method, the problem of inadequate stability of aceclofenac in aqueous solution was overcome. The developed formulation was studied for physical and chemical stability.[22]

Maheshwari R.K. *et al.* employed the mixed hydrotropy concept and observed that, the solubility of frusemide was raised up to 357.87 fold in blend (containing sodium benzoate, urea and sodium citrate in the ratio of 13.3:13.3:13.3) which was about 1.35 times more than the solubility in the blend containing sodium benzoate and urea in the ratio of 20:20. Combination of hydrotropic agents giving synergistic solvent action can minimize the amount of hydrotropic agents employed, minimizing the chances of their individual toxicities. Aqueous injection of furosemide, using the mixed hydrotropic solubilization technique, was developed. The developed formulation was studied for physical and chemical stability. And can be assumed that the formulation will have sufficient chemical and physical stability at room temperature.[23]

Ghada A.A. *et al.* developed a formulation of poorly water-soluble drug zaleplon using mixed hydrotropic solubilization technique and performed its characterization. The plasma GABA level of groups receiving ZP tablet formula at different doses (0.2, 0.4 and 0.6 mg/kg) were significantly different from those receiving the market tablet (Sleep aid®) at the same doses ($p<0.05$). This might be due to the presence of mixed hydrotropic agents (80% Resorcinol and 20% Sodium benzoate) in formula resulting in enhancement of solubility and thereby dissolution of the poorly water-soluble drug Zaleplon. It is clear that the desired concentration of ZP (5 mg) in mixed hydrotropic tablet. Mixed hydrotropic solubilization technique could be considered as a promising tool for enhancing the solubility and thereby the dissolution of the poorly water-soluble drug Zaleplon resulting in enhancement in its neuropharmacological effect. The mixed optimum hydrotropic tablet formula had a significant effect on plasma GABA concentration resulting in an effective CNS depressant effect after oral administration compared to the market tablet.[24]

Kadam P.S. *et al.* employed mixed hydrotropy technique and developed aqueous injection of poorly water-soluble drug. Etodolac is a Biopharmaceutical Classification System (BCS) class II drug and it is insoluble in water hence solubility and dissolution rate enhancement were carried out by using various hydrotropic blends. Etodolac was blended in different proportion with various hydrotropic agents like sodium acetate, sodium benzoate, sodium citrate etc. and other co-solvents. The optimized batches of Etodolac injection formulation were subjected to various evaluation tests and accelerated stability study. Amongst all trial batches, formulation containing 15% Sodium benzoate and 25% Solvent system S and 10% Sodium acetate, 5% Sodium citrate and 25% Solvent system were found to be more stable and passed all tests satisfactorily.[25]

Jyothrimayi P. *et al.* found that the highest solubility of low aqueous soluble drug, lansoprazole was obtained in 10% Urea solution. In order to decrease the individual hydrotrope concentration mixed hydrotropic agents were used. Highest solubility was checked with combination of these hydrotropic agents. Formulation of Immediate release tablets of lansoprazole (LPZ) using mixed hydrotropic technique with different concentrations of super disintegrants such as Crosspovidone, Croscarmellose sodium and sodium starch Glycolate were prepared by using direct compression method. Dissolution studies of prepared tablets were done using USP Type II apparatus. There is miraculous enhancement in solubility and bioavailability, hence it was concluded that the concept of mixed hydrotropic solid dispersion is novel, safe and cost-effective technique for enhancing the bioavailability of poorly water-soluble drugs.[26]

Saibabu S. *et al.* studied that the highest solubility of drug, efavirenz was obtained in 1:6:1 ratio of Urea + Sodium benzoate + Sodium acetate. This optimized combination was utilized in the preparation of solid dispersions by using distilled water as a solvent. Fourier-transform infrared to show no drug-hydrotropes interaction has occurred. Formulation of immediate release tablets of efavirenz using mixed hydrotropic technique with different concentrations of super disintegrants such as crosspovidone, croscarmellose sodium and sodium starch glycolate were prepared by using direct compression method. Dissolution studies of prepared tablets were done using USP Type II apparatus. The miraculous enhancement in solubility and bioavailability of efavirenz was clear indication of the potent mixed hydrotropy to be used in future for other poorly water-soluble drugs in which low bioavailability is a major concern.[27]

Madan J.R. *et al.* aimed to provide a fast-dissolving solid dispersion of nevirapine using novel mixed hydrotropic technique. Then different combinations of 2 and 3 hydrotropic agents namely urea, lactose, citric acid and mannitol in different ratios were used to determine solubility, so that the total concentration of hydrotropic agents was always 40%. The highest solubility was obtained in a solution of lactose and citric acid at the optimum ratio of 15:25. This optimized combination was utilized in preparing solid dispersions by a common solvent technique using distilled water as a solvent. The solid dispersions were evaluated for XRD, DSC and FTIR to show no drug-hydrotrope interaction.[28]

Maheshwari R.K. and Indurkhya applied the mixed hydrotropic concept and concluded that the aqueous solution of hydrotropic blend (20% Urea and 10% Sodium citrate) has been found to increase aqueous solubility of poorly water-soluble drug, aceclofenac. This mixed hydrotropic blend was used to prepare solid dispersion of aceclofenac. The prepared solid dispersions have been characterized by IR and XRD studies. They have been studied for dissolution rate enhancement effect. The prepared solid dispersions were found very stable.[29]

Yadav N.K. *et al.* formulated and concluded that mixed hydrotropic solid dispersion technology precludes the use of organic solvent and also decreases the individual concentration of hydrotropic agents, simultaneously decreasing their toxic potential. The flupirtine loaded solid dispersion was prepared by a solvent evaporation technique using sodium benzoate and a niacinamide hydrotropic mixture. The prepared solid dispersions were valuated regarding their solubility, mean particle size, in-vitro drug release. The prepared solid dispersions were found very stable (chemically). The superior dissolution rate due to its reduced particle size may have contributed to the increased oral bioavailability. This study demonstrated that mixed-solvency may be an alternative approach for poorly soluble drugs to improve their solubility and oral bioavailability.[30]

Agarwal G.P. *et al.* used mixed hydrotropic approaches to enhance the aqueous solubility of poorly water-soluble drug ornidazole using the hydrotropic blend urea and nicotinamide (1:1 ratio). This mixed hydrotropic blend was used to prepare solid dispersion of ornidazole. DSC thermogram, XRD, and IR spectra showed that there is no interaction between drug and hydrotropic agents. Solid dispersions are containing a blend of urea and nicotinamide as water-soluble hydrotropic carriers show fast release of drug as compared with the pure bulk drug sample and physical mixture. The proposed techniques would be economical, convenient, and safe.[31]

Madan J.R. *et al.* worked to develop a solid dispersion which can provide quick onset of action by using the concept of mixed hydrotropy. Initially, solubility of lurasidone was determined individually in nicotinamide, sodium citrate, urea and sodium benzoate at concentration of 10, 20, 30 and 40% w/v solutions using purified water as a solvent. In order to decrease the individual hydrotropes concentration mixed hydrotropic agents were used. Highest solubility was obtained in 15:20:5 ratio of Nicotinamide + Sodium benzoate + Sodium citrate. This optimized combination was utilized in the preparation of solid dispersions by using distilled water as a solvent. Solid dispersions were evaluated for X-ray diffraction, differential scanning calorimetry and Fourier-transform infrared to show no drug-hydrotropes interaction has occurred. This solid dispersion was compressed to form fast dissolving tablets.[32]

Houssieny B.M. *et al.* explored the application of mixed hydrotropic concept to formulate and develop a solid dispersion. Dexibuprofen, is a practically water-insoluble nonsterodial anti-inflammatory drug which has a better anti-inflammatory effect than ibuprofen. A mixed hydrotropic solubilization technique was applied in order to improve the aqueous solubility and dissolution rate of dexibuprofen. Nine formulae were prepared using different concentrations of hydrotropic agents (sodium citrate dihydrate and urea). The prepared formulae were inspected

visually for color and odor. Hygroscopicity, micromeretic properties, solubility, and pH for 1% aqueous solutions were determined. In-vitro dissolution studies of the different prepared formulae were performed adopting the USP XXII dissolution method type I basket apparatus method. The prepared formulae were characterized by infrared (IR) spectroscopy and differential scanning calorimetry (DSC). The prepared formulae were a white color, odorless, slightly hygroscopic and exhibited good flow properties. Formulae containing higher amounts of hydrotropic agents exhibited an increase in the pH, solubility, rate and amount of dexibuprofen released from the dissolution medium. The highest dissolution rate was achieved from the F9 formula at drug, sodium citrate dihydrate, urea ratio (1:3:7.5). IR and DSC thermograph of dexibuprofen, hydrotropic agents and prepared formulae indicated the presence of intermolecular interaction between drug and hydrotropic agents which increased solubility and dissolution rate of drug, also, there is no chemical interaction confirming the stability of the drug with hydrotropic agents.[33]

Ibrahim, N.J *et al*. applied mixed hydrotropic technique to formulate solid dispersion in ratio 1:3 (niacinamide: sodium benzoate). Fourier-transform infrared spectroscopy was used to exclude any drug-hydrotropes interaction. The dissolution rate of nimodipine from solid dispersion and physical mixture were studied using USP type II dissolution test apparatus in acetate buffer (pH 4.5) as a dissolution media. Hydrotropic solid dispersion of nimodipine with a blend (30% Sodium benzoate and 10% Niacinamide) increased the dissolution rate of the drug by 1.5 folds compared to the marketed conventional nimodipine tablet. Fourier-transform infrared analysis did not show any physicochemical interaction between drug and carriers in solid dispersion formulation. Immediate dissolution of practically insoluble drug nimodipine in dissolution media indicates that it has a great potential to solubilize the drug in biological fluids. Thus, a considerable improvement in bioavailability and onset of action of the drug can be predictable. Adding of a hydrotropic agent with nimodipine in solid dispersion increased the dissolution rate of the drug compared to the marketed conventional nimodipine table.[34]

Surwade, K. and Saudagar, R. worked on mixed hydrotropic solid dispersion techniques with the purpose to enhance the solubility of AZ by using the concept of mixed hydrotropy. Initially, solubility of AZ was determined individually in sodium acetate, sodium citrate, urea and sodium benzoate at concentration of 10, 20, 30 and 40% w/v solutions using purified water as a solvent. To decrease the individual hydrotropes concentration mixed hydrotropic agents were used. Highest solubility was obtained in 5:20:15 ratio of Urea + Sodium acetate + Sodium benzoate. This optimized combination was utilized in the preparation of solid dispersions by using distilled water as a solvent. Solid dispersions were evaluated for X-ray diffraction, differential scanning calorimetry and fourier-transform infrared to show no drug-hydrotropes interaction has occurred. This solid dispersion was compressed to form tablets. Dissolution studies of prepared tablets were done using USP Type II apparatus. The batch F6 tablets show 92.79% cumulative drug release within 45 min. The miraculous enhancement in solubility and bioavailability of azilsartan medoxomil was clear indication of the potential of mixed hydrotropy to be used in future for other poorly water-soluble drugs in which low bioavailability is a major concern.[35]

**Table: - 3 Application of mixed hydrotropy in formulation and development**

| S. NO | DRUG | HYDROTROPIC SOLUTIONS USED | NAME OF FORMULATION PREPARED | REFERENCE NO. |
|---|---|---|---|---|
| **1.** | Aceclofenac | Urea,<br>Sodium citrate | Aqueous injection | 22 |
| **2.** | Fruosemide | Sodium benzoate,<br>Urea,<br>Sodium citrate,<br>Sodium acetate | Aqueous injection | 23 |
| **3.** | Zaleplon | Resersinol and<br>Sodium benzoate | Oral Tablets | 24 |
| **4.** | Etodolac | Sodium benzoate,<br>Sodium acetate,<br>Urea,<br>Sodium citrate | Aqueous injection | 25 |
| **5.** | Lansoprazole | Crosspovidone,<br>Crosscarmellose sodium,<br>Sodium starch,<br>glycolate | Immediate release tablets | 26 |
| **6.** | Efavirenz | Urea,<br>Sodium benzoate,<br>Sodium acetate | Immediate release tablets | 27 |
| **7.** | Nevirapin | Lactose,<br>Urea,<br>Citric acid,<br>Mannitol | Solid dispersion | 28 |
| **8.** | Aceclofenac | Urea and sodium citrate | Solid dispersion | 29 |

| | | | | |
|---|---|---|---|---|
| **9.** | Flurpirtine Maleate | Sodium benzoate, Niacinamide, Sodium citrate, Sodium acetate | Solid dispersion | 30 |
| **10.** | Orinidazole | Urea and Nicotinamide | Solid dispersion | 31 |
| **11.** | Lurasidone hydrochloride | Nicotinamide, Sodium benzoate, Sodium citrate | Solid dispersion | 32 |
| **12.** | Dexibuprofen | Urea and Sodium citrate. | Solid dispersion | 33 |
| **13.** | Nimodipine | Sodium benzoate and Niacinamide | Solid dispersion | 34 |
| **14.** | Azilasartan medoxomil | Urea, Sodium acetate, Sodium benzoate | Solid dispersion | 35 |
| **15.** | Furosemide | Urea, Sodium benzoate, Sodium citrate, Sodium acetate | Solid dispersion | 1 |

**4. IN THIN LAYER CHROMATOGRAPHY-**

Salunke P.A. *et al.* performed the thin layer chromatography using mixed hydrotropic method which is used to enhance water solubility of poorly water-soluble drug by using various hydrotropes. As a model sample bromocresol green and phenol red was selected. Both dyes soluble in optimized single hydrotropic solution like as 20% Niacinamide, 25% Niacinamide, 10% Sodium benzoate and mixed hydrotropic solution like 10% Sodium citrate and 10% Urea. Mixed hydrotropic solution of 10% Sodium citrate and 10% Urea used as mobile phase gives better result. $R_f$ value of bromocresol green and phenol red in mixed hydrotropic solution was found to be 0.51 and 0.82 respectively. In single hydrotropic solution dyes get completely soluble but chromatographic separation does not obtained properly. Mixed hydrotropic solution used for enhancement of aqueous solubility of dyes. This same solution when used as a mobile phase proper separation observed from mixture of dyes. The rate of separation was faster in mixed hydrotropic mobile phase by using thin layer chromatography.[36]

Wadhwani H. *et al.* were employed hydrotropic and mixed hydrotropic solutions as mobile phase to perform TLC of some drugs precluding the use of organic solvents. Propranolol hydrochloride, guaifenesin, ciprofloxacin hydrochloride, pyridoxine hydrochloride, lidocaine hydrochloride, thiamine hydrochloride, metformin hydrochloride, piperazine citrate and losartan potassium were selected as model drugs. Sodium benzoate, sodium citrate, sodium acetate, & niacinamide in various combinations. In mixed hydrotropy, the composition of blends containing various hydrotropic agents can be varied in such a way that proper $R_f$ value of drug spot is obtained without tailing effect.[37]

• **CONCLUSION:** Analytical studies such as UV spectrophotometry, titrimetry, TLC and formulation and development of drugs in pharmaceutical industries, government analytical laboratories, and forensic science laboratories, among others, involve the use of hazardous organic solvents such as methanol, hexane, xylene, acetone, chloroform, dimethylformamide, diethyl amine, pyridine, cyclohexane, ethyl acetate, 1,2- dimethoxy ethane, acetone, ethanol, benzene, carbon tetrachloride, formic acid and heptane. The majority of organic solvents

in classes I and II are extremely dangerous to humans. Some of them are also carcinogenic. Organic solvent disposal is widespread and expensive.

We can see from the above literature that all of the proposed methods of TLC, UV spectrophotometry, titrimetry analysis, formulation and development are simple, cost effective, ecofriendly, and safe because they involve the use of mixed hydrotropic agents that have successfully replaced harmful organic solvents. These approaches provided precise and reproducible results in all pharmaceutical fields. In different pharmacopoeia, these analytical techniques are worth adopting. In future, the laboratories intended for developing new analytical procedures can use such environmentally friendly concept successfully.

**REFERENCES-**


1. Maheshwari, R.K.; Jagwani, Y. (2011). "Mixed Hydrotropy: Novel science of solubility enhancement." Indian Journal of Pharmaceutical Sciences, **6**,179-183.
2. Maheshwari, R.K.; Sharma, S.; Rai, N; Rajput, M. (2010). "Simple titrimetric method to estimate ketoprofen in bulk using mixed hydrotropy." Journal of Pharmacy Research, **3**(3): 442-443.
3. Maheshwari, R.K.; Rai, N.; Sharma, S.; Rajput, M.S.; Soni, S. **(**2010). "New titrimetric analysis of frusemide in bulk and tablets using mixed hydrotropy concept." Drug Invent Today, **2**(4): 223-235.
4. Shrivastav, R.; Khare, A.; Agrawal, S.; Patel, S. (2011). "New titrimetric estimation of aceclofenac tablets using mixed hydrotropy." International Journal of Pharmaceutical Sciences Review and Research, **11**(1): 140-141.
5. Maheshwari, R.K.; Pathak, S.; Sahu, P. (2021). "Ecofriendly application of mixed hydrotropy for titrimetric analysis of ibuprofen tablets." International Journal Of Science and Research, **10**(5):954-956.
6. Nair, V.; Rajput, M.S. (2010). "A simple spectrophotometric estimation of Ketoprofen in tablets using mixed hydrotropy." Der Pharma Chemica, **2**(2): 267-271.
7. Maheshwari, R.K.; Rathore, A.; Agrawal, A. (2010). "New spectrophotometric method to determine ketoprofen in tablet dosage form by applying mixed hydrotropy." International Journal of Chemical and Analytical Sciences ,**1**, 62-63.
8. Maheshwari, R.K.; Rajput, M.S.; Sharma, S.; Nair, V. (2010). "New spectrophotometric determination of hydrochlorothiazide in tablets using mixed hydrotropic solubilization technique." Der Pharmacia Letter, **2**(1): 70-74.
9. Sherje, A.P.; Rahigude, A.; Warma, S.; Vanshiv, S.D. (2010). "Mixed hydrotropy in spectrophotometric analysis of nitazoxanide." International Journal of ChemTech. Research, **2**(4): 1965-1969.
10. Sanap, D.D.; Sisodiya, A.M.; Patil, S.H.; Janjale, M.V. (2011). "Novel and validated spectrophotometric determination of budesonide from bulk and tablets using mixed hydrotropic solubilization technique." International Journal of Pharmaceutical Sciences and Research, **2**(9): 2419-2423.
11. Shrivastava, R.; Jain, R.; Patel, S. (2011). "Spectrophotometric analysis of gatifloxacin tablets using mixed hydrotrophy." International Journal of Pharmaceutical Sciences and Research, **2**(10): 2709-2711.
12. Kadam, S.R.; Janjale, M.V.; Akole, S.B.; Bhosle, S.S. (2012). "Application of mixed hydrotropic solubilization technique for simultaneous spectrophotometric estimation of metronidazole and miconazole nitrate from different pharmaceutical dosage forms." International Journal of Pharmaceutical & Biological Archives, **3**(2): 383-390.
13. Jain, R.; Jain, N.; Maheshwari, R.K.; Jain, S.K. (2013). "Quantitative estimation of levofloxacin and ornidazole by UV spectrophotometer: A mixed hydrotropy solubilization approach." International Journal of Pharmaceutical Sciences and Research, **4**(8): 3073-3079.
14. Jain, R; Jain, N; Jain, D.K.; Patel, V.K.; Rajak, H; Jain, S.K. (2013). "Novel UV spectrophotometer methods for quantitative estimation of metronidazole and furazolidone using mixed hydrotropy solubilization." Arabian Journal of Chemistry, **10**(1): 151-156.
15. Remi, S.L.; Varkey, J. (2018). "An ecofriendly novel spectrophotometric estimation and validation of paliperidone in bulk drugs and their dosage forms by mixed hydrotropic solubilisation method." Asian Journal of Pharmaceutical and Health Sciences, **8**(4): 1996-2001.

16. Soni, K.; Sharma, K. (2019). "An ecofriendly spectrophotometric analysis pf poorly-water soluble drug (Nimesulide) using the mixed hydrotropic concept." Asian Journal of Pharmaceutical and Health Sciences, **9**(4): 2181-2184.
17. Mishra, G.P.; Panigrahi, D.; Joshi, H.; Meena, R. (2014). "Simultaneous estimation and validation of acelofenac and paracetamol in bulk and tablets using mixed hydrotropic Agents." Chemical Sciences Transactions, **3**(2): 664-669.
18. Jain, N.; Jain, R.; Thakur, N.; Gupta, B.M.; Banweer, J.; Jain, S. (2010). "Novel spectrophotometric quantitative estimation of toresemide in tablet using mixed hydrotropic agents." Scholar Research Library, **2**(3): 249-254.
19. Rathod, S.B.; Salunke, P.A.; Kulkarni, V.C.; Chavhan, B.R.; Barhate, S.D. (2018). "Method development and validation of indomethacin in bulk drug and capsule formulation by mixed hydrotropy." Research Journal of Pharmaceutical Dosage Forms and Technology, **10**(3): 175-178.
20. Patil, S.S.; Barhate, A.S.; Patil, A.S.; Patil, A.V.; Patil, H.K.; Salunke, P.A.; Wagh, R.S. (2019). "Novel mixed hydroptropic solubilization technique for analytical method development and validation of acyclovir in bulk and tablet formulation by spectrophotometry." Asian Journal of Pharmaceutical Analysis, **9**(1): 25-29.
21. Salunke, P.A.; Rakhonde, A.; Rathod, A.; Rathod, G.; Patil, S.; Wagh,S.; Barhate, S.(2017). "Development and validation of mixed hydrotropic solubilisation method for spectrophotometric determination of ornidazole in bulk drug and tablet." Journal of Pharmacy Research, **11**(11): 1414-1420.
22. Maheshwari, R.K.; Indurkhya, A. (2010). "Formulation and evaluation of aceclofenac injection made by mixed hydrotropic solubilization technique." Iranian Journal of Pharmaceutical Research, **9**(3): 233-242.
23. Maheshwari, R.K.; Jawade, S.; Fouzdar, A. (2015). "Formulation development of aqueous injection of poorly soluble drug using mixed hydrotropic solubilization concept and its evaluation." International Journal of Pharmaceutical Sciences and Drug Research, **7**(1): 8-12.
24. Ghada, A.A.; Maha. A.M.; Mostafa A. (2015). "Novel mixed hydrotropic solubilization of zaleplon: Formulation of oral tablets and In-vivo neuropharmacological characterization by monitoring plasma GABA level." Journal of Drug Delivery Science and Technology, **10**(30): 120-124.
25. Kadam, P.S.; Pande, V.V.; Vibhute, S.K.; Giri, M.A. (2016). "Exploration of mixed hydrotropy strategy in formulation and development of etodolac injection." Journal of Nanomedicine Research, **3**(4): 1-7.
26. Jyothirmayi, P.; Sumathi, S.; Yuvraj, V.; Anusha, A.; Suryakumari, C. (2018). "A novel solubility enhancement method of lansoprazole by mixed hydrotropy for the formulation and evaluation of fast dissolving tablet of lansoprazole." European Journal of Biomedical and Pharmaceutical Sciences, **5**(9): 284-293.
27. Saibabu, S.; Pasam, J.; Ratnaraju, K.; Prathap, M.; Kumar,Y. (2016). "Formulation and evaluation of efavirenz immediate release tablets by using mixed hydrotropic soubilization technique." World Journal of Pharmacy and Pharmaceutical Sciences, **5**(2): 1533–1556.
28. Madan, J.R.; Kamate, V.J.; Dua, K.; Awasthi, R. (2017). "Improving the solubility of nevirapine using a hydrotropy and mixed hydrotropy based solid dispersion approach." Polymers in Medicine, **47**(2): 83-90.
29. Maheshwari, R.K.; Indurkhya, A. (2014). "Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of hydrotropic solid dispersion of aceclofenac." Asian Journal of Pharmaceutics, **4**(3): 235-238.
30. Yadav, N.K.; Shukla, T; Upmanyu, N.; Pandey, S.P.; Khan, M.K. (2018). "Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of solid dispersion of flupirtine maleate." Journal of Drug Delivery and Therapeutics, **8**(5): 481-488
31. Agrawal, G.P.; Maheshwari, R.K.; Mishra, P. (2017). "Preparation of solid dispersions of orinidazole using mixed hydrotropic solubilization technique and their characterization." International Journal of Green Pharmacy, **11**(4): 715-720.
32. Madan, J.R.; Pawar, K.T.; Dua, K. (2016). "Solubility enhancement studies on lurasidone hydrochloride using mixed hydrotrophy." International Journal of Pharmaceutical Investigation, **5**(2): 114-120.
33. Houssieny, B.M.; Dein, E.Z.; Messiry, H.M. (2014). "Enhancement of solubility of dexibuprofen applying mixed hydrotropic solubilization technique." Drug Discoveries & Therapeutics, **8**(4): 178-184
34. Ibrahim, N.J.; Smail, S.S.; Hussein N.R.; Abdullah, T.A. (2020). "Solubility enhancement of nimodipine using mixed hydrotropic solid dispersion technique." Zanco Journal of Medical Sciences, **24**(3): 386-394.

35. Surwade, K.; Saudagar, R. (2015) "Solubility enhancement of azilsartanmedoxomil using mixed hydrotropy." World Journal of Pharmacy and Pharmaceutical Sciences, **4**(7): 1167–79.
36. Salunke, P.A.; Barhate, S.D.; Chavhan, B.R.; Patil, S.S.; Wagh, R.S.; Rathode, S.B. (2019). "Seperation of dyes by mixed hydrotropic thin layer chromatography." Asian Journal of Pharmaceutical Analysis, **9**(3): 151-155.
37. Maheshwari, R.K.; Wadhwani, H.; Jain, A.; Jat, P. (2020). Employment of hydrotropic and mixed hydrotropic solutions as mobile phase to carry out TLC precluding the use of organic solvents." World journal of pharmacy and pharmaceutical sciences, **9**(11): 1377-1385.
38. Maheshwari, R.K.; Jain, A.; Mohadikar, A.; Jat, P.; Kalaria, I.; Wadhwani, H. Employment Of Hydrotropic And Mixed Hydrotropic Solutions As Mobile Phase To Carry Out TLC Precluding The Use Of Organic Solvents. International Journal of Pharmaceutical Sciences and Research. Conference Proceedings: Special issue; March, 2020, 163-167.