OPEN ACCESS

Pharmaceutical Communications

DOI: 10.55627/pharma.001.001.0180

Research Article

# Effects of Hydrotropic Phenomenon on Solubility Enhancement of Ebastine; Formulation and Characterization

**Anum Saif[1], Rashid Ali Khan*[1,2], Shahiq Uz Zaman[1], Muhammad Ali Shahbaz[3], Atif Sarwar[2], Muhammad Nouman Arif[4]**

[1]Riphah Institute of Pharmaceutical Sciences, Riphah International University Islamabad, Pakistan
[2]Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan
[3]University of Eastern Finland, P.O. Box 1627 | 70211 Kuopio | Finland.
[4]Margalla College of Pharmacy, Margalla Institute of Health Sciences Islamabad, Pakistan

*Correspondence: rashid.scps@stmu.edu.pk



## Abstract

Hydrotropes are nontoxic small organic molecules that, at certain concentrations, result in solubility enhancement of poorly water-soluble compounds. In this study, various hydrotropes, including nicotinamide, sodium acetate, and trisodium citrate, were used at varying ratios to observe their effect on the solubility enhancement of Ebastine. Various combinations of drug-hydrotrope complexes were prepared with each of the above-mentioned hydrotropes using a solvent evaporation technique. The resultant residues were subjected to various analytical and characterization techniques for the verification of complexation and solubility enhancement. These techniques included powder X-ray diffraction studies, Fourier transform infrared, and ultraviolet (UV) spectroscopy. Three different formulations were prepared using various hydrotrope-drug complexes, and their stability studies, along with the in-vitro release, were carried out using a simulated environment in dissolution apparatus, and then later UV spectrophotometric studies were conducted. A standard curve was constructed for UV spectroscopic analysis. The UV analysis of %age drug release from final suspension dosage form revealed 67.56%, 55.04 %, and 66.76 % for the complex containing drug-nicotinamide at a ratio of 3:1, drug-sodium acetate at 2:2 and drug-trisodium citrate at 2:2 respectively. This release profile clearly indicated the improvement in the water solubility of Ebastine in the suspension formulated from the drug-hydrotrope complexes.

**Keywords:** Hydrotrope, complexation, Ebastine, solubility enhancement, crystallinity, amorphous

## 1. Introduction

The field of pharmaceutical drug development and dosage form design has always faced tremendous hurdles, of which poor water solubility of therapeutic agents is the major one. Despite many new inventions and techniques yet this problem remains partially unsolved (Varshney and Chatterjee 2012). Attempts to enhance water solubility via chemical modification have reduced many drugs' therapeutic effectiveness (Leuenberger 2002).

Carl A. Neuberg was the first one to put forth the phenomenon of hydrotropy back in the second decade of the 20th century (Oberoi 2004). In later years of the 20th century, the term hydrotrope was further explored by another team of researchers, and they classified them on the basis of their ionic character. According to that classification, hydrotropes exist in the form of ionic species of all three states (cationic, anionic and neutral species. However, the preliminary requirement for them to be classified in this class was to possess both the

**Table 1:** Ebastine formulation with various drug-hydrotrope combinations.

| Sr. No | Ingredient name | Amount / 5ml | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F1a (mg) | F1b (mg) | F1c (mg) | F2a (mg) | F2b (mg) | F2c (mg) | F3a (mg) | F3b (mg) | F3c (mg) |
| 1 | Ebastine | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 2 | Xanthane gum | 15 | 20 | 18 | 15 | 20 | 18 | 15 | 20 | 15 |
| 3 | Sugar | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |
| 4 | Sorbitol | 1500 | 1400 | 1450 | 1500 | 1400 | 1450 | 1500 | 1400 | 1500 |
| 5 | Glycerin | 200 | 300 | 250 | 200 | 300 | 250 | 200 | 300 | 200 |
| 6 | Sodium acetate | 15 | 10 | 13 | 15 | 10 | 13 | 15 | 10 | 15 |
| 7 | Citric acid | 06 | 05 | 06 | 06 | 05 | 06 | 06 | 05 | 06 |
| 8 | Flavoring agent | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |
| 9 | Colorant | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |

water-loving moiety and its counterpart, the lipophilic structure (Saleh and El-Khordagui 1985). Despite many efforts and research work, the exact mechanism of action for hydrotropes towards solubilization of poorly aqueous soluble drugs is yet to be explored to the extent where a definitive statement can be presented. At present several mechanisms have been suggested according to which the hydrotropic molecule results in the increment of solubility of deprived solute (Oberoi 2004).

Ebastine, an anti-allergic, is a second-generation antihistamine (H1-receptor antagonist). It belongs to a class of compounds containing piperidine derivatives and possesses non-sedating features, unlike most other anti-allergic drugs (Roger et al. 2008). Ebastine, because of its hydrophobic nature and very low aqueous solubility, having a partition coefficient value of 7.64, is placed in the class II group according to Biopharmaceutics Classification System (BCS). According to European Pharmacopoeia, Ebastine is, for all intents and purposes, insoluble in water and profoundly dissolvable in natural solvents like ethanol and methylene chloride.

Studies aimed at the longer duration of action and lower sedative effect of Ebastine at normal antihistamine doses have been reported previously (Vincent, Sumner, and Reid 1988). The water solubility of this drug is very low, and it has a high lipophilic character (Maddens et al. 2011). Even though the exact mechanism of hydrotropic solubilization still remains to be controversial, it has proven to be an effective tool for the solubilization of many potent pharmacologic agents and has produced multifold improvements in the solubility of several poorly water-soluble drugs (Aggarwal and Jain 2011).

The classification of drugs by Dr. Gordon Amidon (BCS) was based on studies related to the solubility and permeability issues of the drugs (Varshney and Chatterjee 2012). The concept of the BCS classification system has paved the path toward bio waver technique for bioavailability determination of orally administered drug substances (Chavda, Patel, and Anand 2010).

Almost all the compounds classified in class II according to BSC are lipophilic, and their absorption depends on the drug release from the dosage form (Maddens et al. 2011).

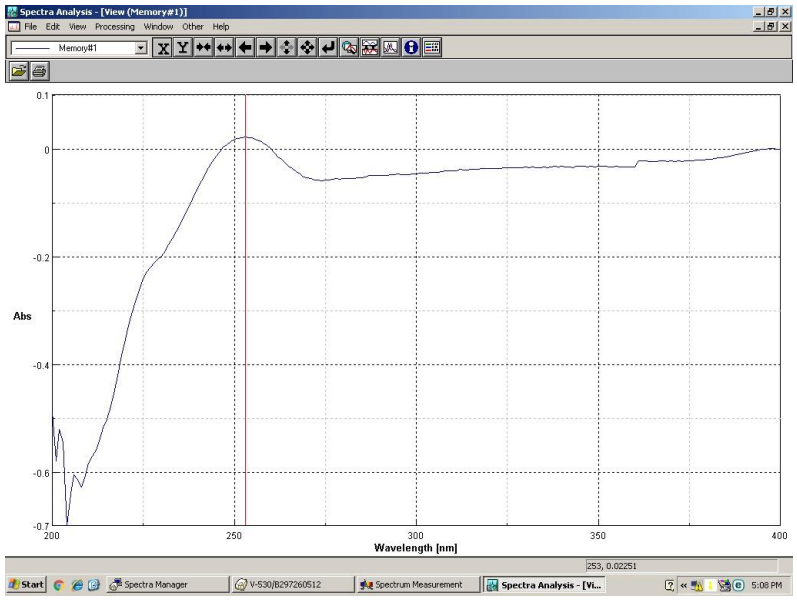


**Figure 1: This figure represents the lambda max of Ebastine.**

The desired blood levels for any drug administered via the oral route are largely based upon its ability to get dissolved in aqueous media. According to the published data, only eight out of a hundred newly known therapeutic agents are capable of getting dissolved in both the aqueous and organic media, whereas one-fourth of the drugs discovered have water-repellent properties (Varshney and Chatterjee 2012). According to the United States, pharmacopeia approximately 30% of the drugs possess reduced aqueous water solubility (Jain et al., 2010).

The use of hydrotropes has also been reported not only to enhance the drug solubility but the drug release pattern has also been affected in a positive manner by the use of hydrotrope in the solid dispersion method hydrotrope does this by its interaction with drug molecules via Vander Val phenomenon as well hydrogen bonding. Along with increasing the amorphousity of the system, hydrotropes also increase drug solubility (Dhapte and Mehta 2015). Almost a 1000x increase in solubility of some aromatic compounds has been reported to occur due to hydrotropes (Balasubramanian et al. 1989). A synthesized derivative of nicotinamide, N, N-dimethynicotinamide (NNDENA), has been reported to cause an increase in the aqueous solubility of paclitaxel up to 6 folds (Lee et al. 2003). In this study, we investigated the effects of various hydrotropes, including nicotinamide, sodium acetate, and trisodium citrate, at varying ratios, on the solubility enhancement of Ebastine.

## 2. Materials and Methods

Ebastine, nicotinamide, sodium acetate, trisodium citrate, urea, and other materials required for characterization and suspension preparations were obtained courtesy pharmaceutical company and were of analytical grade and fully in compliance with the desired properties of chemicals.

### 2.1 Procedure for Determination of λ max for Ebastine.

Stock solution for determination of **λ** max was prepared by dissolving 10 mg of Ebastine in 10ml of ethanol, mixed at a vortex mixer for 30 minutes, and then further diluted with ethanol up to 100 ml in a volumetric flask to obtain the concentration of 100µg/ml (Matsuda, Mizuki, and Terauchi 2001, Wagh et al. 2011). Further, 10ml of the above-prepared solution was taken and diluted up to 100ml to obtain the final concentration of 10

**Table 2. The following table shows the Master formulation.**

| Sr.No | Ingredients | Amount/5ml |
|---|---|---|
| 1 | Ebastine | 10mg |
| 2 | Xanthan gum | 15mg |
| 3 | Sugar | 1000mg |
| 4 | Sorbitol | 1500mg |
| 5 | Glycerin | 200mg |
| 6 | Sodium Benzoate | 15mg |
| 7 | Citric acid | 6mg |
| 8 | Flavoring agent | 0.001 |
| 9 | Colorant | 0.001 |

μg/ml. This stock solution was used to prepare further dilutions of 9μg/ml, 8 μg/ml, 7 μg/ml, 6 μg/ml, 5 μg/ml, 4 μg/ml, 3 μg/ml, 2 μg/ml, 1 μg/ml with ethanol. The λmax was determined using a standard solution of 10 μg/ml and then scanning it within the UV range of 200-400 nm to obtain a complete absorption spectrum, and the point where the absorption was noted to be maximum was named lambda maximum (λ max). This λ max was later used for which was used for absorption measurement. (Fig.1)

**2.2 Procedure for UV Analysis**

UV spectrophotometry was utilized to calculate the amount of medication in the specimens, and a calibration curve was framed to relate absorbance to build up an equation of a straight line for the estimation of absorbance. (Fig.2) Selection criteria for solvent were based upon the considerations such as safety and ease of availability, the desired properties of solvent included the ability to solubilize both the drug and the hydrotrope and secondly the nontoxic properties to avoid any harmful effects in the final preparations.

**2.3 Preparation of Physical Mixtures**

The mixture of drug moiety and the solubility enhancer was prepared by dissolving both ingredients in ethanol. The solvent was later evaporated by adopting certain temperature and pressure conditions (Oberoi 2004). The resultant residues obtained were smaller and spherical in shape (Takeuchi et al., 2004). The master formulation equation laid out in Table 1.0 was used for setting up the suspension of Ebastine. Various formulations, as mentioned in (Table 2.0**)** were prepared by the following procedure.

Xanthene gum was weighed and absorbed the required measure of water, blended with an attractive stirrer, and left overnight to build hydration and softening. For the preparation of Ebastine suspension with a concentration of 10mg/milliliter, approximately twelve grams of Ebastine complex powder was weighed and taken (Radwan and Aboul-Enein 2004) and triturated using pestle mortar. After completion of the milling, using a pestle and mortal addition of sorbitol solution was carried out at a slow pace by keeping the trituration rate constant.

In the last step, to retain the flavoring agent's integrity, it was added in the last step, and then all the system contents were taken and poured into the container. The remnants in the mortar were washed with distilled water and then poured into the same container containing the above-prepared mixture. For uniform dispersion and mixing of the suspension, an electric stirring device was used to make the process simpler and more efficient.

**2.4 Evaluation of the Mixtures**

**2.4.1. Appearance of Phases**

Visual inspection was carried out to analyze the properties of both the dispersed and dispersion medium

**2.4.2. Angle of Repose**

The angle of repose determination is one of the important parameters that help understand the flow properties of powders. This test was carried out to evaluate and assess the flow parameters of the mixture powder necessary for suspensions. To carry out this experiment, a conical glass funnel having a diameter of approximately 1.0 cm was taken and fixed on a tripod stand and the distance kept between the funnel support and the

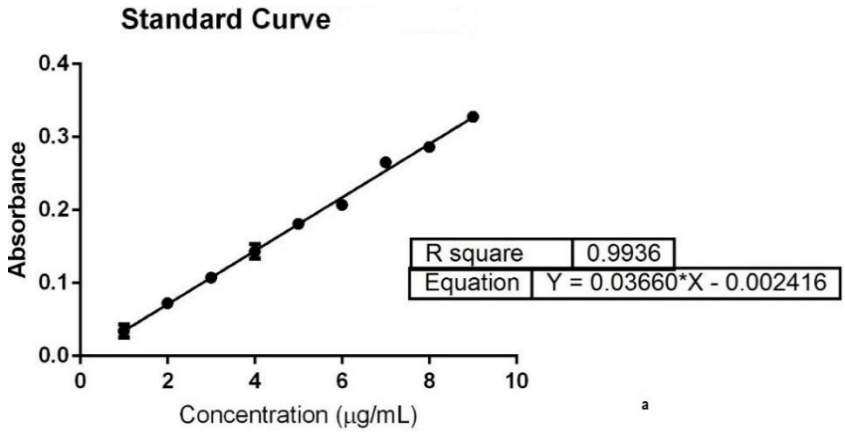


**Figure 2. This figure represents the standard curve.**

the horizontal surface was kept at approximately 10 cm above the horizontal surface level. The powder was dropped and passed through this funnel, and the height of the heap, represented by (h), and the radius of the heap, represented by the (r) were measured after passing the mixture powder through it. The equation used for the determination of the angle of repose was $\Phi = \tan^{-1}(h / r)$

**2.4.3. Determination of the Sedimentation Volume**

The volume of Sedimentation was determined for the prepared suspension dosage form in reconstituted suspension was studied by measuring sedimentation volume for 10 days without agitation during storage at particular time intervals. It was represented and recorded as a ratio of the ultimate/final settled height (Hu) to the initial height (Ho)

Equation: $F = Hu / H_0$ where F represents sedimentation volume

**2.4.4. Determination of the Redispersibility**

The phenomenon of redispersibility is not only a signifying character for the determination of quantitative features but also helps understand various rheological parameters as well.

For the determination of sedimentation volume, the container was shaken and mixed manually. According to Anil Reddy 2010, the suspension is considered easy to disperse if it shows 100 % inversion upon first invert. While performing redispersibility analysis, expecting a decrease of approximately 5 % on every subsequent inversion is always important.

**2.4.5. Rheological Studies**

Any formulation's flow properties are indicative factors of its stability. The rheological studies can be helpful in the evaluation of flow properties of the final finished dosage form. The Brookfield viscometer was employed to determine the rheological studies of all the suspension formulations. Environmental factors such as temperature and pressure were controlled before rheological studies were conducted. The temperature was maintained at 25 ± 1$^{o}$C. (Devrim, Bozkir et al. 2011).

**2.4.6. pH Values**

Hanna **HI2211**pH meter was used to measure the pH of various suspension formulations.

**2.4.7. Determination of Density**

The prepared suspension's density was determined using the pycnometer/density bottle method. First of all, a well neat, clean & dry pycnometer was selected and washed; after that, it was calibrated by filling it with distilled water and recording its weight. At that point, the unfilled bottle weight was subtracted from the total weighed pycnometer, and the density was computed, accepting the density of water to be 0.99602.

**2.4.8 Pourability**

To check the flow properties and Pourability of final preparation and to ensure patient

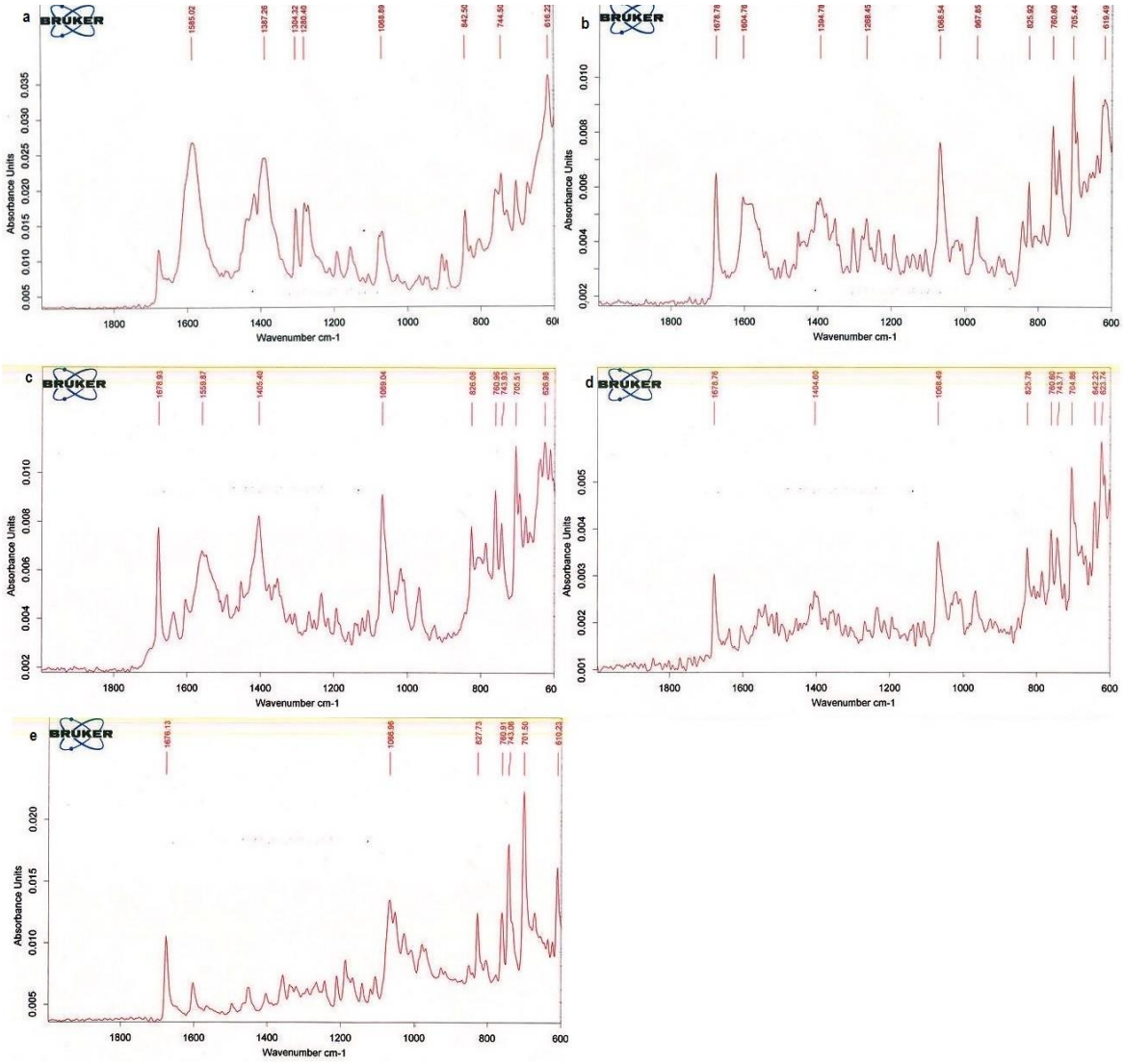


**Figure 3. The a, b, c, d, and e represents the FTIR Spectrum of Ebastine-nicotinamide, Ebastine-Sodium Acetate, Ebastine- Tri sodium citrate, Ebastine-Urea, and Ebastine, respectively.**

compliance, Pourability analysis was carried out for the final dosage form, i.e., suspension.

**2.5 Characterization of the Mixtures**

Characterization of the blended mixture and prepared final dosage form was done utilizing different systematic strategies, for example, UV spectroscopy, powder x-beam diffraction, differential examining calorimetry, and different techniques.

**2.5.1. Ultraviolet-Visible Spectroscopy (UV-Vis) studies**

Shimadzu UV-Spectrophotometer was used for these studies, and ethanol was used as the solvent. In order to get the absorbance values below 1, multiple dilutions of the stock solution were prepared(Ford and Timmins 1989).

**2.5.2. X-ray Diffraction (XRD)**

XRD discovers the physicochemical way of a substance, regardless of whether it is in crystalline

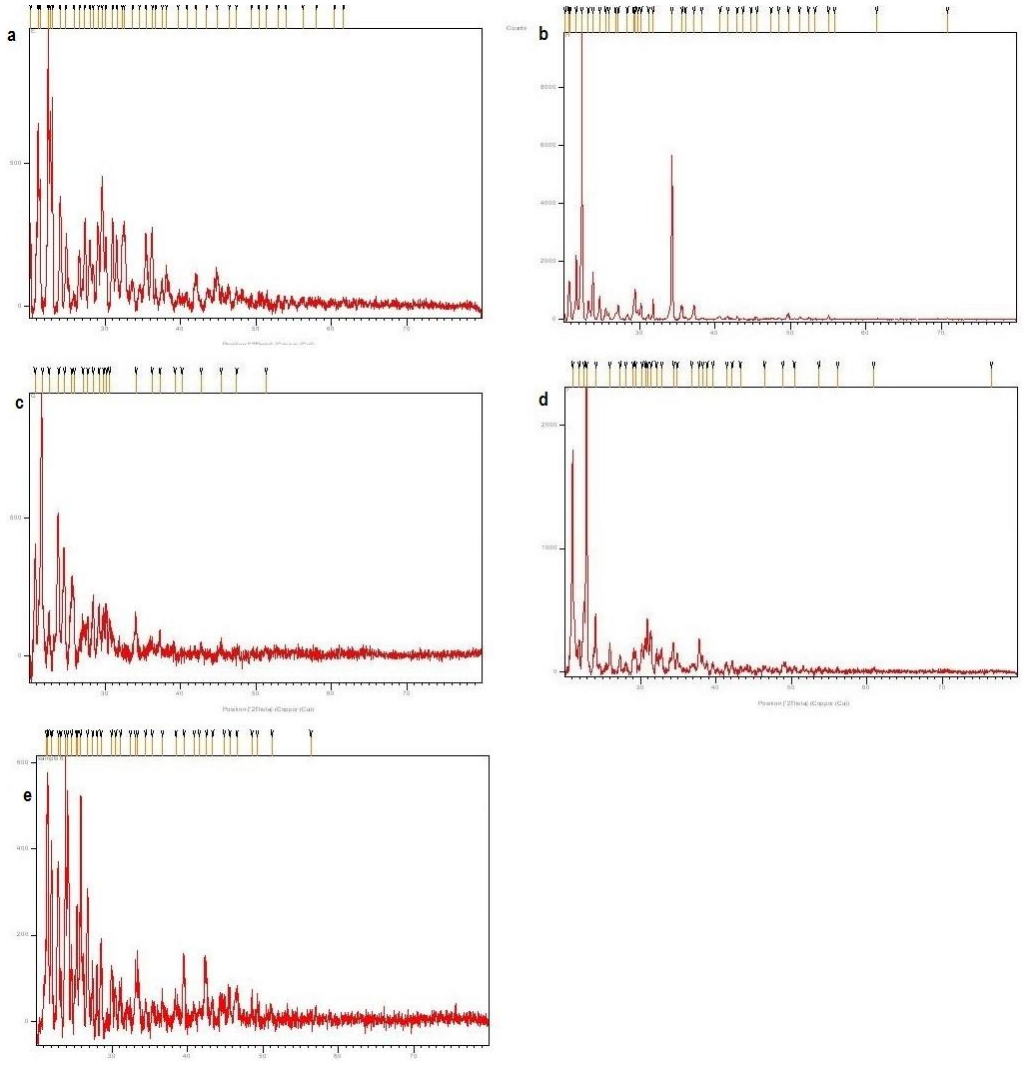


**Figure 4. The a, b, c, d, and e represents Powder X-ray Diffraction Spectrum of Ebastine-nicotinamide, Ebastine-Sodium Acetate, Ebastine-Tri sodium citrate, Ebastine-Urea, and Ebastine, respectively.**

or nebulous shape. In case the additional sharp peaks are gotten in the range, then the substance is transcendently crystalline in nature. Thus, XRD additionally decides the arrangement of solid dispersion formulations. In the case of solid dispersion, the sharpness of peaks of the medication is diminished, along with enhancement of its dissolvability characteristics (Yu, Amidon et al. 2002). Model RIGAKU was used for the said purpose.

**2.5.3. Differential Scanning Calorimetry (DSC)**

Differential scanning calorimetry (DSC) is a technique involving temperature regulations in which a test substance and a reference material are subjected to a controlled temperature. The distinctions in the warmth stream into the substance and the reference are measured as a function of the test substance temperature. The fundamental distinction between differential scanning calorimetry and differential thermal examination is that the previous is a calorimetric technique where contrasts in vitality are measured, while later, the distinctions in temperature are recorded. Thermo Model FC100AX0TA was employed to carry out the above test and evaluate the parameters.

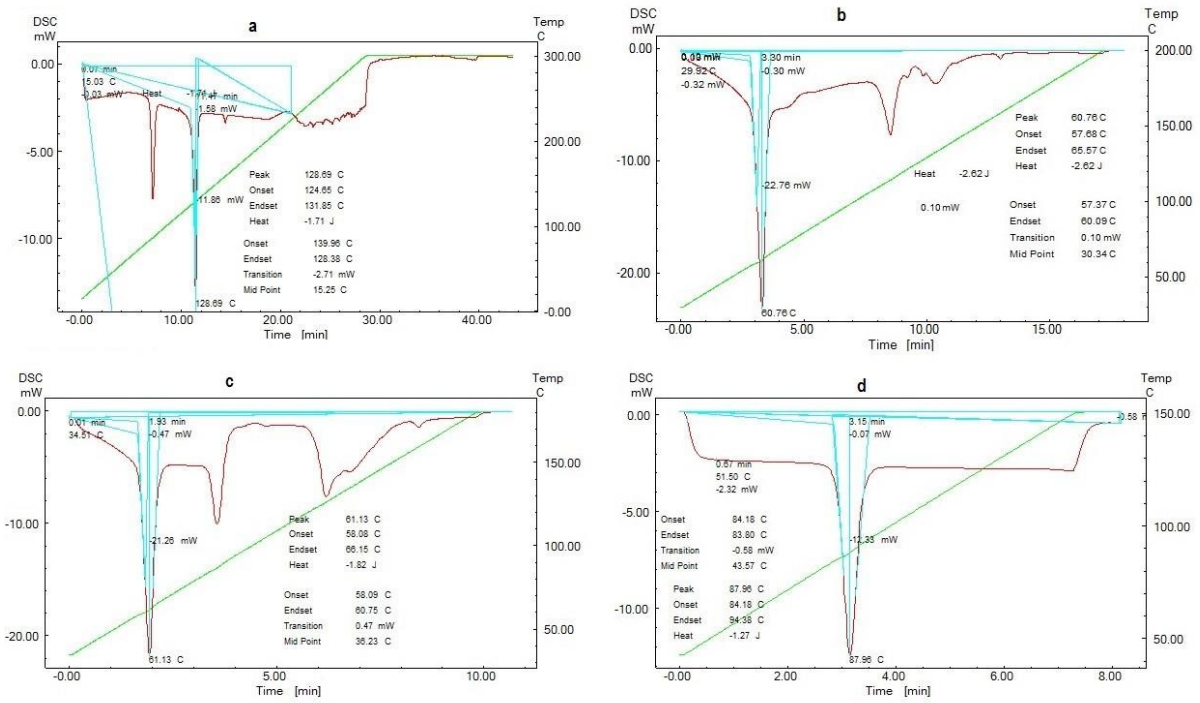


**Figure 5. The a, b, c, and d represent the DSC Spectrum of Ebastine-nicotinamide, Ebastine-Urea, Ebastine-Sodium Acetate, and Ebastine- Tri sodium citrate, respectively.**

### 2.5.4. Fourier Transform Infrared Spectroscopy

Radiations with average numbers ranging from about 12,800 to 10 cm-1 or wavelengths from 0.78 to 1000 μm come under the infrared region of the spectrum. The infrared spectrum is conveniently divided into near, mid, and far-infrared radiation for the stance of both application and instrumentation.

The electronic transitions encountered in the ultraviolet and visible radiation are generally not found with infrared radiation as they are not energetic enough. Absorption of infrared radiation is thus confined largely to molecular species for which small energy differences exist between various vibrational and rotational states. A molecule must undergo a net change in dipole moment due to its vibrational or rotational motion to absorb infrared radiation. Bruker Optics Fourier Transform Infrared Spectrometers (FTIR: Model ALPHA T) were used to perform the FTIR analysis of the prepared complex.

### 2.6. In-Vitro Dissolution Studies

The release rate of Ebastine from suspension was determined using dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl at 37± 0.5 °C and 50 RPM.

## 3. Results

### 3.1 Determination of Maximum Wavelength of Ebastine

The absorbance of Ebastine's 10 μg/ml solution was measured at 200nm to 400nm. The maximum wavelength of Ebastine was found to be 253 nm. (Fig.1)

### 3.2 Standard Graph of Ebastine in Ethanol

The absorbance of Ebastine was measured at different concentrations using a UV-visible spectrophotometer. (Fig. 2)

### 3.3 FTIR Analysis

For the determination of functional groups peaks, to observe any deviation in their peaks and as a first-line method to identify the complexation

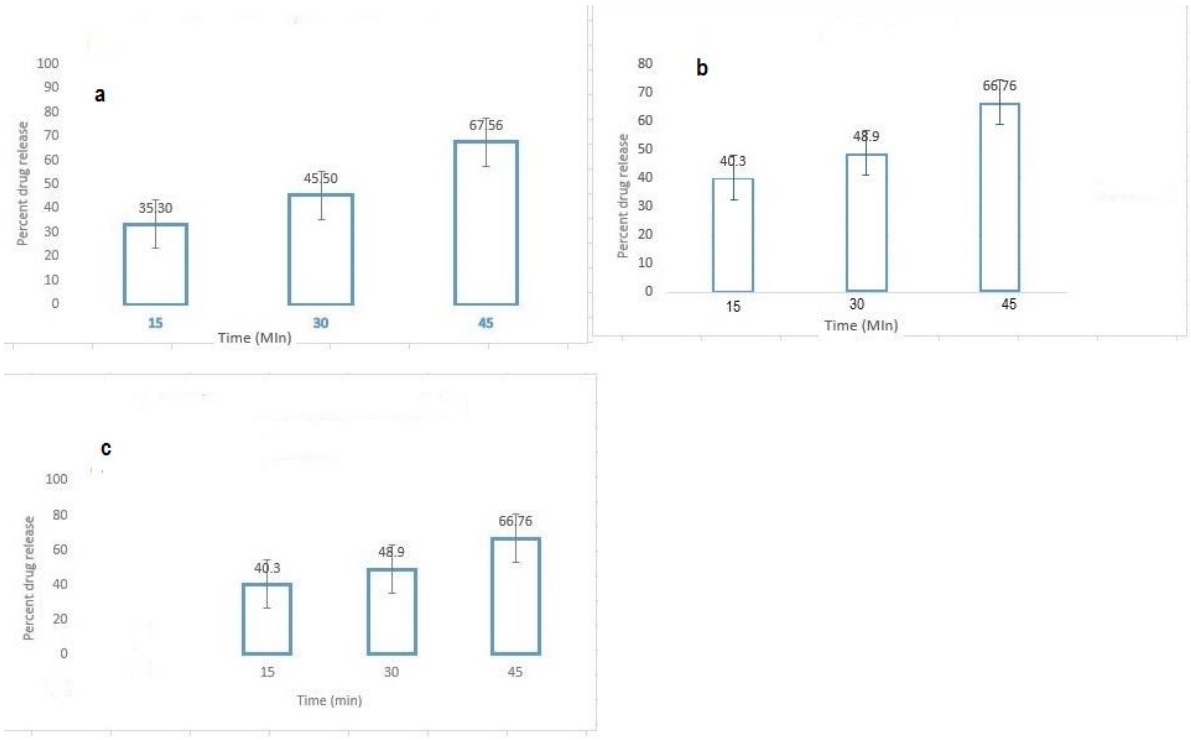


**Figure 6. The a, b, and c represent the percentage drug release profile of Ebastine-nicotinamide, Ebastine-Urea, and Ebastine- Tri sodium citrate, respectively.**

Phenomenon. FTIR analysis was conducted using BRUKER FTIR at a range of $2000^{-1}$cm – $600^{-1}$cm (fingerprint region) of chemical compounds and as a primary tool for the analysis of complexation. The FTIR spectrum of the complex showed the disappearance of various peaks in the fingerprint region, which clearly indicates the complexation of hydrotrope with the drug.

This suggests that the molecules of hydrotrope occupy the spaces between the

Molecules of the drug and the stacking phenomenon of hydrotropes lead toward the solubility enhancement of the drugs in the complex formation. (Fig.3)

**3.4 Powder X-Ray Diffraction Studies**

From powder X-Ray diffraction studies, it was evident that the crystalline nature of the solid dispersion remarkably reduced in almost all of the complexes prepared as compared to the two individual components (Oberoi, Alexander, and Riga 2005).

The increment in the solubility of the complex is thought to be courtesy of a reduction in the crystalline nature of the compounds present in the complex. The peaks observed in the XRD scan of both the drug that is Ebastine, and the formulated hydrotropes (Fig.4) were consistent with the individual segmental peaks of both the individual components (Passerini et al. 2002).

As a result of scattered spectra of the peaks produced in the complex of the drug and hydrotrope, the recognition of individual peaks that could have been measured in the case of individual ingredients was not significantly identifiable; as a result of this, the reduction in crystallinity in terms of percentage could not be measured accurately (Brittain 2001).

**3.5 DSC Studies**

DSC studies showed that there is a certain physical interaction between the Ebastine and the hydrotropes, of which the clear and strong interaction was observed to be between Ebastine and nicotinamide. (Fig.5)

The endothermal peak observed in all the combinations of the hydrotropes was found to be almost at the midpoint of the endothermal peak of the individual components of the mixtures.

The endothermal heat of fusion and clarity of peaks went on the incremental side upon the addition of drug concentration up to 75% until it started to drop again upon further addition.

This clearly indicated a possibility for a complexation reaction that results in a single compound giving a melting endotherm at an intermediate temperature. Sharp endotherm was observed at the concentration of 75% drug and 25 % hydrotrope. This composition corresponds to the most probable stoichiometric concentration at which the possibility of the complex formation increases in the solid state. The reduction in the melting point of the drug in complex form is a piece of evidence of the increment in solubility of the drug moiety in the complex state. The figures depicts the Differential scan chromatographic scan for various combination of Ebastine with different hydrotropes.

**3.6 Dissolution Studies**

The release rate of Ebastine from suspension was determined using dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37± 0.5 °C and 50 RPM. A sample solution of 5 ml from each combination was withdrawn from the dissolution apparatus at 15-minute intervals up to 45min (USP) and filtered through a 0.45-micron membrane filter. The samples were analyzed by UV spectroscopic method; the resulting profile is presented in graphical form in Fig.6.

**4. Discussion**

An important objective of this study was to examine the nature of the solid-state interaction between the drug and hydrotropes-nicotinamide, tri-sodium citrate, and sodium acetate using thermal and spectroscopic techniques, along with the effect that this complexation imparts on solubility enhancement of Ebastine. Another objective was to estimate the effectiveness and usefulness of the selected hydrotrope as a solubility-enhancing agent and to develop a suitable efficacious formulation.

The phenomenon of hydrotropy refers to the process of solubility enhancement of one (usually sparingly or partially water soluble) compound by courtesy of another compound in larger concentration (Maheshwari et al. 2008, Oberoi 2004). Hydrotropes are tiny organic substances with both lipophilic and hydrophilic properties but differ from surfactants in their molecular organization and structural makeup (Eastoe, Hatzopoulos, and Dowding 2011). The phenomenon of hydrotropism can best be described by the process of the salt formation called hydrotropic salts. Hydrotropic salts that tend to enhance the solubility of the drug particle are known to show salting in, while those that act in the opposite manner show a salting out phenomenon (Kumar, Raja, and Jayakumar 2014). The idea of complexation via hydrotropes is applied in the current study by virtue of which the solubility of the poorly water-soluble drug, Ebastine, was significantly increased. The resultant suspension of Ebastine possessed 8X enhanced aqueous solubility as compared to its other available dosage forms. In this work, nicotinamide, Urea, Tri-Sodium citrate, and sodium acetate have efficiently been employed to enhance the aqueous dissolution of Ebastine. Usually, high concentrations of the hydrotropic agent are required to achieve any substantial improvement in the drug solubility. It is for this reason that the concept has not become popular. In this context, nicotinamide has proven to be a successful hydrotrope since it is nontoxic and can be used for solubility enhancement. According to a large study, when higher concentrations of nicotinamide were administered, some beneficial clinical effects were observed in individuals suffering from various chronic states like inflammation of joints, granuloma, diabetes

mellitus, and some forms of cancers; however, no mechanism is known.

The three most probable mechanisms by which a hydrotrope could lead towards solubility enhancement include the generation of complexes between hydrotropes and drugs, breakdown in the water molecule structure, and self-stacking organization of hydrotropic molecules against the solute in the solution (Booth, Abbott, and Shimizu 2012). Of all the presented mechanisms, the most accepted one is the self-association or self-stacking phenomenon above certain hydrotropic concentrations at which these molecules are thought to form micelle-like interlinked groups (Eastoe, Hatzopoulos, and Dowding 2011).

The phenomenon of hydrotropy has been reported to occur mostly at higher molecular concentrations of hydrotropes. Hydrotropes are responsible for a proportional increase in solubilization of certain poorly soluble drugs till a specific concentration, after which the solubility remains unchanged; along with this, hydrotropes have been shown to affect the rate of reaction towards its higher rates (Buurma, Blandamer, and Engberts 2002). The minimum hydrotropic concentration needs not be mixed with perilous micellar concentration because the minimum concentration for hydrotrope arises as a resultant cooperative linking between the solute particles and the hydrotrope (Booth, Abbott, and Shimizu 2012).

The selection of suspension as a dosage form for this study was appropriate based on its ability to be able to provide the effective concentration where a hydrotrope can perform its function to enhance the solubility at its best. Upon evaluation of the various peaks in the FTIR spectra of the complexes, it can be observed that many broad peaks disappeared, which is a clear indication that the hydrotopic moieties have resided and taken place in the intermolecular localities of the Ebastine and have prevented weak intermolecular interactions. The analysis of FTIR studies indicates that the higher solubilization rates of the complexes are by virtue of the absence of weak hydrogen bonding in the complexes.

PXRD studies showed that the crystallinity of the complex is remarkably reduced, which again predicted greater solubility for the complex. It was observed that the solubility enhanced with increasing concentration of nicotinamide. Our study has aided in understanding that the solubility of poorly water-soluble drugs can be enhanced via another cost-effective and safe method of hydrotropic complexation. Hydrotropic solubilization is a simple, economical, and safe technique that has proved to be very beneficial for the solubility enhancement of various clinical drugs.

## 5. Conclusions

The current study showed that pharmacologically important drugs that cannot be formulated into proper dosage form due to their poor aqueous solubility could be shaped into suitable pharmaceutical dosage forms by the hydrotropic methodology. This technique is not only simple, & cost-effective but also less tedious as compared to the already known solubility enhancing methodologies.

## Conflict of interest

The authors declare that they have no conflicts of interest.


## Funding

There was no external funding available for this research project.


## Study Approval

Yes. The study was approved by the Institutional Review Board of the Riphah International University Islamabad, Pakistan.

## Consent Forms

NA.

## Authors Contribution

MAK, and ZI; conceptualized the study, MAK; wrote the final manuscript, SG, SP helped in the formal analysis, TH, and AT; did the experimental analysis, and ZI; supervised the whole project.

**Acknowledgments**
All the authors of the manuscript highly acknowledge Centralized Resource Laboratory (University of Peshawar) for their expertise in FTIR, TGA and XRD.

**References**

Aggarwal, Amit, and Shweta Jain. 2011. "Physicochemical Characterization and Dissolution Study of Solid Dispersions of Ketoconazole with Nicotinamide." *Chemical & pharmaceutical bulletin* 59:629-38. doi: 10.1248/cpb.59.629.

Balasubramanian, D, V Srinivas, VG Gaikar, and MM Sharma. 1989. "Aggregation behavior of hydrotropic compounds in aqueous solution." *The Journal of Physical Chemistry* 93 (9):3865-3870.

Booth, Jonathan J, Steven Abbott, and Seishi Shimizu. 2012. "Mechanism of hydrophobic drug solubilization by small molecule hydrotropes." *The Journal of Physical Chemistry B* 116 (51):14915-14921.

Brittain, Harry G. 2001. "X-ray diffraction III: pharmaceutical applications." *Spectroscopy* 16 (7):14-18.

Buurma, Niklaas J, Michael J Blandamer, and Jan BFN Engberts. 2002. "Association of hydrotropes in aqueous solution studied by reaction kinetics." *Advanced Synthesis & Catalysis* 344 (3-4):413-420.

Chaumeil, JC. 1998. "Micronization: a method of improving the bioavailability of poorly soluble drugs." *Methods and findings in experimental and clinical pharmacology* 20 (3):211-216.

Chavda, H, C Patel, and I Anand. 2010. "Biopharmaceutics classification system." *Systematic reviews in pharmacy* 1 (1):62.

Dhapte, Vividha, and Piyush Mehta. 2015. "Advances in hydrotropic solutions: An updated review." *St. Petersburg Polytechnical University Journal: Physics and Mathematics* 1 (4):424-435.

Eastoe, Julian, Marios Hopkins Hatzopoulos, and Peter J Dowding. 2011. "Action of hydrotropes and alkyl-hydrotropes." *Soft Matter* 7 (13):5917-5925.

Ford, James L, and Peter Timmins. 1989. *Pharmaceutical thermal analysis: techniques and applications*: Ellis Horwood.

Jones, Marie-Christine, and Jean-Christophe Leroux. 1999. "Polymeric micelles–a new generation of colloidal drug carriers." *European journal of pharmaceutics and biopharmaceutics* 48 (2):101-111.

Kumar, V Sampath, C Raja, and C Jayakumar. 2014. "A review on solubility enhancement using hydrotropic phenomena." *Int. J. Pharm. Pharm. Sci* 6 (6):1-7.

Lee, Jaehwi, Sang Cheon Lee, Ghanashyam Acharya, Ching-jer Chang, and Kinam Park. 2003. "Hydrotropic solubilization of paclitaxel: analysis of chemical structures for hydrotropic property." *Pharmaceutical research* 20:1022-1030.

Leuenberger, Hans. 2002. "Spray freeze-drying–the process of choice for low water soluble drugs?" *Journal of Nanoparticle Research* 4:111-119.

Maddens, T, I Vélaz, R Machín, JR Isasi, C Martín, MC Martínez-Ohárriz, and A Zornoza. 2011. "Complexation of ebastine with β-cyclodextrin derivatives." *Journal of Inclusion Phenomena and Macrocyclic Chemistry* 70:415-419.

Maheshwari, RK, D Arif, P Mittal, P Manchandani, A Indurkhya, and S Jawade. 2008. "A novel method for quantitative determination of aceclofenac in bulk drug and tablets using ibuprofen sodium as a hydrotropic solubilizing agent." *J Appl Chem Resh* 5:63-8.

Matsuda, Michiaki, Yasuyuki Mizuki, and Yoshiaki Terauchi. 2001. "Simultaneous determination of the histamine H1-receptor antagonist ebastine and its two metabolites, carebastine and hydroxyebastine, in human plasma using high-performance liquid chromatography." *Journal of Chromatography B: Biomedical Sciences and Applications* 757 (1):173-179.

Millard, Jeffrey W, FA Alvarez-Nunez, and SH Yalkowsky. 2002. "Solubilization by cosolvents: Establishing useful constants for the log–linear model." *International Journal of Pharmaceutics* 245 (1-2):153-166.

Oberoi, Lalit M. 2004. *Formulation of a fast-acting ibuprofen suspension by using nicotinamide as hydrotropic agent-application of DSC, spectroscopy and microscopy in assessment of the type of interaction*: The University of Toledo.

Oberoi, Lalit M, Kenneth S Alexander, and Alan T Riga. 2005. "Study of interaction between ibuprofen and nicotinamide using differential scanning calorimetry, spectroscopy, and microscopy and formulation of a fast-acting and possibly better ibuprofen suspension for osteoarthritis patients." *Journal of pharmaceutical sciences* 94 (1):93-101.

Passerini, Nadia, Beatrice Albertini, Marisa L González-Rodríguez, Cristina Cavallari, and Lorenzo Rodriguez. 2002. "Preparation and characterisation of ibuprofen–poloxamer 188 granules obtained by melt granulation." *European Journal of Pharmaceutical Sciences* 15 (1):71-78.

Radwan, Mahasen A, and Hassan Y Aboul-Enein. 2004. "In vitro release and stereoselective disposition of flurbiprofen loaded to poly (D, L-lactide-co-glycolide) nanoparticles in rats." *Chirality* 16 (2):119-125.

Roger, A, J Fortea, S Mora, and M Artés. 2008. "Ebastine fast-dissolving tablets versus regular tablets: acceptability and preference in patients with allergic rhinitis." *Expert Review of Clinical Pharmacology* 1 (3):381-389.

Saleh, AM, and LK El-Khordagui. 1985. "Hydrotropic agents: a new definition." *International journal of pharmaceutics* 24 (2-3):231-238.

Strickley, Robert G. 2004. "Solubilizing excipients in oral and injectable formulations." *Pharmaceutical research* 21:201-230.

Torchilin, Vladimir P. 2001. "Structure and design of polymeric surfactant-based drug delivery systems." *Journal of controlled release* 73 (2-3):137-172.

Tripathi, KD. 2008. "Essentials of Medical Pharmacology by Jaypee Brothers Medical Publishers." *India.*

Varshney, HM, and A Chatterjee. 2012. "Solubility enhancement of poorly hydrophilic drugs by using different newer techniques: A Review." *International journal of Therapeutic applications* 6 (8):13.

Vemula, Varun Raj, Venkateshwarlu Lagishetty, and Srikanth Lingala. 2010. "Solubility enhancement techniques." *International journal of pharmaceutical sciences review and research* 5 (1):41-51.

Vincent, J, DJ Sumner, and JL Reid. 1988. "Ebastine: the effect of a new antihistamine

on psychomotor performance and autonomic responses in healthy subjects." *British journal of clinical pharmacology* 26 (5):503-508.

Wagh, RS, RA Hajare, AG Tated, PA Gadbail, FA Khan, and SD Kayal. 2011. "Method development and validation for simultaneous determination of ebastine and phenylephrine hydrochloride in tablet formulation by RP-HPLC." *International Journal of Pharmaceutical Research and Development* 3 (7):214-220.