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# SOLUBILITY ENHANCEMENT OF PIROXICAM BY MIXED HYDROTROPY TECHNIQUE

**Jalde Swapna Raghunath*, Jaiswal N. R., Chavan G. C., Zambare K. K. and Rahul M. Sagde**

SBSPM'S B Pharmacy College, Ambajogai-431517, Maharashtra.

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***Corresponding Author**
**Jalde Swapna Raghunath**
SBSPM'S B Pharmacy College, Ambajogai-431517, Maharashtra.

## ABSTRACT

The current research paper is based upon the method used to increase the solubility of the one of the drug Piroxcam by the mixed Hydrotropy technique. Various Parametres are used to determine the increased solubility of the chosen drug. The results found are discussed in the last section of the project.

**KEYWORDS:** Solubility, Piroxicam, Hydrotrophy, Parametres, etc.

## INTRODUCTION

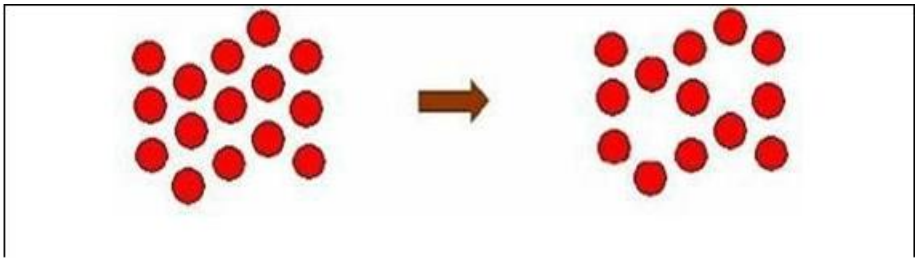
As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility, while it was still indicated recently that about 50% failure of drug candidates was due to poor "drug-like" properties. It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are poorly water-soluble. Poor "drug like" properties of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics. In the pharmaceutical analysis and formulation development fields it is most often required to increase the aqueous solubility of poorly water-soluble drugs. Most of the newly developed drug molecules are lipophillic in nature and poor solubility is one of the most difficult problems of these drugs. Drug delivery system (DDS) is defined as this process includes the administration of the therapeutic product, the release of the active ingredient by the product, and the subsequent transport of the active ingredients

across the membranes to the site of action. To provide a safe and convenient delivery of accurate dosage. The Drug delivery system is employed can control the pharmacological action of drug, influencing its pharmacokinetic and subsequent therapeutic profile.[1]

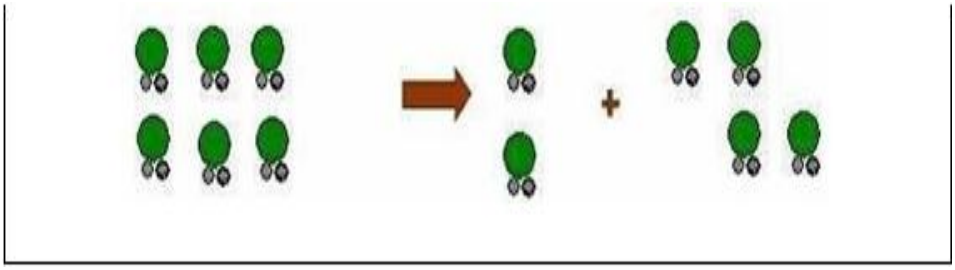
**Solubility:** Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to from a homogenous molecular dispersion. A saturated solution is one in which the solute is as equilibrium with the solvent. The solubility of a drug may be expressed as part, percentage, molarity, molality, volume fraction and mole fraction.[2,3] Drug solubility is the maximum concentration of drug / solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution in a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate. The pharmacopoeia lists solubility in term of millilitre of solvent required to dissolve 1 gm of solute. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemiccirculation for desired pharmacological response.

**Solubility expression:** For substances whose solubilityare not definitely known, the values are described in pharmaceutical compendia by the use of certain general terms. The U.S. Pharmacopoeia and National Formulary list the solubility of drugs as the number of milliliters of solvent in which 1 gm of solute will dissolve. For example, the solubilityof boric acid in 18 ml of water is given in the U.S. Pharmacopoeia as follows: 1g of boric acid dissolves in 18 ml of water, in 18 ml of alcohol, and in 4 ml of glycerin.[4]

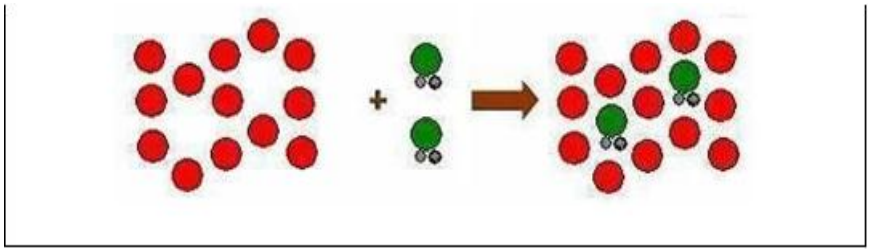
**Mechanism of solubility[5]:** The process of Solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.



***Step 1: Holes open in the solvent.***



**Step 2: Molecules of the solid breaks away from the bulk.**



***Step 3: The free solid molecule is integrated into the hole in the solvent.***

**Fig 1: Mechanism of solubility.**

**Factors affecting solubility**[6]

Particle size

Temperature

Pressure

Temperature of the Solute and Solvent

Molecular size

Polarity

Polymorphs

**Techniques for solubility enhancement**[7,8]

In pharmaceutical field, it is often required to prepare aqueous solutions of a variety of insoluble drugs. The ability to increase the aqueous solubility can be a valuable aid for increasing theefficacy and/or reducing adverse effects for certain drugs. Followingapproaches

can be employed to enhance the aqueous solubility of poorly soluble drugs.

- Micronization
- Nanonisation
- Supercritical fluid recrystallization
- Spray freezing into liquid and lyophilization
- Evaporative precipitation into aqueous solution
- Use of surfactants
- Use of salt forms
- Use of precipitation inhibitors
- Alteration of pH of the drug microenvironment
- Use of amorphous, anhydrates, solvates and metastable polymorphs
- Solvent deposition
- Precipitation
- Precipitation
- Selective adsorption on insoluble carriers
- Solid solution
- Eutectic mixtures
- Solid dispersions
- Molecular encapsulation with cyclodextrin
- Use of cosolvents
- Complexation
- Hydrotropic solubilization

**Hydrotropic method**

Additives may either increase or decrease the solubility of a solute in a given solvent. These salts that increase solubility are said to salt in and those salts that decrease the solubility are said to salt out ofthe solute. The effect of an additive depends very muchon the influence; it has on the structure of water or its ability to compete with the water molecules. A convenient quantitation of the effect of a solute additive on the solubility of another solute may be obtained by the **Setschetow** equation:

Log S0/S = KcaWhere,

S = solubility in the presence of the additiveCa = concentration of the additive

S0 = solubility in the absence of the additive

K = salting coefficient, which is a measure of the sensitivity of the activity coefficient of the solute towards the salt

Several salts with large anions or cations which are themselves very soluble in water result in a salting in of non-electrolytes and are called Hydrotropic Salts,, and the phenomenon is known as HYDROTROPISM,,. The term hydrotropic agent was first introduced by **Newberg** (1916), to designate anionic organic salts. According to **Newberg,** hydrotropic agents are metal salts of organic acids which at fairly high concentration considerably increase the aqueous solubility of organic substances normally slightly soluble in water. According to **Saleh** and **El-Khordagui**,hydrotropic agents are freely soluble organic compounds which at a concentration sufficient to induce a stack-type aggregation considerably enhance the aqueous solubility of organic substances, practically insoluble under normal conditions. These compounds may be anionic, cationic or neutral molecules. However, the term has been used in the literature to designate non-micelle forming substances either liquids or solids, organic or inorganic capable of solubilising insoluble compounds.

The chemical structure of the conventional **Newberg's** hydrotropic salts (prototype, sodium benzoate) consist generally of two essential parts, an anionic group and a hydrophobic aromatic ring or ring system. The anionic group is obviously involved in bringing high aqueous solubility which is a prerequisite for a hydrotropic substance. The type of anion or metal ion appeared to have a minor effect on the phenomenon.On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization. This should imply that hydrotropic agents are molecules having a planar hydrophobic structure brought into solution by a polar group. Hence, it seems rational to propose that molecules with a planar hydrophobic part and a polar group, which is not necessarily anionic, can act as hydrotropic agent.

At concentrations higher than a minimal hydrotrope concentration, hydrotropic agents self-associate and form noncovalent assemblies of lowered polarity. i.e. nonpolarmicrodomains, which solubilize hydrophobic solutes. The self-aggregation of hydrotropic agents is different from surfactant self-assemblies (i.e., micelles) in that hydrotropes form planar or open-layer structures instead of compact spheroid assemblies. Hydrotropic agents are structurally characterized by having a short, bulky, compact moiety such as an aromatic ring, while surfactants are characterized by long hydrocarbon chains. In general hydrotropic agents have a shorter hydrophobic segment, leading to higher water solubility, than do surfactants.

**Winsor (1950)** considered hydrotropy a solubilization phenomenon. Ueda proposed the formation of molecular complexes at low hydrotrope concentration and a salting in effect at high concentration. The degree of salting in by homologous series of ions increases with increasing the size of the ion. This effect has been observed with sodium salts of normal fatty acid and it has been suggested that salting in progress continuously to the associated phenomenon of solubilization as the series is ascended.

**Mechanisms proposed for hydrotropic solubilisation[9]**

The mechanism by which the hydrotropic effect occurs is not clear. Some workers have speculated that hydrotropy is simply another type of solubilization, with the solute dissolved in oriented clusters of the hydrotropic agents. Hydrotropic solutions do not show colloidal properties however. Others feel that this phenomenon is more closely related to complexation involving a weak interaction between the hydrotropic agent and the solute. Still other reason that the phenomenon must be due to a change in solvent character because of the large amount of additive needed to bring about the increase in solubility. Another view, which is somewhat related to the aggregation proposition, was suggested by **Breslow** and assumes that these additives act in a bridge like manner, concentrating themselves around the hydrophobic solute, but without any specific interaction with it. The influence of large concentration of sodium benzoate on the solubility of caffeine is a classic example of this phenomenon applied to a pharmaceutical system. Other example includes the solubilization of benzoic acid with sodium benzoate. concentration of sodium benzoate on the solubility of caffeine is a classic example of this phenomenon applied to a pharmaceutical system. Other example includes the solubilization of benzoic acid with sodium benzoate. Moreover, hydrotropic agents were shown to affect macromolecular systems. For instance, these agents render coagulable protein uncoagulable on heating, convert starch into a paste-on the cold, and inhibit the gelling of substances like gelatin and reversibly denaturation ofmethemoglobin. Examples of hydrotropic agents used as excipients in the literature are urea, sodium salicylate, sodium gentisate, sodium gluconate, sodium benzoate, sodium ascorbate, sodium citrate, sodium ibuprofen, nicotinamide, lysine, tryptophan, sodium acetate, and isoniazid. Each hydrotropic agent is effective in increasing the water solubility of selected hydrophobic drugs; no universal hydrotropic agent has been found effective to solubilize all hydrophobic drugs. Thus, finding the right hydrotropic agents for a poorly soluble drug requires screening a large number of candidate hydrotropes.

**Advantages of hydrotropic solubilisationtechnique[10,11]**

1) Hydrotropy is suggested to be superior to other solubilisation method, such as miscibility, micellarsolubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not requireemulsification.
2) It only requires mixing the drug with the hydrotrope in water.
3) It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.
4) It can replace organic solvents which are employed in various titrimetric and spectrophotometric estimations of poorly water soluble drugs. Also the hydrotropic solutions can be employed for TLC of poorly water soluble drug precluding the use of organic solvent. So it is economic, safe and user friendly method.

**Considerations for rational Design/Selection of hydrotropic agents[12]**

The efficacy of a hydrotropic agent in enhancing the water solubility of a pharmaceutical compound depends on suitably matching the structural features of the hydrotropic agent with those of the drug.

1. High Water Solubility:
2. High Hydrophobicity:
3. Separation of Hydrophilic and Hydrophobic Segments:

**Applications of hydrotropy[13,14]**

1) In TLC:
2) In Simultaneous Spectrometric Estimation:
3) In Pharmaceutical Formulation Development:
4) Other:

**Commonly used hydrotropes[15]:** Urea, Sodium benzoate, Nicotinamide, Potassium citrate, Potassium acetate, Benzosulfonate, Polyethylene glycol 400 (PEG 400), Propylene glycol (PG), Caffeine, Sodium ascorbate, Sodium p-Benzoate, Sodium acetate, Sodium salicylate, Sodium citrate, Piperazine, Resorcinol, etc.

**Mixed hydrotropy**

Increase in solubility of poorly soluble drugs by the addition of more than one hydrotropic agent. Hydrotropic agents used in combination may enhance the solubility of poorly soluble drugs by miraculous synergistic effect in addition to the additive effect.

**Advantages of mixed hydrotropy**

- It may reduce the total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentrations.
- It is new, simple, cost effective, safe, accurate, precise and environmentally friendly method for the analysis of poorly water soluble drugs precluding the use of organic solvents.
- It precludes the use of organic solvents and thus avoids the problem of residual solvent toxicity, error due to volatility, pollution, cost, etc.

**Marketed formulations**

| Sr. no. | Brand name | M.f.g. By | Dosage form | Strengths |
|---|---|---|---|---|
| 1 | Inflavan | Khandelwal | Tablet | 10/20 mg |
| 2 | Brexic | Wockhardt | Dispersibletablet | 20 mg |
| 3 | Dolokam | Cadila | Tablet | 20 mg |
| 4 | Dolonex | Pfizer | Capsul/tablet | 20 mg |
| | | | Injection | 20mg&40mg/ml |
| | | | Gel / cream | 0.5 % |
| 5 | Minicam | Blue cross lab | Gel / cream | 0.5% |
| 6 | Proxy c | Emcure | Patch | 40 mg |
| 7 | Movon | Ipca | Tablet | 20 mg |
| 8 | Flecam dt | Sunpharma | Gel | 0.5% |
| | | | Tablet/capsule | 10/20 mg |
| 9 | Micropec | Dr.reddys | Tablet/capsule | 20 mg |
| 10 | Mobicam | Cipla | Dispersibletablet | 20 mg |
| 11 | Zeepain | Lark lab | Tablet | 20 G |

**Experimental work**

**A. Melting point determination**

Melting point was determined using digital melting point apparatus (Labatronics) by capillary method, The glass capillary one end seal with on heating over burner and fill with drug sample and place the filled capillary in digital melting point apparatus and start the analysis, the sample are melt then shows melting point temperature in digital display

**B. Determination of partition coefficient of Piroxicam**

Partition Coefficient in Octanol-Water system was determined by equilibrating small amount of Piroxicam (not exceeding the aqueous solubility of drug) for 24 hours in the mixture of Octanol-Water system (1:1). After attaining the equilibrium, the two phases were separated and the partitioned amount of drug in each phase was determined. The separated phases were analyzed after appropriate dilution on UV Spectrophotometer.

### C. Spectral characteristics of piroxicam

Stock solution of Piroxicam (1 mg/ml) was prepared by using Water, as a solvent. From this stock solution, suitable volume was diluted with distilled water to get the final concentration 25 µg/ml. The water was used as a blank. The spectrum of drug was recorded on UV-Visible Spectrophotometer. The wavelength (λmax) of maximum absorbance was found to be 356 nm as shown in **Figure 3**, same procedure was followed for Phosphate buffer ( pH-7.4 ), only for 0.1 M MethanolicHCl(final conc. 10 µg/ml), Phosphate buffer ( pH-7.4 ), 0.1 M MethanolicHClwhich were shown in **Figure 4, 5,**respectively

### D. UV spectral characteristics of hydrotropes

The powders of five different hydrotropic agents‟ sodium benzoate, urea, sodium citrate and sodium acetate, sodium were dried in vacuum for 24 hours prior to use and stored in well closed containers. The solutions of each hydrotropic agents of known concentration 1000 µg/ml in distilled water were prepared and scanned on UV/Visible spectrophotometer against same reagent solution in the region from 200-400 nm. The cut off wavelength (nm) and corresponding absorbance‟s are given in the **table 1.**

### E. Preparation of calibration curve of piroxicam

Stock solution of Piroxicam (1mg/ml) was prepared by using Water, Phosphate buffer ( pH-7.4 ), 0.1 M MethanolicHCl, each with water as a solvent. The standard solutions were prepared in the concentration range of **5 to 25 µg/ml**, only for 0.1 M MethanolicHCl concentration was **2 to 10 µg/ml** by diluting stock solution with distilled water. The solutions were scanned for λmax on UV-Visible Spectrophotometer in the wavelength range of 200-400 nm. Then these solutions were analyzed at the λmax of drug. A linear relationship was obtained in **Lambert-Beer Plot** having high degree of correlation in the ranges of concentration described above. **Lambert-Beer Plot** of Piroxicam was shown in **Figure 11 to 13,** for Water, MethanolicHCl, and Phosphate buffer with Water respectively

### F. Differential scanning calorimetry (DSC) of Drug and Hydrotropes

The thermal behavior of pure Piroxicam drug and mixed Hydrotropes with Piroxicamwere examined by DSC, using a Lab: METTLER differential scanning calorimeter. The system was calibrated with a high purity sample of Indium. Piroxicam were scanned at the heating rate 20°C /min over a temperature range of 40-300°C.

### G. Infrared spectra for pure Drug and Hydrotrope

The infrared spectroscopy of pure Piroxicam drug and with mixed Hydrotrope were performed for identification of drug. Piroxicam drug powder was compressed into a pellet along with KBr (KBr pellet technique) using Shimadzu hydraulic press. The FTIR (**Bruker alpha T, India**) spectrum of drug was recorded in the wave number region of 400-4000 $cm^{-1}$

### H. Analytical method development (UV spectrophotometric)

All the system suitability and validation parameters (Accuracy, Precision, Limit of detection, Limit of quantitation, Linearity, Range) were studied as per standard procedures as per ICH Q2 R1 guideline on Analytical Method Validation.

### I. Solubilisation studies

Determination of solubility comprises of preparing a saturated solution of the given substance and finding out the amount present in a definite quantity of the solution. Rapid solution can be obtained by constant agitation of the solvent and an excess amount of the drug substance. After a given period of stirring, the clear solution is analyzed. The result is taken as the solubility at that particular temperature.

### J. Determination of equilibrium solubility of piroxicam in distilled water

Sufficient excess amount of Piroxicam was added to amber colored glass vials containing10 ml of distilled water. The vials were shaken mechanically for 12 hours at room temperature in **Rotary** Shaker. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes at 2000 rpm using a centrifuge. The supernatants of each vial were filtered through **Whatman** filter paper. An aliquot of each filtrate was diluted suitably with distilled water and analyzed spectrophotometrically at 356 nm.

### K. Determination of equilibrium solubility of piroxicam in bufferblend

Prepare the different buffer system of various pH (Acetate buffer pH 2.8, Phosphate buffer pH 7, Borate buffer pH 9.) separately. Add excess amount of Piroxicam to amber coloured glass vials containing 10 ml of buffer solution. The vials were shaken mechanically for 12 hours at room temperature in **Rotary** Shaker. The solutions were allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes at 2000 rpm using a centrifuge. The supernatants of each vial were filtered through **Whatman** filter paper. An aliquot of each filtrate was diluted suitably with distilled water and analyzed spectrophotometrically.

## L. Determination of solubility

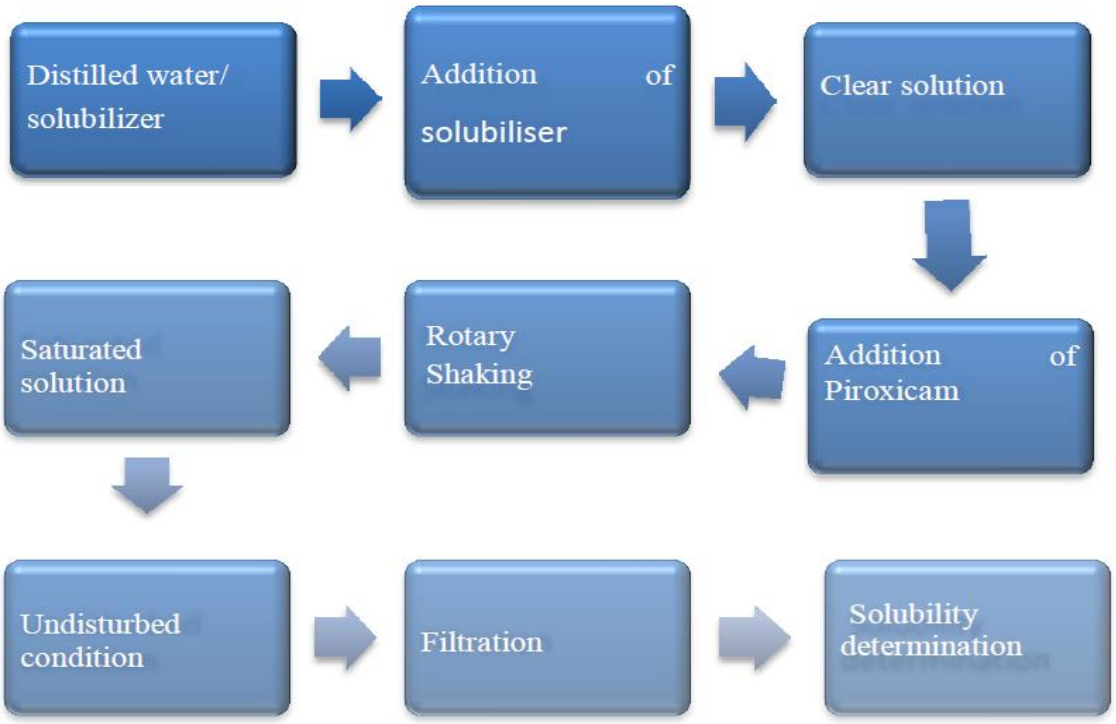



**Figure 2: General procedure of solubility determination.**

Since, the present investigation is the beginning of the hydrotropic solubilization phenomenon so, the widely used hydrotropic agents, sodium benzoate, urea, sodium acetate, and sodium citrate, sodium salicylate, nicotinamide were selected as modelhydrotropic agents to solubilize the drug Piroxicam which is practically insoluble in water.

It is evident from the literature survey that more is the concentration of hydrotrope more is the aqueous solubility of poorly water-soluble drug. Therefore moderately high concentrations (10-40%) of hydrotropic agents were tried in order to select suitable hydrotropes (for sufficient enhancement in solubility) for poorly water-soluble drug Piroxicam, following method (an approximate solubility determination) was used. This is modified form of the method used by the **Simamore et al.**

## M. Approximate solubility determination

10 ml of hydrotropic solution was taken in a 10 ml glass bottle and gross weight (including the cap) was noted. Then, few mg (by visual observation) of fine powder of drug was transferred to the bottle. This bottle was shaken vigorously (by hand). When drug got dissolved more drug (few mg by visual observation) was transferred to the bottle and again the bottle was shaken vigorously. Same operation was repeated till some excess drug

remained un dissolved (after constant vigorous shaking for 10 minutes). Then again gross weight was noted. From the difference in two readings (of weight), an approximate solubility was determined and solubility enhancement ratios were calculated.

**Solubility enhancement ratio was calculated by using following equation:** Solubility enhancement ratio = Solubility in particular hydrotropic solution/solubility inwater.

**Selected hydrotropic agents by approximate solubility study**

| Sr. no. | Selected hydrotropic agents |
|---|---|
| 1 | Sodium Benzoate |
| 2 | Sodium Acetate |
| 3 | Urea |
| 4 | Sodium citrate |
| 5 | Nicotinamide |

**N. Solubilization of piroxicam in individual and combination ofhydrotropic agents**

Aqueous solution of hydrotrope (sodium benzoate, urea, sodium citrate, sodium acetate, Nicotinamide) of known concentration (0% to 40%) were prepared in distilled water. Sufficient excess amount of Piroxicam was added to glass vials containing fixed volume of hydrotropic solution separately. The vials were shaken mechanically for 12 hours at room temperature. The solutions were allowed to equilibrate for next 24 hours. The eachvials were filtered through **Whatman** filter paper. An aliquot of each filtrate was diluted suitably with distilled water and the resulting solutions were analyzed on UV/Visible spectrophotometer at 334 nm against respective blank solution

## RESULT AND DISCUSSION

**Melting point of piroxicam:** The melting point of Piroxicam was found to be 199°C which is same as reported inliterature (198 – 200°C).

**Partition coefficient in octanol:** Water system: The partition coefficient was found to be 2.675 which is same as per Reference value (2.8)

UV Spectra for Piroxicam

*In Distilled Water*

The absorbance maxima found for Piroxicam at 356 nm.

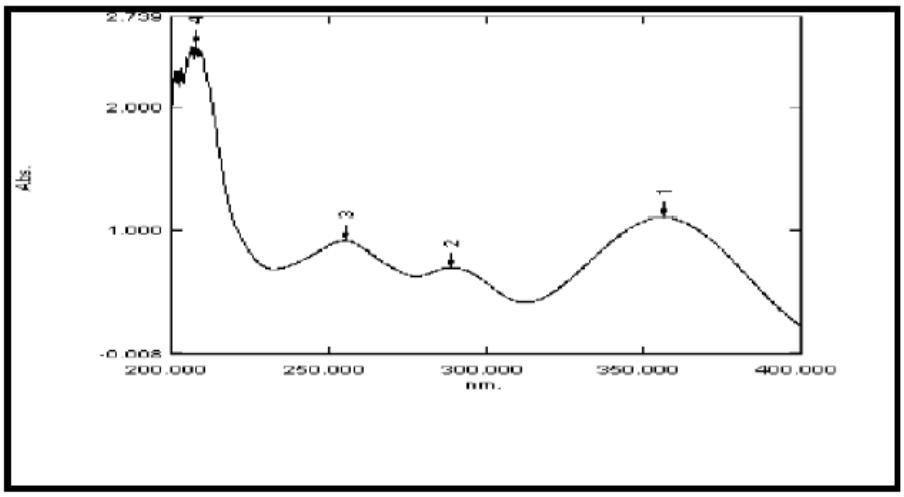



**Figure 3: UV Spectra of Piroxicam in water.**

*In Phosphate buffer pH 7.4*

The absorbance maxima found for Piroxicam at 355 nm

*Figure 4: UV Spectra of Piroxicam in Phosphate buffer (pH-7.4)*

**In 0.1 M MethanolicHCl**

The absorbance maxima found for Piroxicam at 334 nm

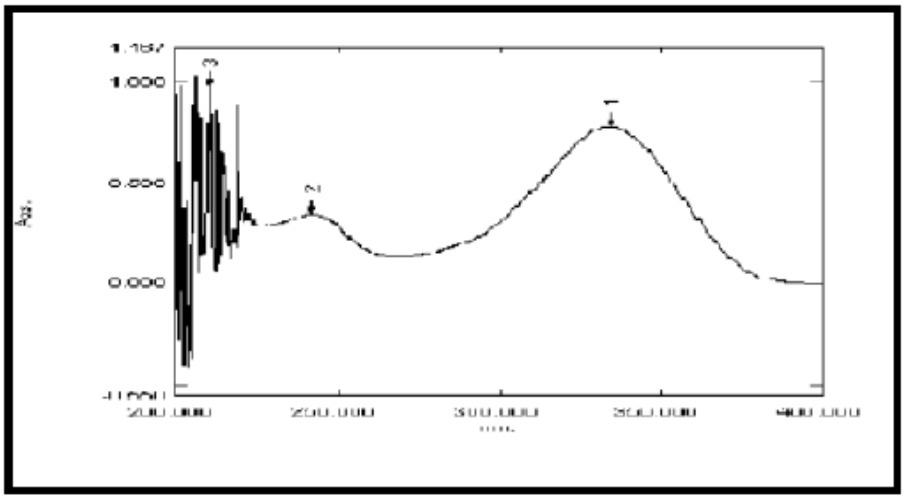



**Figure 5: UV Spectra of Piroxicam in 0.1 M methanolic HCl.**

UV spectral characteristics of hydrotropes

*Spectra of urea*

The absorbance maxima found for Urea at 260 nm

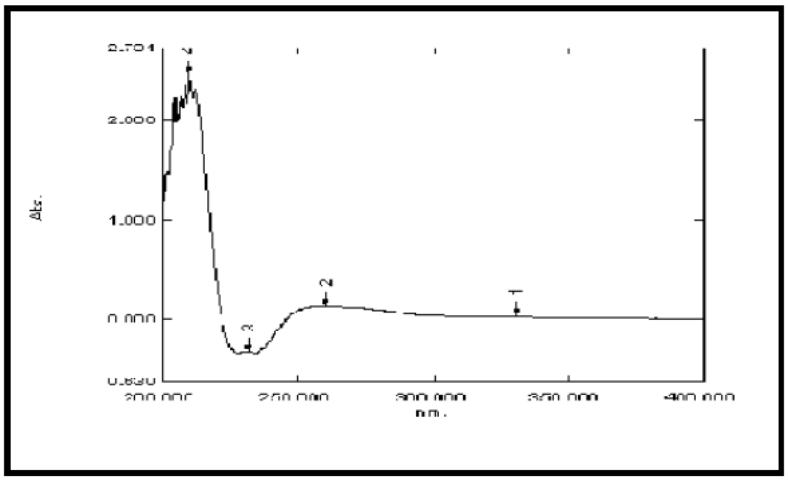



**Figure 6: UV Spectra of urea.**

*Spectra of Sodium Benzoate*

The absorbance maxima found for Sodium Benzoate at 224 nm

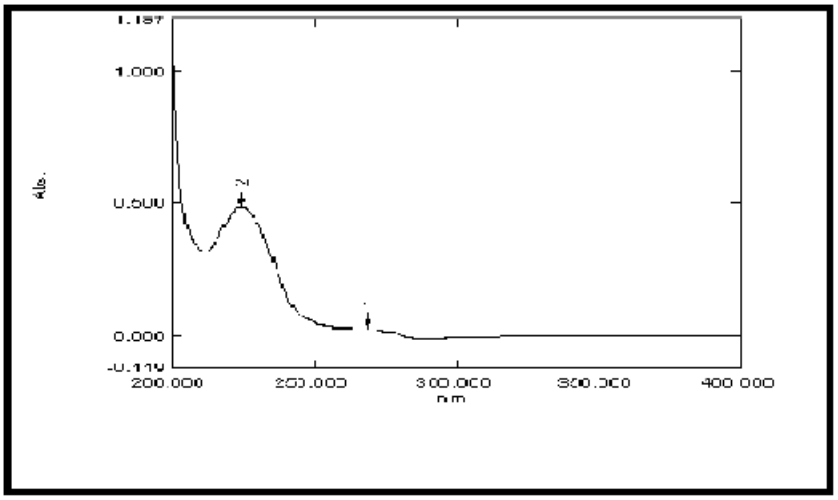



**Figure 7: UV spectra of sodium benzoate.**

*Spectra of Sodium Citrate*

The absorbance maxima found for Sodium p

Citrate at 228 nm

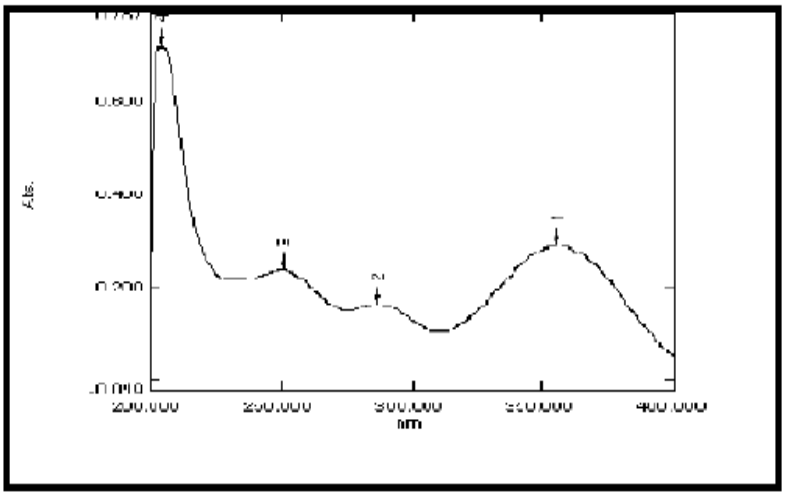



**Figure 8: UV spectra of sodium citrate.**

*Spectra of nicotinamide*

The absorbance maxima found for nicotinamide at 236 nm

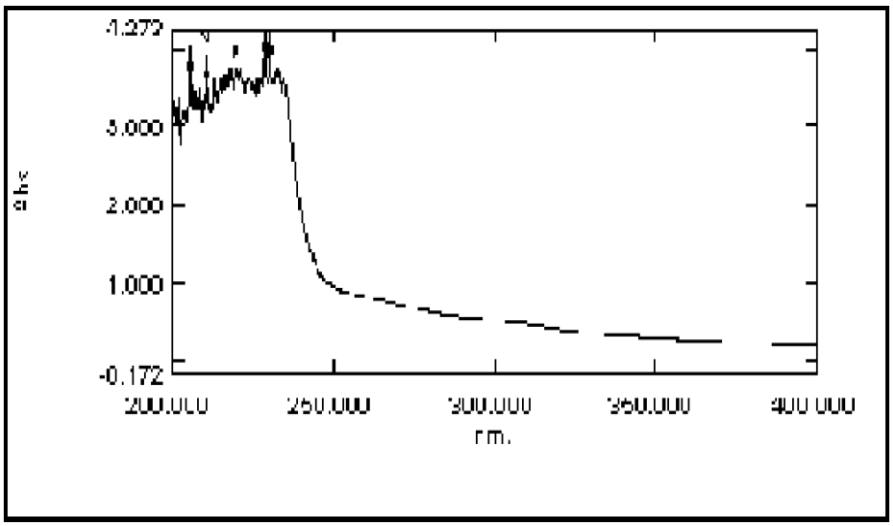



**Figure 9: UV Spectra of nicotinamide.**

*Spectra of sodium acetate*

The absorbance maxima found for sodium acetate at 256 nm

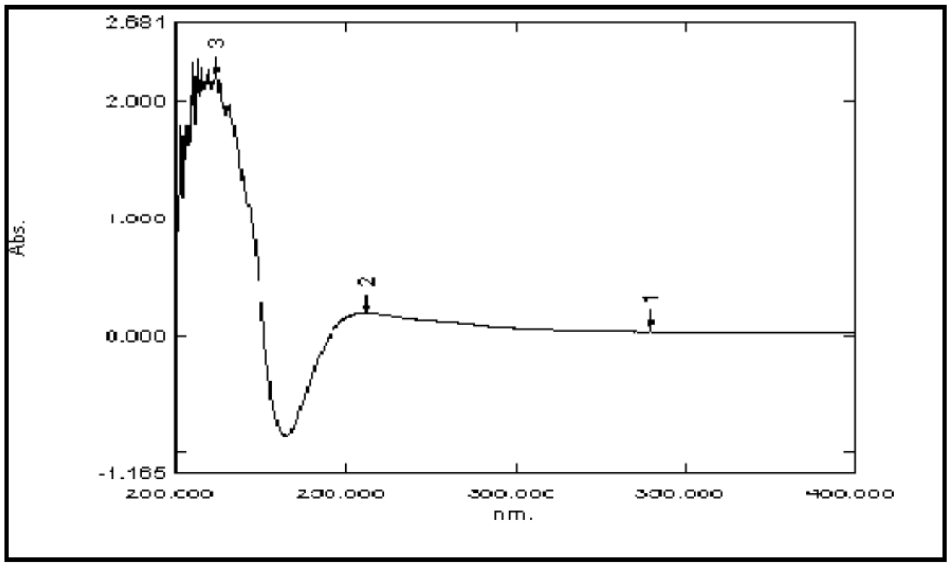



**Figure 10: UV Spectra of sodium acetate.**

***Table 9: UV spectral analysis data of hydrotropic agents for cut-off wavelength.***

| Sr. no. | Hydrotropic agent | Cut-off wavelength (λmax. nm) |
|---|---|---|
| 1 | Urea | 260 |
| 2 | Sodium benzoate | 224 |
| 3 | Sodium acetate | 256 |
| 4 | Sodium citrate | 228 |
| 5 | Nicotinamide | 236 |

It is evident from table above that the cut-off wavelength for each of the selectedhydrotropes is less than 260 nm which indicates that they do not interfere in the spectrophotometric estimation of Piroxicam at 334 nm.

Preparation of calibration curve of Piroxicam

*Calibration of piroxicam in water*

**Table 10: Calibration curve of piroxicam in distilled water at 356 nm.**

| Sr. no. | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 5 | 0.297 |
| 2 | 10 | 0.603 |
| 3 | 15 | 0.955 |
| 4 | 20 | 1.270 |
| 5 | 25 | 1.581 |

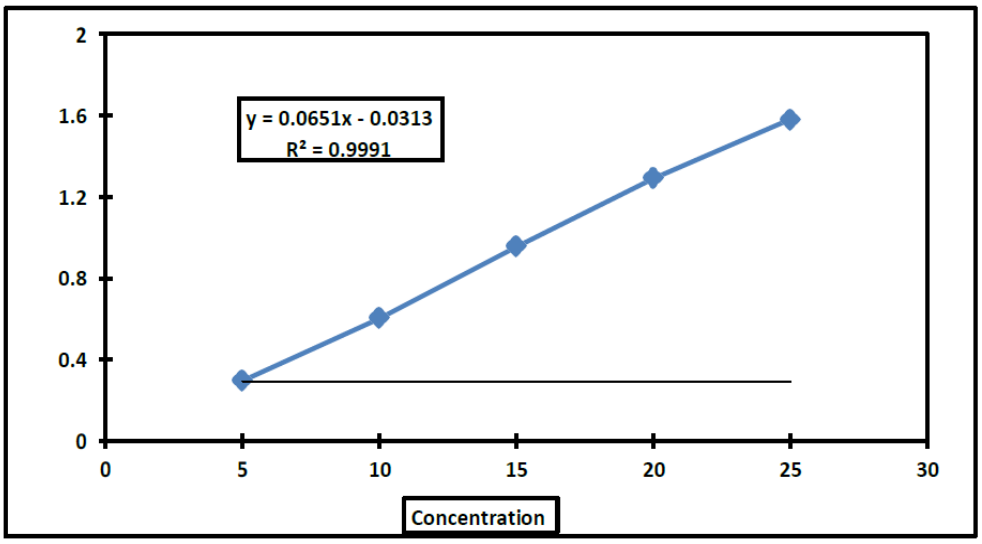



**Figure 11: Calibration of piroxicam in water.**

*Calibration of Piroxicam in 0.1 M. MethanolicHCl.*

**Table 11: Calibration curve of piroxicam in 0.1 M methanolic HCL at 334 nm.**

| Sr. no. | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 2 | 0.149 |
| 2 | 4 | 0.294 |
| 3 | 6 | 0.434 |
| 4 | 8 | 0.581 |
| 5 | 10 | 0.742 |

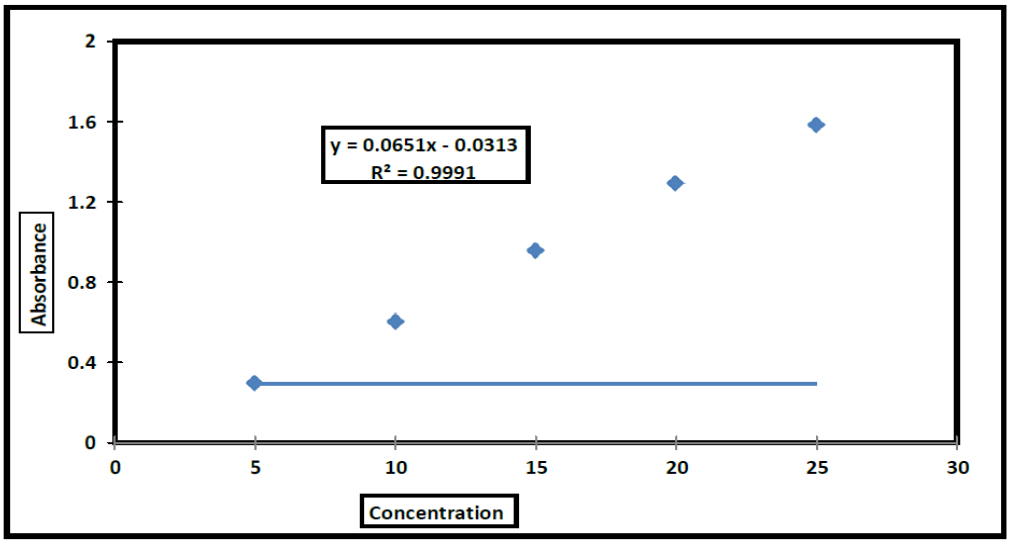



***Figure 12: Calibration curve of Piroxicam in 0.1 M. MethanolicHCl.***

**Calibrationof piroxicam in phosphate buffer PH-7.4**

**Table 12: Calibration curve of piroxicam in phosphate buffer PH-7.4.**

| Sr. no. | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 5 | 0.245 |
| 2 | 10 | 0.419 |
| 3 | 15 | 0.608 |
| 4 | 20 | 0.762 |
| 5 | 25 | 0.940 |

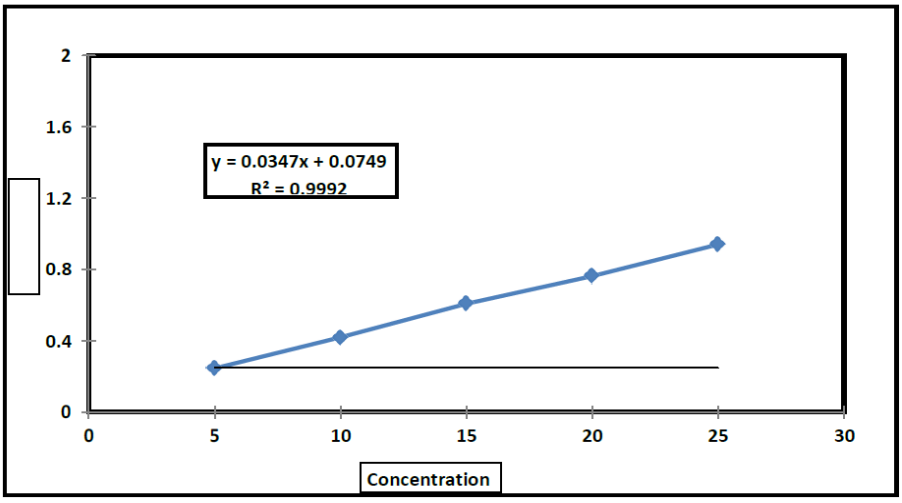



**Figure 13: Calibration curve of piroxicam in phosphate buffer.**

FT-IR Spectra for Piroxicam

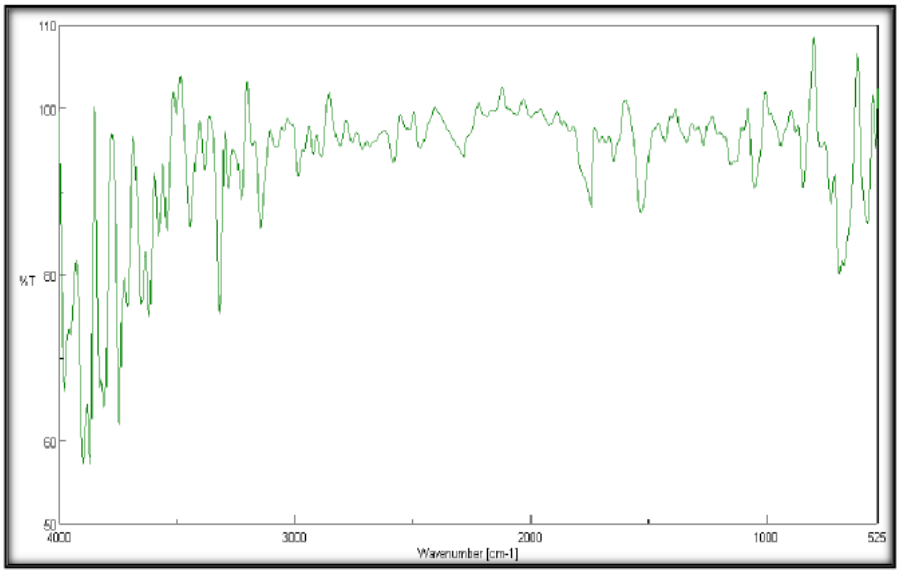



**Figure 14: FT-IR spectra for Piroxicam.**

**Table 13: IR Interpretation of piroxicam.**

| Sr. no. | Wave number ($cm^{-1}$) | Functional groups |
|---|---|---|
| 1 | 1450 & 1375 | $CH_3$ -bending |
| 2 | 1600 & 1475 | C=C bending |
| 3 | 1050 | S=O stretching |
| 4 | 3400-3200 | O-H stretching |
| 5 | 1350-1000 | C-N stretching |
| 6 | 1680-1630 | C=O stretching |
| 7 | 3000-2850 | C-H stretching |

The FTIR spectrum of Piroxicam sample has shown identical peaks and all peaks are in range.

Drug excipient chemical compatibility study

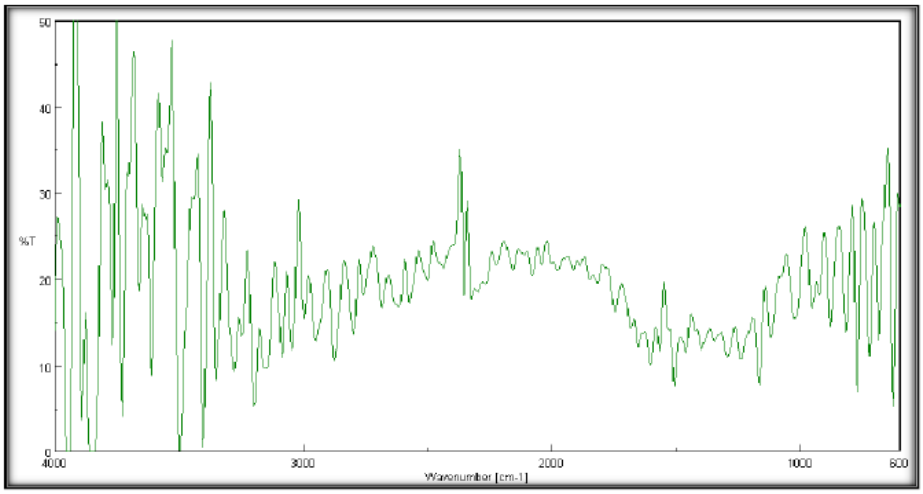



**Figure 15: IR spectra for Piroxicam with combination of Sodium benzoate & Nicotinamide**.

**Table 14: IR interpretation of Piroxicam + Sodium Benzoate + Nicotinamide.**

| Sr. no. | Wave number ($cm^{-1}$) | Functional groups |
|---|---|---|
| 1 | 1450 & 1375 | $CH_3$ -bending |
| 2 | 1600 & 1475 | C=C bending |
| 3 | 1050 | S=O stretching |
| 4 | 3400-3200 | O-H stretching |
| 5 | 1350-1000 | C-N stretching |
| 6 | 1680-1630 | C=O stretching |
| 7 | 3000-2850 | C-H stretching |
| 8 | 1300-1000 | C-O stretching |
| 9 | 1690-1640 | C=N stretching |

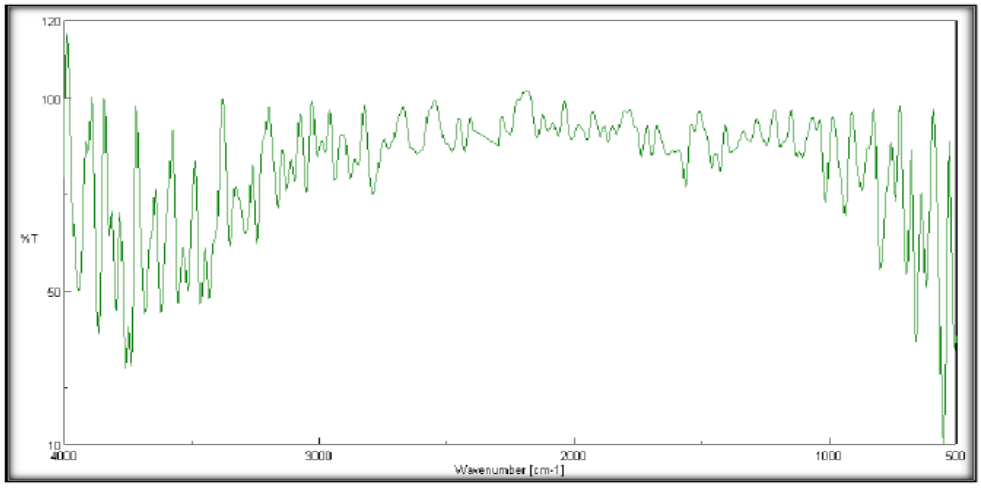



**Figure 16: IR spectra for Piroxicam with combination of Sodium benzoate + Nicotinamide + Sodium citrate.**

**Table 15: IR interpretation of Piroxicam + Sodium Benzoate + Nicotinamide + SodiumCitrate.**

| Sr. no. | Wave number ($cm^{-1}$) | Functional groups |
|---|---|---|
| 1 | 1450 & 1375 | CH3 -bending |
| 2 | 1600 & 1475 | C=C bending |
| 3 | 1050 | S=O stretching |
| 4 | 3400-3200 | O-H stretching |
| 5 | 1350-1000 | C-N stretching |
| 6 | 1680-1630 | C=O stretching |
| 7 | 3000-2850 | C-H stretching |
| 8 | 1300-1000 | C-O stretching |
| 9 | 1690-1640 | C=N stretching |
| 10 | 1465 | CH 2 bending |
| 11 | 3400-2400 | O-H stretching |

From the IR graph of drug and (drug + hydrotropes) it reveals that the selected Hydrotrope is chemically compatible with drug. That means there is no any structural change in the drug when it is in contact with hydrotrope.

Differential Scanning Calorimetric (DSC) of Piroxicam:

The thermal behaviour of Piroxicam was examined by DSC, using a Mettler Toledo DSC- 60 differential scanning calorimeter. The system was calibrated with a high purity sample of Indium. Piroxicam were scanned at the heating rate 20°C /min over a temperature range of 100-250°C.

### *1. DSC of Piroxicam*

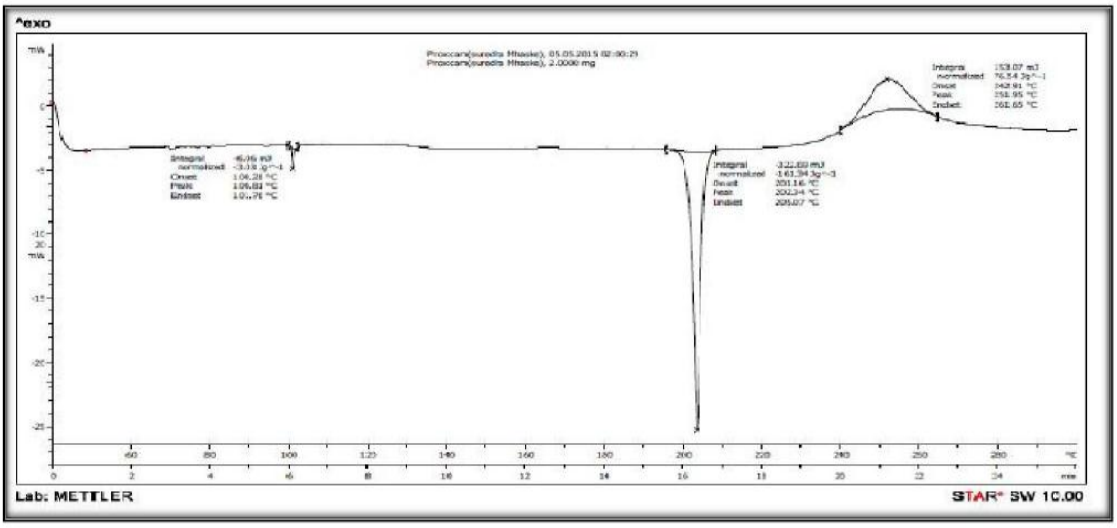



**Figure 17: DSC of piroxicam**.

The melting point of Piroxicam was found to be 200°C by DSC which is same as reported in literature (198-200°C).

### 2. DSC of Piroxicam with combination of hydrotrope

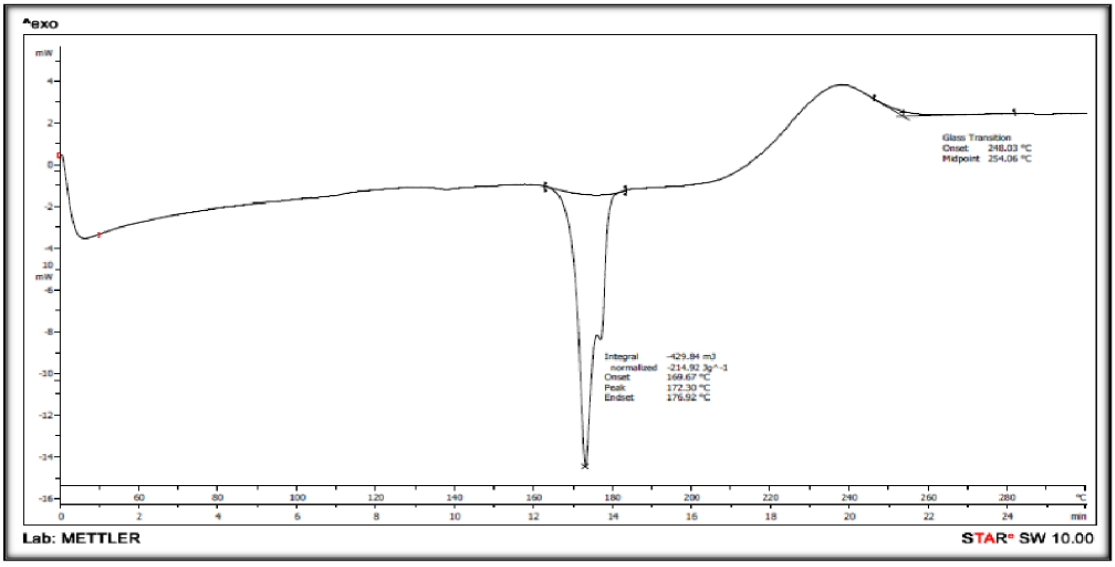



**Figure 18: DSC of Piroxicam with combination of hydrotrope.**

### Analytical validation

The developed method was validated as per ICH guidelines (ICH Q1B, 1996, ICH Q2 R1, 2005) for following parameters. The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Precision of the method was determined in terms of repeatability and intraday and Interday Precisions. Repeatability of the method was determined by analyzing six samples of same concentrations of drug. Intraday precision was determined by analyzing the drugs at three different concentrations and each concentration for three times, on the same day. Interday precision was determined similarly, but the analysis being carried out daily for three consecutive days. Accuracy, LOD, LOQ and **Sand ell's** sensitivity are determined and the results are summarized.

**Table 16: Analytical validation parameters.**

| Sr. no. | Parameter | | Results | ICH Standard |
|---|---|---|---|---|
| 1 | Accuracy | | 99.87% | 98%-102% |
| 2 | Precision: | | | |
| | Intraday precision | | 0.4773 | |
| | | | | RSD <2 |
| | Interday precision | day1 | 0.616 | |
| | | day2 | 0 | |
| | | day3 | 0.452 | |
| 3 | LOD | | 0.1581 µg/ml | |
| 4 | LOQ | | 0.4791 µg/ml | |
| 5 | Linearity $R^2$ | | 0.999 | ≥ 0.997 |
| 6 | Std. regression eq$^n$ | | y = 0.0737x - 0.00240 | |
| 7 | Range | | 2-10 µg/ml. | |

Obtained result of Linearity, λmax, Accuracy, precision, LOD, and LOQ are within range of ICH standard.

Determination of Equilibrium Solubility of Piroxicam in DistilledWater:

**Table 17: Solubility of piroxicam (mg/ml) in distilled water.**

| Sr. no | Concentration ( mg/ml ) | | | Average | S.D. |
|---|---|---|---|---|---|
| | I | II | III | | |
| 1 | 0.145 | 0.146 | 0.144 | 0.145 | 0.001 |

The observed solubility of Piroxicam was **0.145 mg/ml.**

Determination of Equilibrium Solubility of Piroxicam in bufferblend

**Table 18: Solubility of Piroxicam (mg/ml) in buffer blend**

| Name of buffer | Concentration(mg/ml) | | | Average | S.D. |
|---|---|---|---|---|---|
| | I | II | III | | |
| Acetate buffer pH-2.8 | 0.417 | 0.42 | 0.423 | 0.42 | 0.003 |

| | | | | | |
|---|---|---|---|---|---|
| Phosphate buffer pH-7 | 0.648 | 0.656 | 0.659 | 0.654 | 0.0056 |
| Borate buffer pH-9 | 1.76 | 1.73 | 1.75 | 1.746 | 0.015 |

Determination of Equilibrium Solubility of Piroxicam in SodiumBenzoate

**Table 19: Solubility of piroxicam (mg/ml) in sodium benzoate blend.**

| Sr. no. | Concentration (mg/ml) | | | Average | S.D. | SER |
|---|---|---|---|---|---|---|
| | % hydrotrope | I | II | | | |
| 1 | 5% | 0.555 | 0.620 | 0.587 | 0.045 | 4.048 |
| 2 | 10% | 1.000 | 1.126 | 1.063 | 0.089 | 7.331 |
| 3 | 15% | 1.523 | 1.654 | 1.588 | 0.092 | 10.951 |
| 4 | 20% | 2.704 | 2.655 | 2.679 | 0.034 | 18.475 |

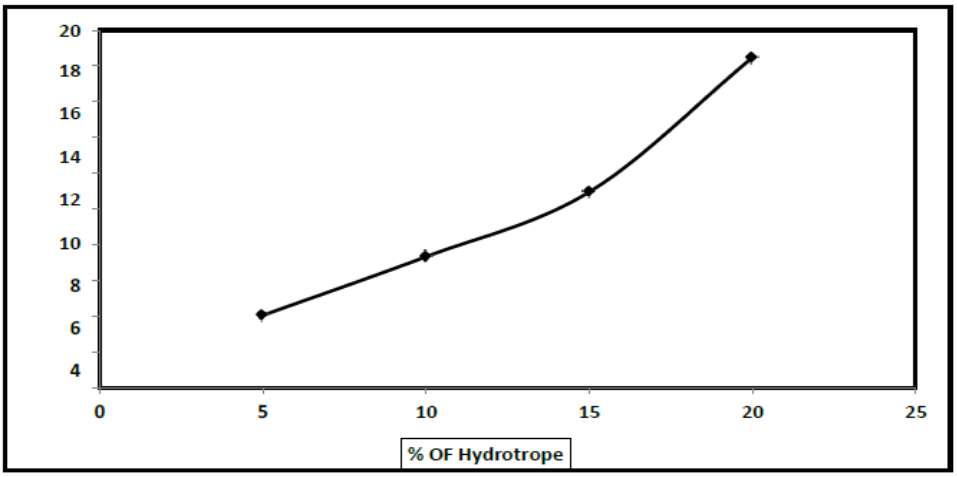



**Figure 19: Plot of SER vs% sodium benzoate.**

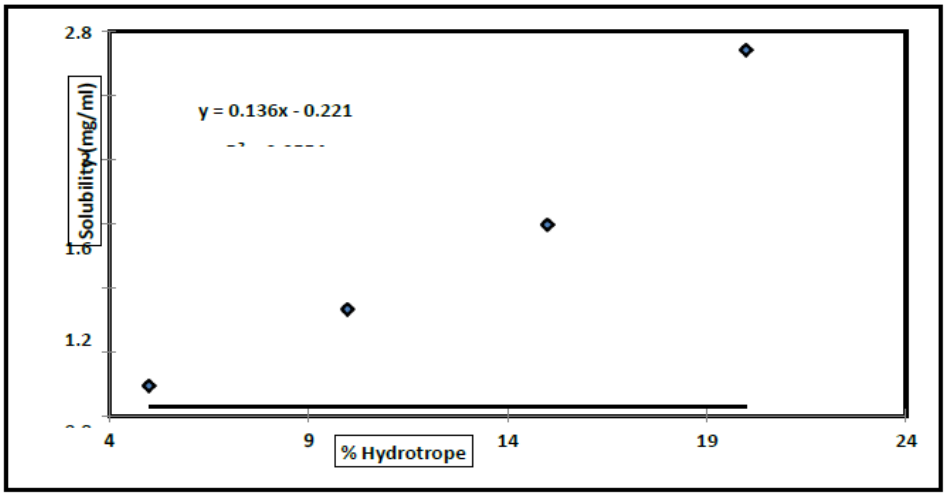



**Figure 20: Plot of piroxicam solubility (mg/ml) vs% of sodium benzoate.**

Determination of equilibrium solubility of piroxicam in sodiumcitrate

**Table 20: Solubility of piroxicam (mg/ml) in sodium citrate blend.**

| Sr. no. | Concentration ( mg/ml ) | | | Average | S.D. | SER |
|---|---|---|---|---|---|---|
| % of hydrotrope | | I | II | | | |
| 1 | 5% | 0.421 | 0.378 | 0.399 | 0.030 | 2.751 |
| 2 | 10% | 0.448 | 0.437 | 0.442 | 0.007 | 3.013 |
| 3 | 15% | 0.589 | 0.572 | 0.580 | 0.012 | 4 |
| 4 | 20% | 0.735 | 0.737 | 0.736 | 0.0014 | 5.075 |

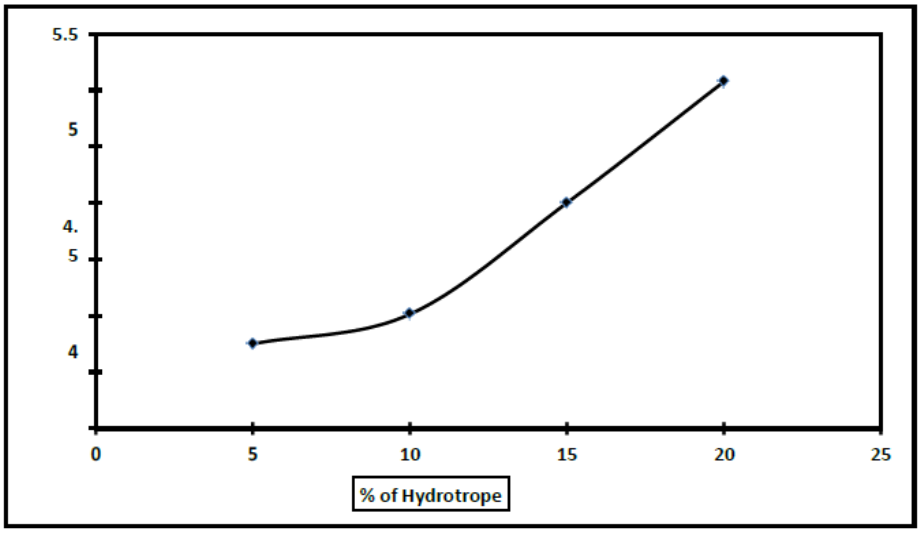



**Figure 21: Plot of SER vs % sodium citrate.**

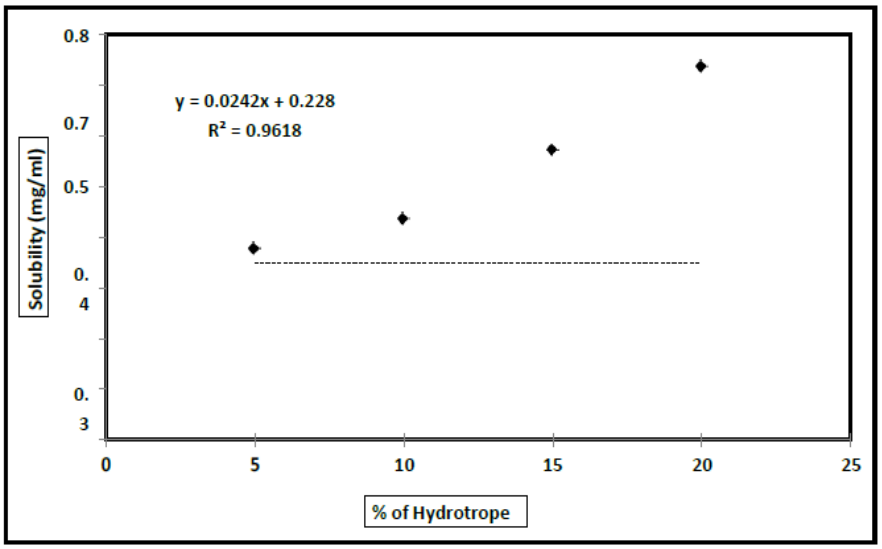



**Figure 22: Plot of piroxicam solubiblity (mg/ml) vs sodium citrate.**

Determination of Equilibrium Solubility of Piroxicam in Urea

**Table 21: Solubility of piroxicam (mg/ml) in urea blend.**

| Sr. no. | Concentration (mg/ml) | | | Average | S.D. | SER |
|---|---|---|---|---|---|---|
| % of hydrotrope | | I | II | | | |
| 1 | 0% | 0.074 | 0.076 | 0.075 | 0.001 | 0.517 |
| 2 | 5% | 0.552 | 0.561 | 0.556 | 0.006 | 3.834 |
| 3 | 10% | 0.685 | 0.687 | 0.686 | 0.001 | 4.731 |
| 4 | 15% | 0.636 | 0.829 | 0.732 | 0.136 | 5.717 |
| 5 | 20% | 0.973 | 0.983 | 0.978 | 0.007 | 6.779 |
| 6 | 25% | 1.111 | 1.090 | 1.100 | 0.014 | 7.586 |
| 7 | 30% | 1.736 | 1.786 | 1.761 | 0.035 | 12.137 |
| 8 | 35% | 1.241 | 1.219 | 1.231 | 0.015 | 8.482 |
| 9 | 40% | 1.564 | 1.492 | 1.531 | 0.050 | 10.551 |

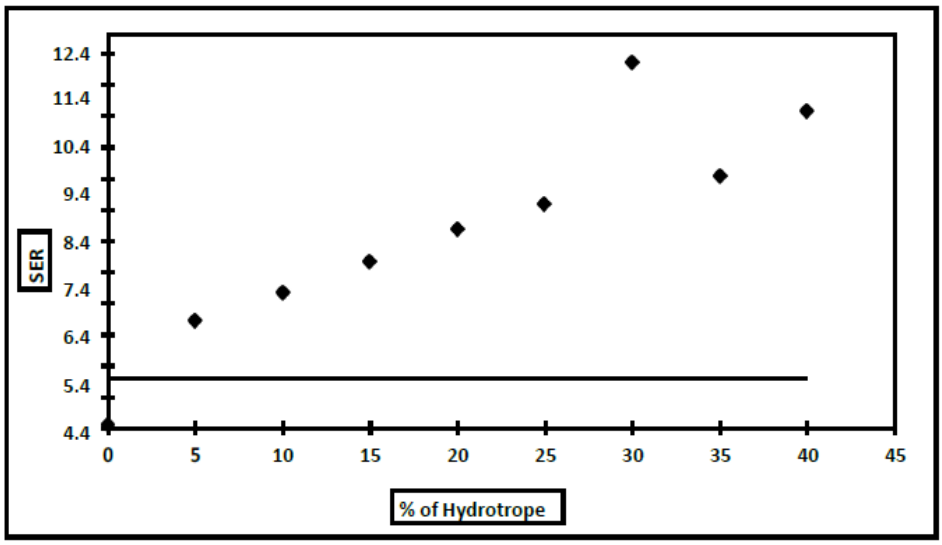



**Figure 23: Plot of SER vs % of urea.**

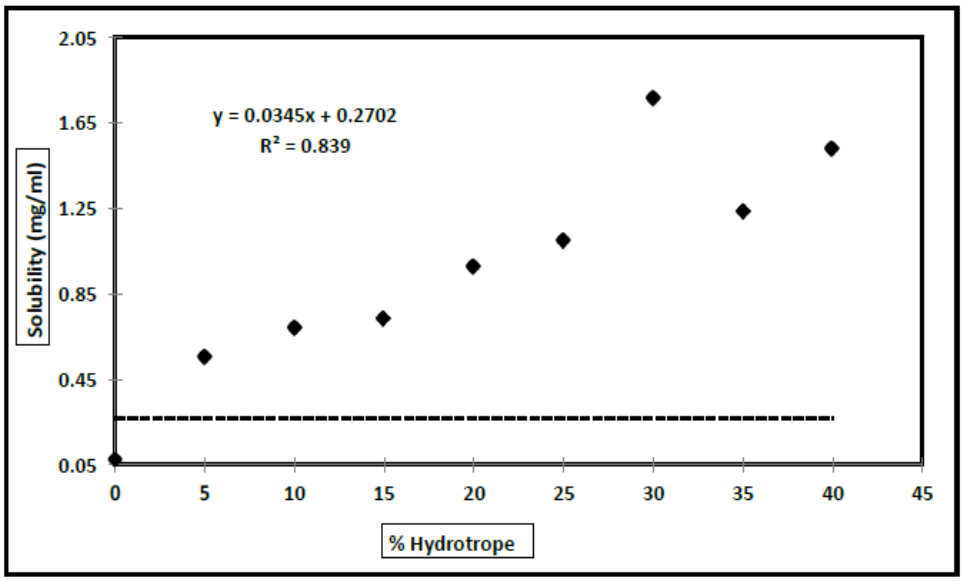



**Figure 24: Plot of Piroxicamsolubilituy (mg/ml) vs Urea.**

Determination of Equilibrium Solubility of Piroxicam in SodiumAcetate

**Table 22: Solubility of piroxicam (mg/ml) in sodium acetate blend.**

| Sr. no | Concentration ( mg/ml) | | | Average | S.D. | SER |
|---|---|---|---|---|---|---|
| % of hydrotrope | | I | II | | | |
| 1 | 0% | 0.079 | 0.078 | 0.079 | 0.0005 | 0.544 |
| 2 | 5% | 0.566 | 0.565 | 0.565 | 0.0007 | 3.896 |
| 3 | 10% | 0.713 | 0.695 | 0.704 | 0.0127 | 4.855 |
| 4 | 15% | 0.896 | 0.841 | 0.868 | 0.0388 | 5.986 |
| 5 | 20% | 1.148 | 1.064 | 1.106 | 0.0593 | 7.627 |
| 6 | 25% | 1.286 | 1.237 | 1.261 | 0.0346 | 8.696 |
| 7 | 30% | 1.556 | 1.441 | 1.498 | 0.0813 | 10.331 |
| 8 | 35% | 1.589 | 1.555 | 1.572 | 0.0240 | 10.841 |
| 9 | 40% | 1.265 | 1.222 | 1.243 | 0.0304 | 8.572 |

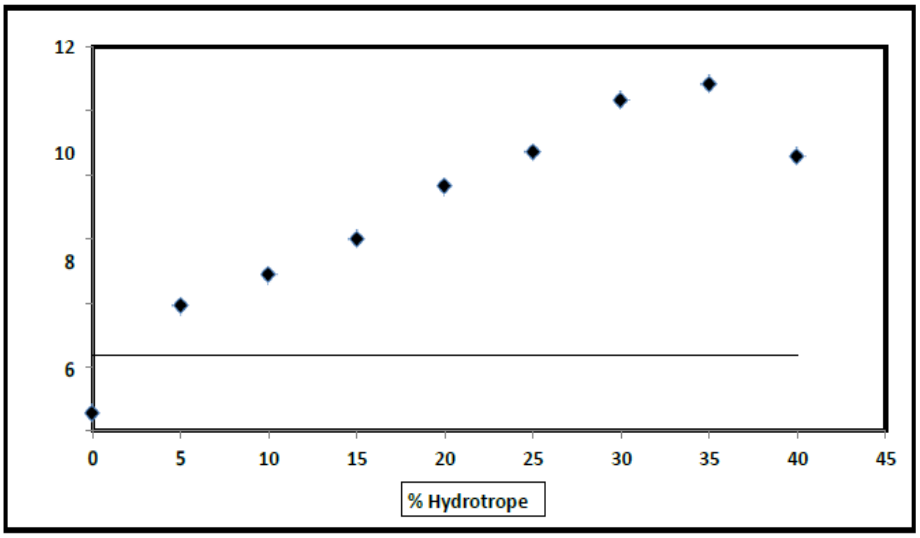



**Figure 25: Plot of SER vs % of sodium acetate.**

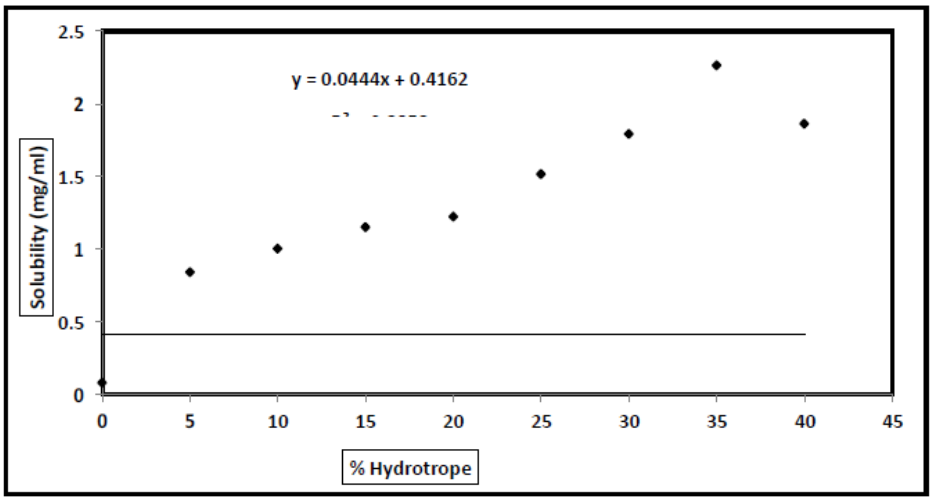



**Figure 26: Plot of piroxicam solubility (mg/ml) vs % of sodium acetate.**

Determination of Equilibrium Solubility of Piroxicam in nicotinamide

**Table 23: Solubility of piroxicam (mg/ml) in nicotinamide blend.**

| Sr. no. | Concentration( mg/ml ) | | | Average | S.D. | SER |
|---|---|---|---|---|---|---|
| % of hydrotrope | | I | II | | | |
| 1 | 0% | 0.069 | 0.069 | 0.069 | 1.414 | 0.482 |
| 2 | 5% | 0.535 | 0.522 | 0.528 | 0.008 | 3.641 |
| 3 | 10% | 0.928 | 0.916 | 0.922 | 0.008 | 6.358 |
| 4 | 15% | 1.41 | 1.377 | 1.393 | 0.023 | 9.606 |
| 5 | 20% | 1.669 | 1.700 | 1.684 | 0.022 | 11.613 |
| 6 | 25% | 2.232 | 2.211 | 2.221 | 0.014 | 15.317 |
| 7 | 30% | 3.07 | 3.04 | 3.055 | 0.021 | 21.068 |
| 8 | 35% | 3.7 | 3.655 | 3.677 | 0.031 | 25.358 |
| 9 | 40% | 4.23 | 4.2 | 4.215 | 0.021 | 29.06 |

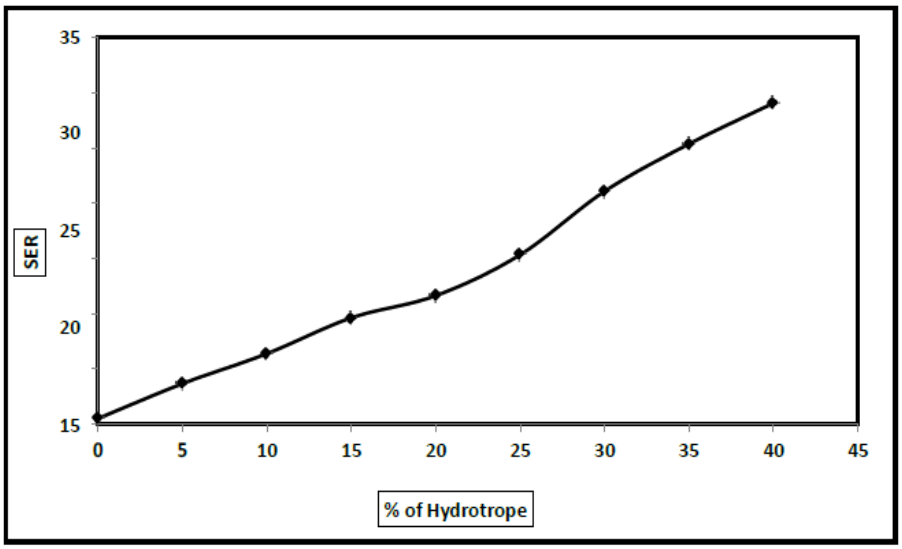



**Figure 27: Plot of SER vs % of nicotinamide.**

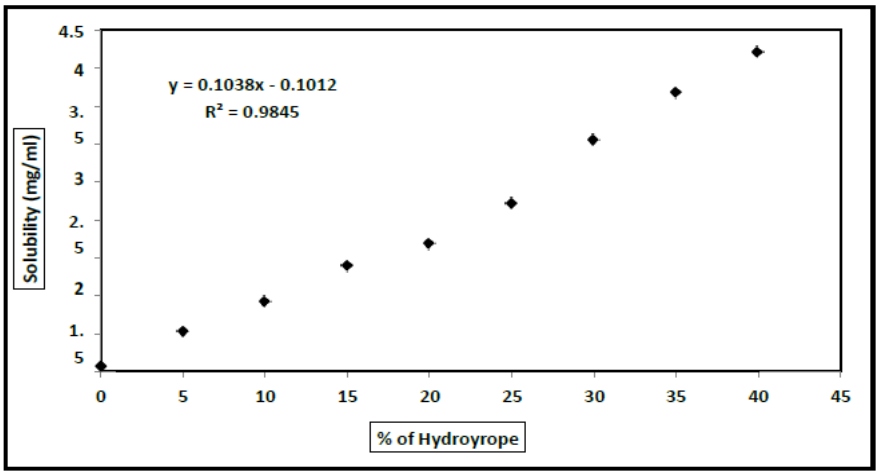



**Figure 28: Plot of piroxicam solubility (mg/ml) vs% of nicotinamide.**

Determination of Equilibrium Solubility of Piroxicam in PotassiumAcetate

**Table 24: Solubility of piroxicam (mg/ml) in potassium acetate.**

| Sr. no. | Concentration( mg/ml) | | Average | S.D. | SER |
|---|---|---|---|---|---|
| % of hydro trope | I | II | | | |
| 1 | 0% | 0.083 | 0.082 | 0.082 | 0.0007 | 0.565 |
| 2 | 5% | 0.852 | 0.843 | 0.847 | 0.0069 | 5.841 |
| 3 | 10% | 0.996 | 1.005 | 1.000 | 0.0063 | 6.896 |
| 4 | 15% | 1.097 | 1.152 | 1.124 | 0.0388 | 7.751 |
| 5 | 20% | 1.187 | 1.225 | 1.206 | 0.0268 | 8.298 |
| 6 | 25% | 1.54 | 1.517 | 1.528 | 0.0162 | 10.543 |
| 7 | 30% | 1.753 | 1.773 | 1.763 | 0.0141 | 12.161 |
| 8 | 35% | 2.260 | 2.269 | 2.264 | 0.0063 | 15.621 |
| 9 | 40% | 1.884 | 1.844 | 1.864 | 0.0282 | 12.859 |

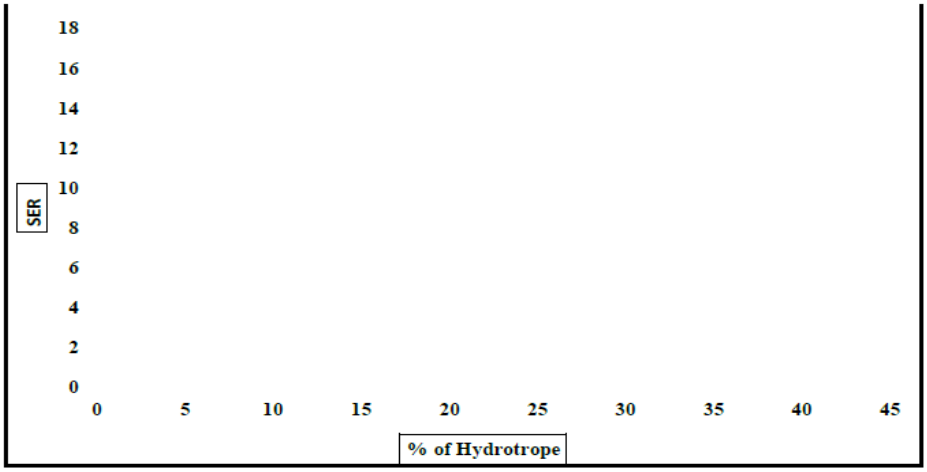



**Figure 29: Plot of SER vs % of potassium acetate.**

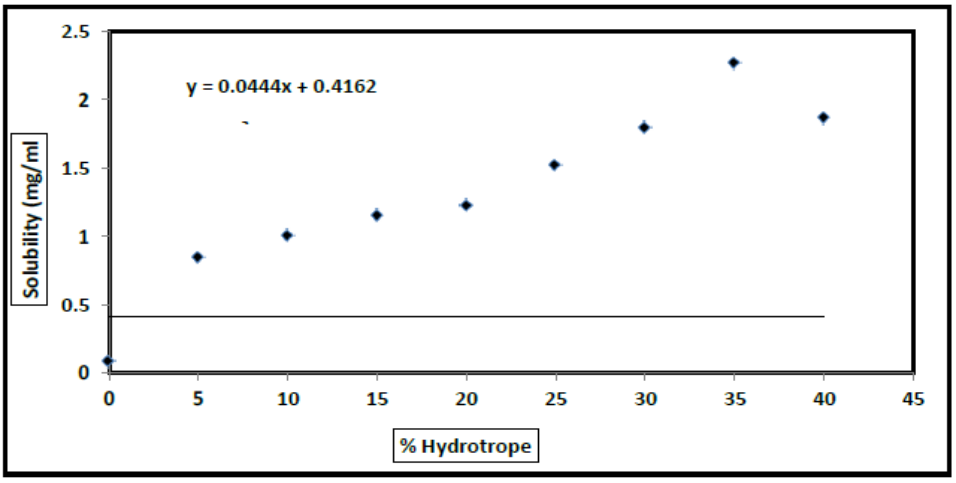



**Figure 30: Plot of piroxicam solubility (mg/ml) vs % of potassium acetate.**

Determination of Equilibrium Solubility of Piroxicamin sodiumBenzoate vsNicotinamide

**Table 25: Solubility of Piroxicam (mg/ml) in sodium Benzoate +Nicotinamide Mixed blend.**

| sr. no. | Concentration (mg/ml) | | | | Average | S.D. | SER |
|---|---|---|---|---|---|---|---|
| | % hydrotrope | | I | II | | | |
| 1 | 5:5 | A | 21.21 | 22.25 | 21.72 | 0.74 | 149.82 |
| 2 | 5:10 | B | 24.35 | 24.91 | 24.62 | 0.38 | 169.79 |
| 3 | 5:15 | C | 27 | 27.55 | 27.27 | 0.38 | 188.06 |
| 4 | 10:5 | D | 24.41 | 25.15 | 24.77 | 0.53 | 170.82 |
| 5 | 10:10 | E | 31.65 | 32.31 | 31.97 | 0.45 | 220.48 |
| 6 | 10:15 | F | 33.7 | 33.95 | 33.82 | 0.17 | 233.24 |
| 7 | 15:5 | G | 24.8 | 25.81 | 25.31 | 0.70 | 174.48 |
| 8 | 15:10 | H | 28.05 | 28.85 | 28.45 | 0.56 | 196.20 |
| 9 | 15:15 | I | 34 | 35.11 | 34.55 | 0.77 | 238.27 |
| 10 | 20:5 | J | 29.71 | 30.21 | 29.95 | 0.35 | 206.55 |
| 11 | 20:10 | K | 32.85 | 34.91 | 33.85 | 1.44 | 233.58 |
| 12 | 20:15 | L | 46.51 | 46.95 | 46.72 | 0.31 | 322.20 |
| 13 | 25:5 | M | 32.31 | 33.21 | 32.75 | 0.63 | 225.86 |
| 14 | 25:10 | N | 40.15 | 40.75 | 40.45 | 0.42 | 278.96 |
| 15 | 25:15 | O | 53.21 | 55 | 54.11 | 1.27 | 373.10 |

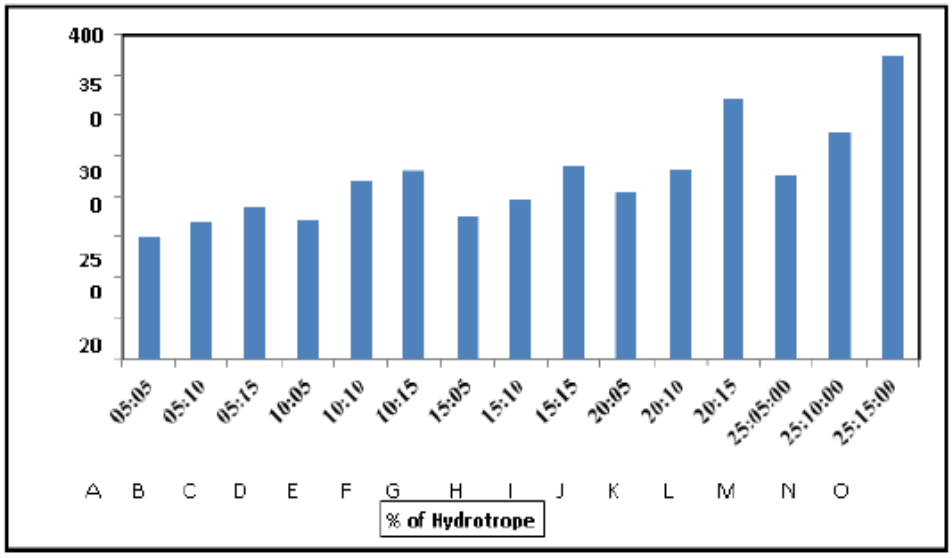



**Figure 31: Plot of SER vs % of Sod. Benzoate + Nicotinamide Mixed blend.**

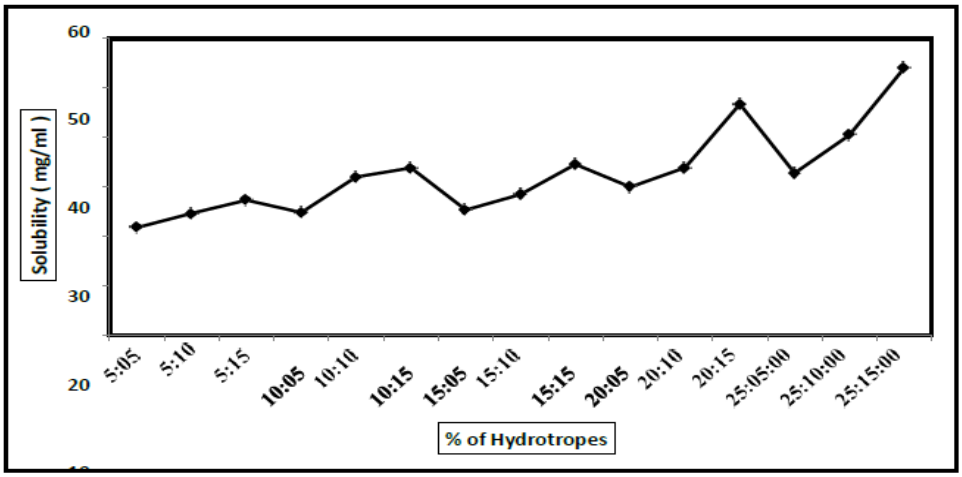



**Figure 32: Plot of Piroxicam Solubility (mg/ml) vs Sod. Benzoate + Nicotinamide Mixed blend.**

Determination of Equilibrium Solubility of Piroxicamin sodiumBenzoate vs Nicotinamide & Sodium Citrate.

**Table 26: Solubility of Piroxicam (mg/ml) in Sodium Benzoate + Nicotinamide + Sodiumcitrate mixed blend.**

| sr. no. | Concentration ( mg/ml ) | | | | Average | S.D. | SER |
|---|---|---|---|---|---|---|---|
| | % of hydrotrope | | *I* | *II* | | | |
| 1 | 5:5:5 | A | 25.75 | 26.15 | 25.95 | 0.28 | 178.96 |
| 2 | 5:10:10 | B | 30.45 | 30.75 | 30.61 | 0.21 | 211.03 |
| 3 | 5:15:15 | C | 33.35 | 33.91 | 33.62 | 0.38 | 231.86 |
| 4 | 10:5:5 | D | 30.45 | 30.85 | 30.65 | 0.28 | 211.37 |
| 5 | 10:10:10 | E | 40.35 | 41.11 | 40.72 | 0.53 | 280.82 |
| 6 | 10:15:15 | F | 42.81 | 43.35 | 43.07 | 0.38 | 297.03 |
| 7 | 15:5:5 | G | 33.21 | 33.71 | 33.45 | 0.35 | 230.68 |
| 8 | 15:10:10 | H | 39.25 | 37.35 | 38.31 | 1.34 | 264.13 |
| 9 | 15:15:15 | I | 44.81 | 44.65 | 44.72 | 0.10 | 308.41 |
| 10 | 20:5:5 | J | 32.95 | 33.45 | 33.21 | 0.35 | 228.96 |
| 11 | 20:10:10 | K | 46.21 | 46.41 | 46.31 | 0.14 | 319.31 |
| 12 | 20:15:15 | L | 56.81 | 57.51 | 57.15 | 0.49 | 394.13 |
| 13 | 25:5:5 | M | 38.71 | 39 | 38.85 | 0.21 | 267.93 |
| 14 | 25:10:10 | N | 44.85 | 45.25 | 45.05 | 0.28 | 310.68 |
| 15 | 25:15:15 | O | 66.1 | 65.41 | 65.75 | 0.49 | 451.03 |

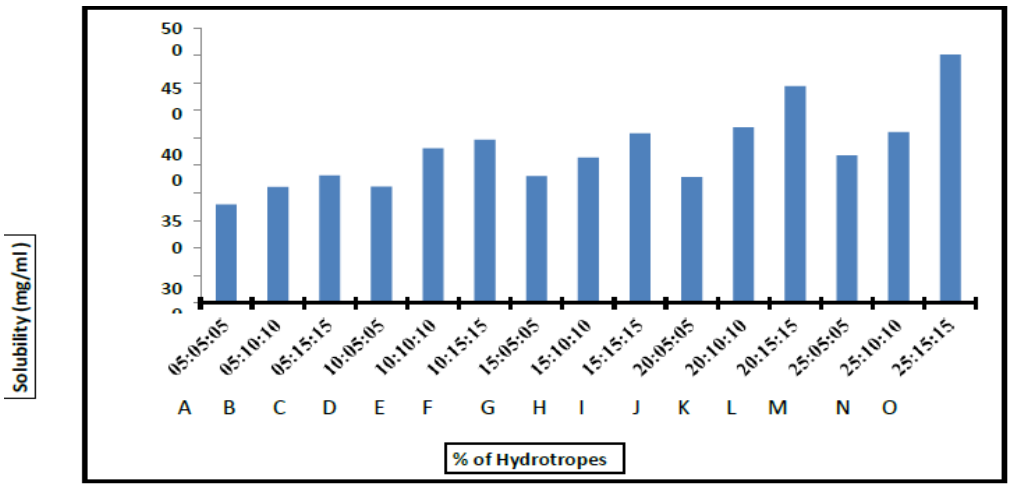



**Figure 33: Plot of SER vs % of hydrotrope.**

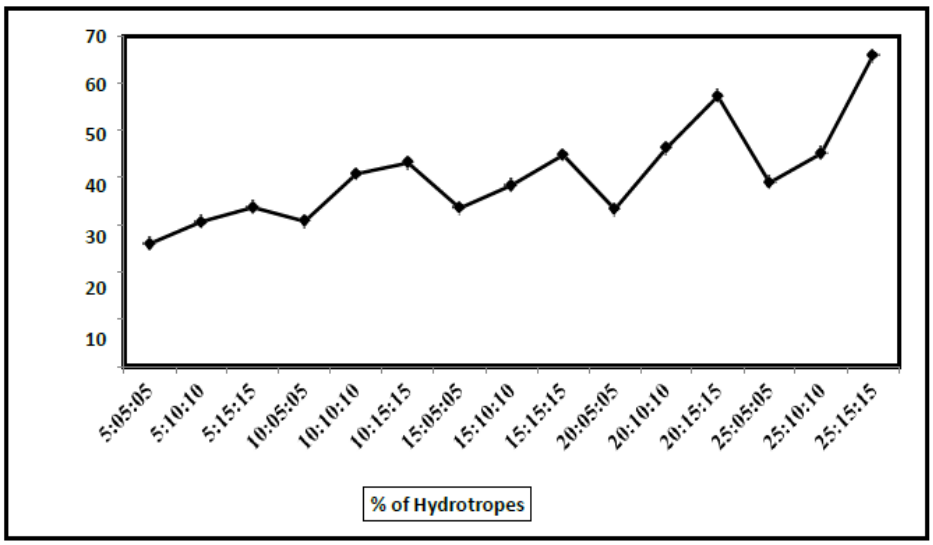



**Figure 34: Plot of Piroxicam Solubility (mg/ml) vs Sodium Benzoate + Nicotinamide + Sodium citrate mixed blend.**

## SUMMARY AND CONCLUSION

### Summary

- The aim of the present research study was to explore the possibility of employing hydrotropy techniques in the formulation of a poorly water soluble drug Piroxicam.
- In the present study practically insoluble drug, Piroxicam was tried to solubilise by employing the combination of physiologically compatible hydrotropic agents.
- The melting point determination and spectrophotometric analysis showed purityof drug sample. The drug complied with the tests prescribed in the monograph. The Infrared spectra of the dug showed major peaks at wave numbers that are characteristic of Piroxicam.

- In the drug and hydrotrope interference study, no interference was observed in UV Spectrophometric analysis of Piroxicam in presence of employed hydrotrope.
- The approximate solubility of drug in sodium benzoate, nicotinamide, and Sodium citrate, were found to be very good.
- Also in mixed hydrotropic method it was observed good improvement in solubility of Piroxicam.
- The solubility determination of drug in hydrotropic solutions was carried out at room temperature. The solubility of drug in individual hydrotropes was found in decreasing order as:

  *Sodium benzoate >Nicotinamide> Sodium citrate > Sodium acetate> Urea.*
- The linearity of calibration curve showed that the Beer Lamberts law was obeyed in the concentration range of 2-10 µg/ml at the $\lambda_{max}$ of 334 nm. From the equilibrium solubility curves of Piroxicam in Hydrotrope it was concluded that increase in the solubility was linear function with respect to the hydrotrope concentration.
- The results showed that the enhancement in solubility of the drug was not entirelydue to pH effect but mostly due to Hydrotropicsolubilization phenomenon.

## CONCLUSION

Piroxicam was poorly water soluble drug, having water solubility less than 0.0836mg/ml. By the use of mixed hydrotropy approach to improve the solubility of Piroxicamup to 65.400 mg/ml (Increase in solubility).

Hydrotropy is a novel, safe and effective way to enhance solubility of poorly aqueous soluble drugs. Dissolution of practically insoluble drug i.e. Piroxicam in aqueous dissolution media indicates it‟s great potential to solublize the drug in biological fluids and thus appreciable enhancement in bioavailability and onset of action can be expected. Thus the concept of mixed hydrotropy is an emerging field which can serve as a milestone for solubility enhancement and therefore deserves an urgent attention of scientific community to asses it‟s efficiency and applicability.

## REFERENCES

1. Sriwastawa, S.B. et al. Drug delivery systems: an updated review. International Journal of Pharmaceutical Investigation, 2012; 2(1): 2–11.
2. Lobenberg R, Amidon G.L. Solubility as a limiting factor to drug absorption, In: Oral

Drug Absorption, Prediction and Assessment, Marcel Dekker Inc., New York, 2000; 139.

3. Neuberg C. Hydrotropy, a novel approach in poorly water soluble drugs, Biochem. Z, 1961; 76: 107-109.
4. Indian pharmacopoeia, Ministry of health and family welfare, Government of India, edition, The Controller of Publication, Delhi, 1996; 1: 332.
5. Aulton, M. E. Eds. Pharmaceutics: The Science of Dosage Form Design, Churchill Livingstone: Edinburgh, 2005; 518-522.
6. Silva. D, et al, Investigations on the mechanism of aqueous solubility increase caused by some hydrotropes. Thermochimica Acta, 1999; 328: 161-167.
7. Satish K. Pat, et al. Strategies For Solubility Enhancement Of Poorly Soluble Drugs. Review Article, 2011; 8: 160-168.
8. Vemula. V, et al. Solubility Enhancement Techniques. Review Article, November – December, 2010; 5: 260-275.
9. Thorat Y. S. et al, Solubility enhancement techniques: a review on conventional and novel approaches. IJPSR, 2011; 2-10.
10. Da Silva et al, Investigations on the mechanism of aqueous solubility increase caused by some hydrotropes. Thermochimica Acta, 1999; 328: 161-167.
11. Kumar. S V, et al. A review on solubility enhancement using hydrotropic phenomena.International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6: 320-324.
12. Kapadiya N, et al. Hydrotropy: A Promising Tool for Solubility Enhancement: A Review. International Journal of Drug Development & Research, 2011; 3: 26-33.
13. Park, K., et al., Pharmaceutical applications of hydrotropic agents, polymers, thereof, and hydrogels thereof, US Patent, 2003; 0031715: 118-126.
14. Maheshwari, R, K. et al, hydrotropy: a novel approach in estimation of poorly aqueous soluble drugs by Tlc. International Journal of Pharmacy and Pharmaceutical Sciences, 2013, ISSN- 0975-1491 5, (2).
15. Maheshwari. R K. et al, Novel application of mixed hydrotropic solubilization technique in the formulation and evaluation of hydrotropic solid dispersion of aceclofenac. A sian journal of pharmaceutics, 2010; 4(3): 235-238.
16. Khant. B, Sheth V. et al. Enhanced Solubility of Candesartan Cilexitil Using Different Hydrotropic agent. An International Journal of Pharmaceutical Science, 2013; 4: 405-411.