DOI: 10.55522/jmpas.V12I1.4067 ISSN NO. 2320–7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Research article

Solubility enhancement of terbinafine hydrochloride by hydrotropic technique

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ABSTRACT

Terbinafine hydrochloride is an antifungal drug belonging to the class of allylamines. The drug exhibits poor aqueous solubility and thus results in decrease in oral bioavailability. In the present study, an attempt was made to enhance the solubility of terbinafine hydrochloride using hydrotropic solubilization technique employing different hydrotropesnamely sodium benzoate and ureain different proportions and their combinations. The different hydrotropes were selected based on the saturation solubility exhibited by the drug. Among them best batches of the drug-hydrotrope combinations of varying concentrations of 5% w/v, 10% w/v and 15% w/v were further subjected for the *in vitro* dissolution studies and solid-state characterization studies. The results so obtained were an indicative of solubility enhancement of terbinafine hydrochloride in combination of 10% urea, and combinationhydrotropes of 10% urea and 15% sodium benzoate. Thus, the experimental investigation concluded that there is an 1.53, 3.77 fold increase in dissolution profile for drug with 10% urea and combination of drug with 10% urea and 15% sodium benzoate respectively at the end of 120 minutes.

Keywords: Hydrotropy, Terbinafine Hydrochloride, Sodium Benzoate, Urea, Solubility

Received - 22-07-2022, Accepted- 07-01-2023

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INTRODUCTION

Hydrotropy is a process in which a significant amount of a second solute increases the aqueous solubility of a third solute. Hydrotropes are alkaline salts of various organic acids. The salt that promotes solubility in a particular solvent is termed as salt in, while the salt that lowers the solubility is called salt out. Hydrotropism is a phenomenon in which several salts with large anions or cations that are themselves very soluble in water result in salting in of non-electrolytes called hydrotropic salts. Hydrotropic solutions are non-colloidal and have weak interactions between the hydrotropic agent and the solute. Water solubility can be increased by means of hydrotropic solubilization technique [1].

The hydrotropic solubilization is much similar to complexation technique of enhancement of solubility, which involves a weak contact between hydrotropic agents such as sodium benzoate, sodium acetate, sodium alginate, and urea and poorly soluble medicines. Solvents can increase or decrease the solubility of a drug molecule. The effect of an addition is mostly determined by its influence on the structure of water or its capacity to compete with water molecules in the solvent [2].

The bioavailability is an important factor which influences the therapeutic effectiveness of a drug. Therefore, the solubility is directly influencing on the drug bioavailability. Larger the drug concentration in the systemic circulation the larger will be the bioavailability. About 8% of the new drugs have both good solubility and permeability at the moment [3].

Terbinafine hydrochloride, an antifungal drug has a low solubility and dissolution profile and hence results in less bioavailability. The hydrotropic solubility enhancement technique is employed to enhance the solubility of the drug [4, 5]. Firstly, the saturation solubility is determined using the different hydrotropes with the drug. The solubility enhancement ratio is calculated and from the best batches is determined and the *invitro* dissolution studies were conducted on these batches.

Lastly, to determine any incompatibility between the drug and hydrotropic blend, the studies such as Differential Scanning Calorimetry (DSC), Fourier Transform Infra-Red (FTIR)studies were conducted. To determine the crystallinity and surface morphology of the drug and the hydrotropes X-ray Powder diffraction (XRPD) and scanning electron microscopy (SEM) analysis was performed.

MATERIALS AND METHODS

Materials

Terbinafine hydrochloride was received as a gift sample from Unnati Pharmaceuticals Ltd, India. Hydrotropes such as sodium benzoate and urea were purchased from SD Fine Chemicals Ltd.

Methodology

Development of a standard calibration curve

A stock solution of terbinafine hydrochloride (TBH) was prepared by dissolving 5mg of TBH in 25ml in phosphate buffer pH 7.4. Then sub stock solution was prepared from the solution by taking 5ml from stock solution and diluting with 50ml phosphate buffer pH 7.4. From the sub-stock solution of TBH, it was subsequently diluted with phosphate buffer to obtain a series of dilution containing 1,2,3,4 and 5µg/ml. The absorbance of the above solutions was measured using UV-visible spectrophotometer (Shimadzu, 1700-series, Japan) 283 nm against blank [6].

Solubility studies

Equilibrium solubility studies in different hydrotropes

For the determination of saturation solubility of terbinafine hydrochloride in water, initially 5%, 10%, 15% of hydrotropic agent's urea, sodium benzoate was prepared in water. From this a 5ml of above solutions is taken in 10ml vial 100mg of Terbinafine hydrochloride was added. Each vial is kept in orbital shaker for 24 hours with 37°C. Filtered through a Whatman filter paper. Diluted with distilled water and analyzed in UV spectroscopy by measuring the absorbance at 283nm [7,8].

Equilibrium solubility studies in mixed hydrotropic blends

Different hydrotropes are mixed in 1:1 ratio with 5ml of above solutions is taken in a 10ml vial to which 100mg of TBH was added. Each vial is kept in orbital shaker for 24 hours with 37°C. Filtered through Whatman filter paper. Diluted with distilled water and analyzed in UV spectroscopy by measuring the absorbance at 283nm [9].

Fourier Transform Infrared (FTIR)

A compatibility study was investigated to ascertain the possibility of a contact between the drug, sodium benzoate, urea and their blends. The IR absorption spectra of the materials (between 4000 and 400 cm^{-1}, with a resolution of 4 cm^{-1}) were obtained using FTIR (FT/IR-4700 type A). The collected spectra were compared and analyzed to determine the shift of key functional peaks and the disappearance of functional peaks associated [10].

Powder X-ray Diffraction (PXRD)

The X-ray beam diffraction examples of terbinafine hydrochloride and their respective hydrotropes were recorded utilizing at PANalytical/X Pert3 Powder of 40 kV and 20 mA. The checking speed was changed by 2 degrees each moment, and the examples were exposed to Cu-K radiation at 2θ points going from 5° to 50° degrees [11].

Scanning Electron Microscopy (SEM)

SEM studies were carried out to determine the surface morphology and shape of the terbinafine hydrochloride alone and in hydrotrope mixture. The sample was diluted at 1:500 (v/v) in distilled water. On a silica wafer that had been carbon taped to metallic help, a drop of the suspension was kept. The help was set in a desiccator short-term to empower liquids to disperse. Following that, the examples were covered with gold (10 nm) utilizing the Q150RES splash coater in an argon climate (Quorum Technologies Ltd., Laughton, UK). SEM pictures were gained utilizing an EVO18 magnifying lens (Carl Zeiss Micro imaging, Jena, Germany) [12].

Differential Scanning Calorimetry (DSC)

The thermal properties of terbinafine and their hydrotropic mixture were investigated by utilizing differential scanning calorimetry. The samples were compacted in the ordinary aluminum pan and warmed up to the scope of 50°-250°C at a pace of 10°C/min while being ceaseless with dry nitrogen at a pace of 30ml/min. DSC thermograms were gathered utilizing a computerized warm analyzer instrument (DSCQ-200) and for reference, an empty pan fixed in the specific cycle was kept inside the instrument. Alignment of temperature was done utilizing an indium as reference standard. The thermograms produced by the DSC were analyzed and utilized to decide the exothermic and endothermic peaks of the samples [13].

In vitro dissolution studies

The dissolution studies were carried out using USP II dissolution apparatus following paddle method, freshly prepared phosphate buffer solution (pH 7.4 - 250 ml) was placed in the dissolution flask and allowed to attain a temperature 37 ± 0.5ºC. The pure drug and hydrotropic formulation quantity that is equivalent to 50 mg was placed in the basket and immersed in the dissolution medium. The basket was rotated at 50 rpm for 2 hours. Five milliliters of the sample were withdrawn at the different time intervals of 0, 15, 30, 45, 60, 90 and 120 minutes. After each withdrawal, the medium was replaced with equal amount of fresh buffer to maintain the sink condition. The drug content was estimated by measuring the absorbance at 283 nm against blank [14].

RESULTS AND DISCUSSION

Development of calibration curve for terbinafine hydrochloride in phosphate buffer pH: 7.4:

The purpose of the calibration curve was to evaluate the linear relationship among the various concentrations of the drug and their absorbance. After the construction of the calibration graph, it was found that a perfect linear relationship was observed among the concentrations of1µg/ml,2µg/ml,3µg/ml, 4µg/ml, 5µg/ml terbinafine hydrochloride in phosphate buffer and the λ max of the drug was also measured of UV range from 400-200nm the obtained UV absorbance values at 283nm. The regression value of the calibration plot is found to be 0.9989indicatingthegood linearity among the variables [15].

Determination of Solubility

Saturation solubility studies of terbinafine hydrochloride with different blends were conducted using two different hydrotropes sodium benzoate and urea 5%, 10%, 15% of each hydrotropes and

their mixed combinations.

Table 1: Solubility studies of terbinafine hydrochloride with different blends

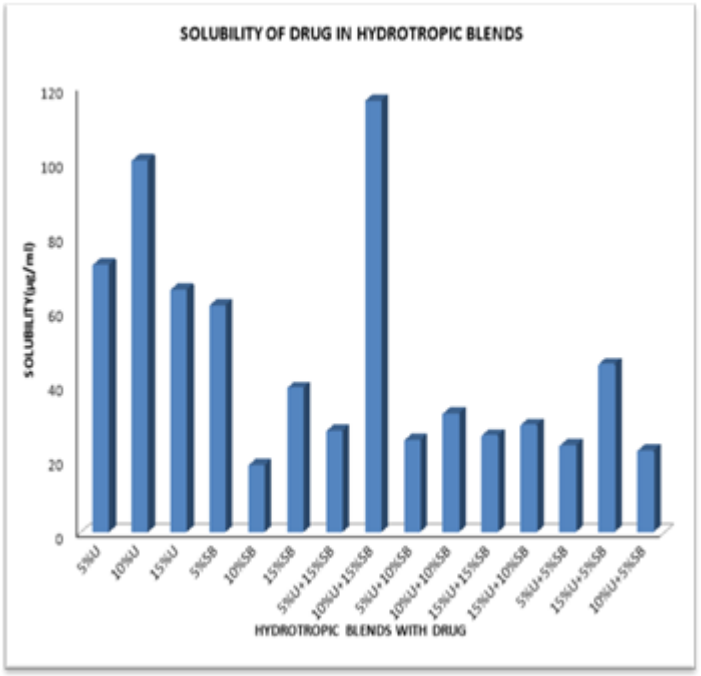
Blends	Total Concentration (ml)	Drug (mg)	Solubility (µg/ml)	Solubility Enhancement Ratio
5%U	5	50	71.69	3.73
10%U	**5**	**50**	**99.72**	**5.193**
15%U	5	50	65.00	3.38
5%SB	5	50	60.83	3.16
10%SB	5	50	17.77	0.925
15%SB	5	50	38.611	2.019
5%U+15%SB	2.5+2.5	50	26.94	1.403
10%U+15%SB	**2.5+2.5**	**50**	**115.83**	**6.032**
5%U+10%SB	2.5+2.5	50	24.44	1.27
10%U+10%SB	2.5+2.5	50	31.66	1.64
15%U+15%SB	2.5+2.5	50	25.83	1.34
15%U+10%SB	2.5+2.5	50	28.611	1.49
5%U+5%SB	2.5+2.5	50	23.05	1.20
15%U+5%SB	2.5+2.5	50	45	2.34
10%U+5%SB	2.5+2.5	50	21.66	1.12

This revealed that 10% urea shows solubility about 99.72 µg/ml which have solubility enhancement ratio of 5.193 and 10% urea+15% sodium benzoate shows solubility about 115.83µg/ml which have solubility enhancement ratio of 6.032. So, it can be concluded that 10% urea and 10% urea+15% sodium benzoate are the best batches showed increased solubility enhancement ratio's [16].

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is one of the tools for determining the interactions between drug and additives. In the present study, FTIR spectrum of terbinafine hydrochloride showed characteristics peaks for the functional groups *C≡C* (Alkynes - 2439), C=C (Aromatic - 1509), C-H (Aromatic - 3041) and C-N (Tertiary Nitrogen - 1133).

Figure 1: Solubility of terbinafine hydrochloride in different hydrotropic agents



These are the peaks were also found in the combinations of terbinafine hydrochloride + sodium benzoate + urea is shown in Figure 1-3. From the above observation it can be concluded that there is no interaction observed between the hydrotropes and drug [17, 18].

Figure 2: FTIR Spectra of terbinafine hydrochloride

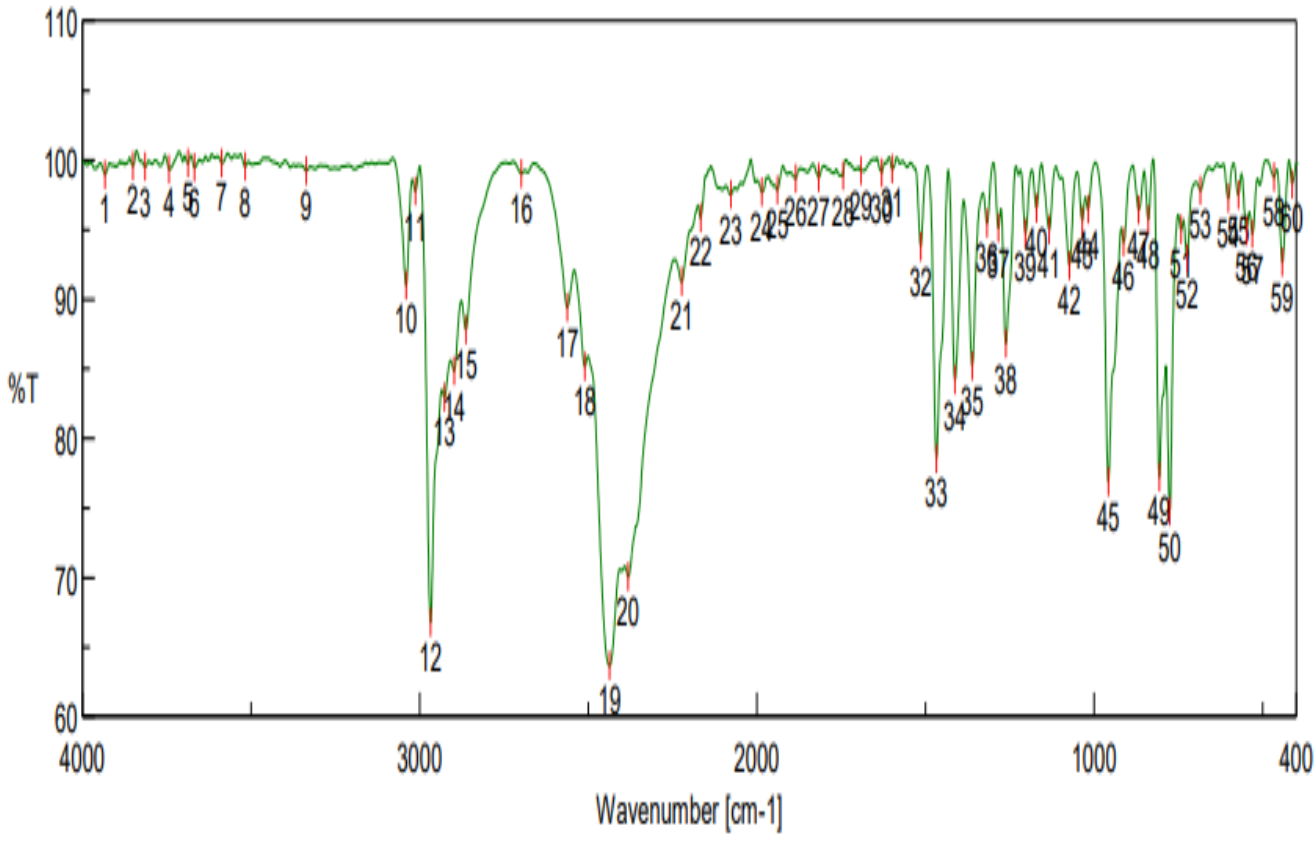
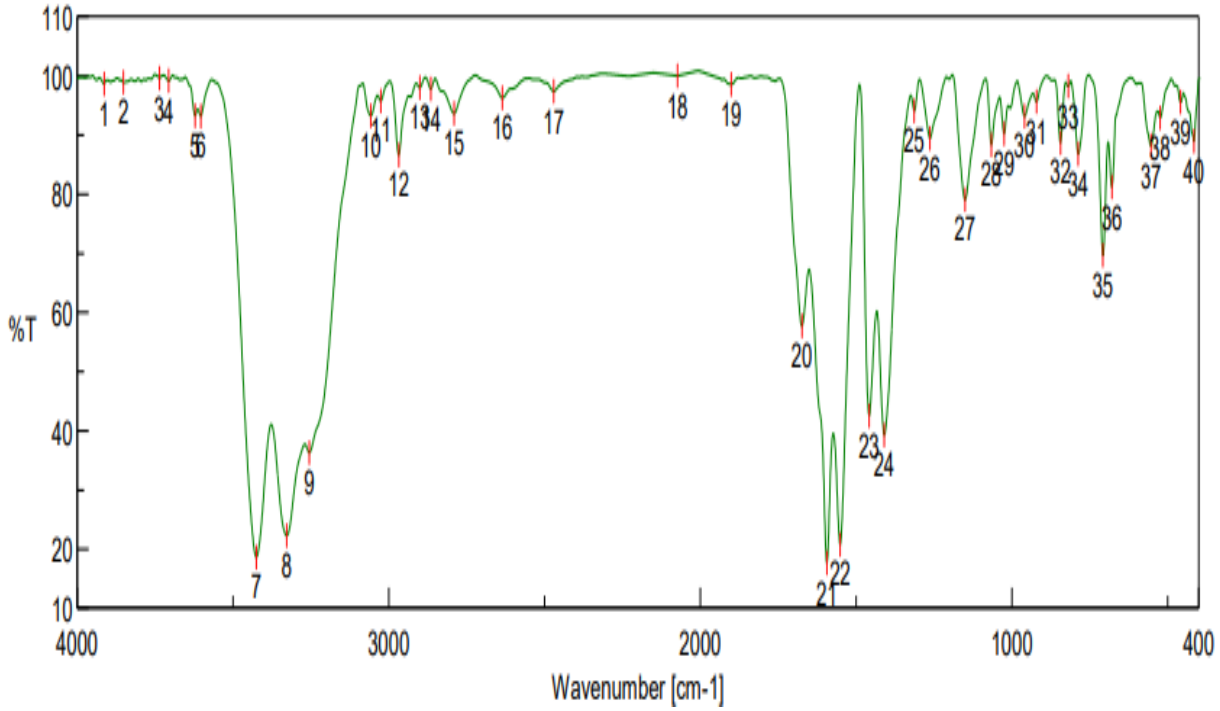


Figure 3: FTIR Spectra of terbinafine +sodium benzoate +urea



Differential Scanning Calorimetry (DSC)

The DSC thermogram of terbinafine hydrochloride exhibited an endothermic peak at 210.46°C. The melting point of physical mixtures (Terbinafine hydrochloride +Sodium benzoate +Urea) shows two endothermic peaks as shown in Figure 4-5. One endothermic peak was observed at 59.73°C and another was reflected at 210.32°C. This reveals that there are no interactions between the drug terbinafine hydrochloride and selected hydrotropic blends.

Figure 4: DSC thermogram of terbinafine hydrochloride

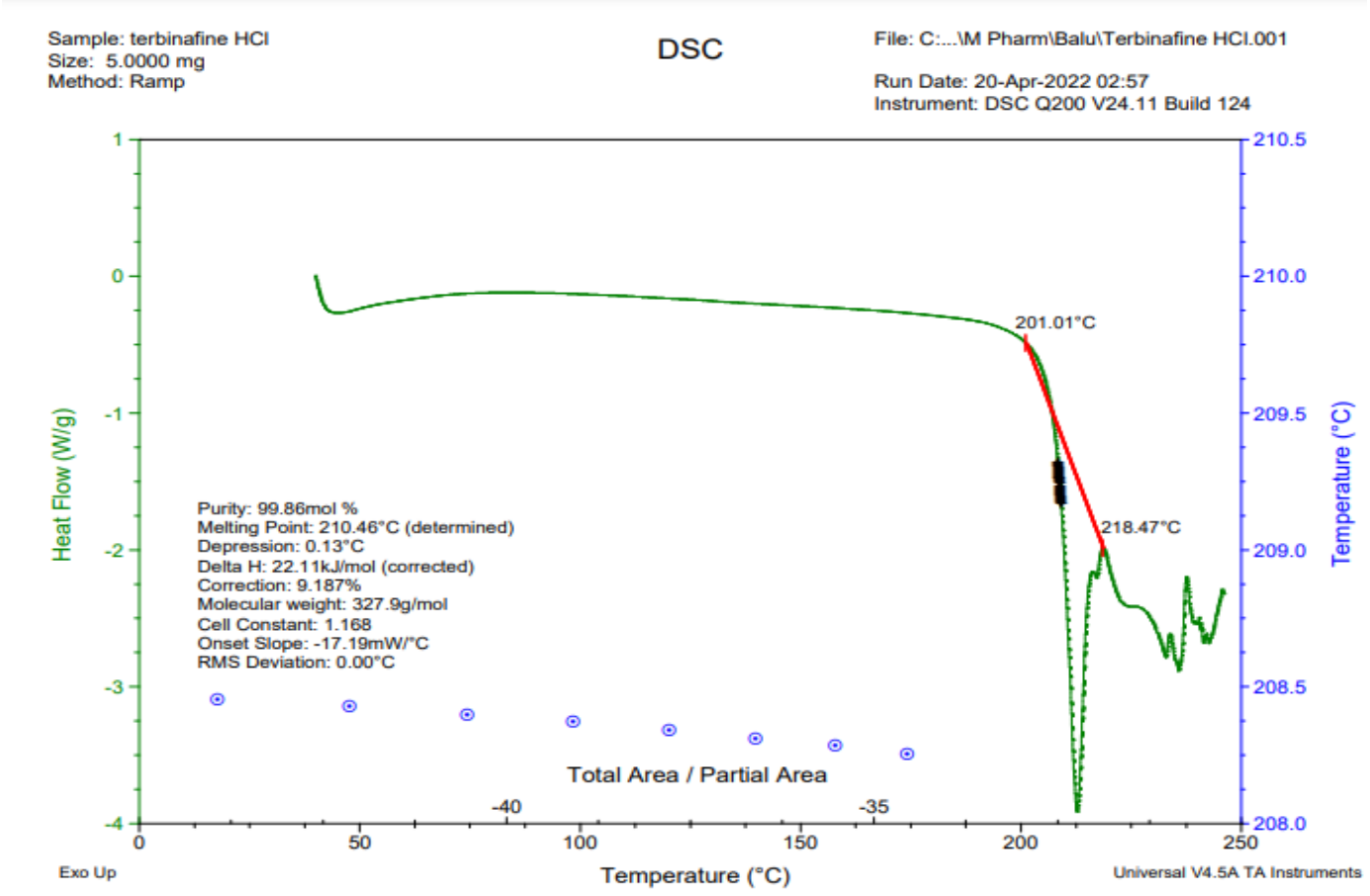
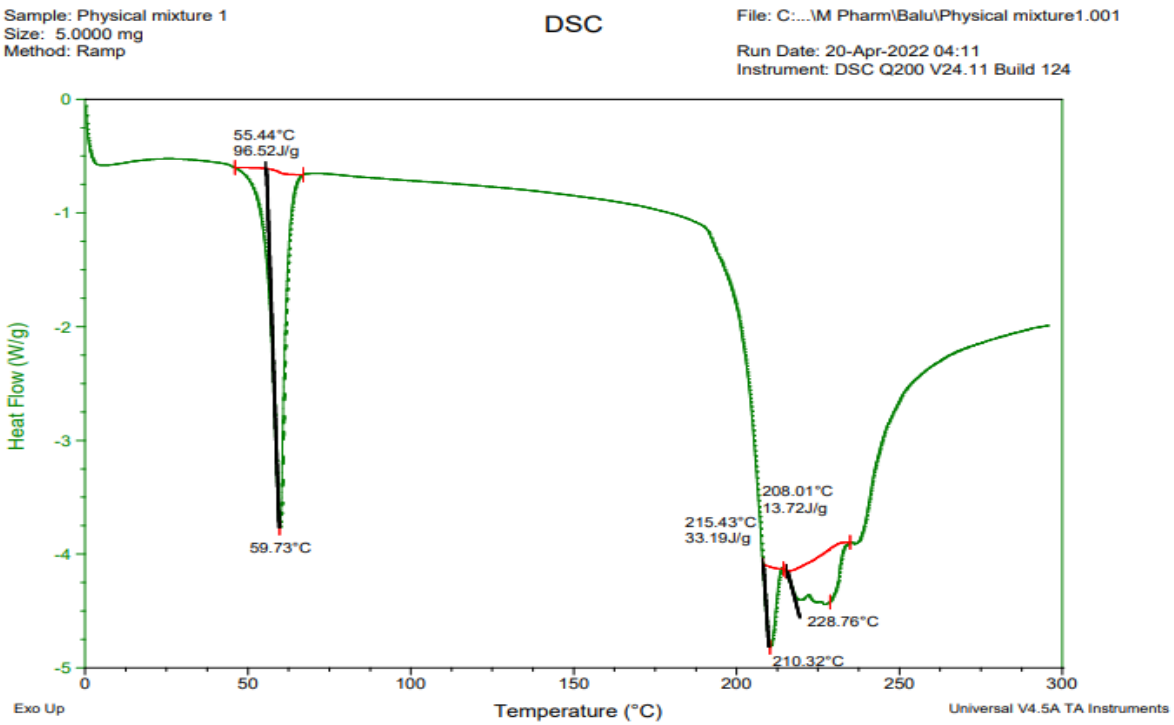


Figure 5: DSC thermograms of terbinafine hydrochloride+urea+sodium benzoate



X-Ray powder diffraction analysis (XRPD)

The XRPD patterns of terbinafine hydrochloride exhibited a sharp and intense peak at 5.94°, 9.7°, 15.90°, 21.56°, 20.03°, 19.65°, 24.12°, 25.36°. Whereas, the XRPD pattern of physical mixtures showed diffraction peaks (°2θ) at 9.8°, 5.94°, 21.60°, 20.05°, 19.64°, 24.12°, 5.94°, 22.17°, 20.05°, 19.64°, 21.60°, 24.12°, 35.49° and 25.48° respectively. The 2θ of the drug were reported in the physical mixtures revealed that there was a reduction in intensity and broadening of peak shown in Figure 6-7. From this it can be concluded that the drug in the hydrotrope is available in the form of amorphous. This indicates the change of form from crystalline to amorphous.

Figure 6: XRPD of Terbinafine hydrochloride

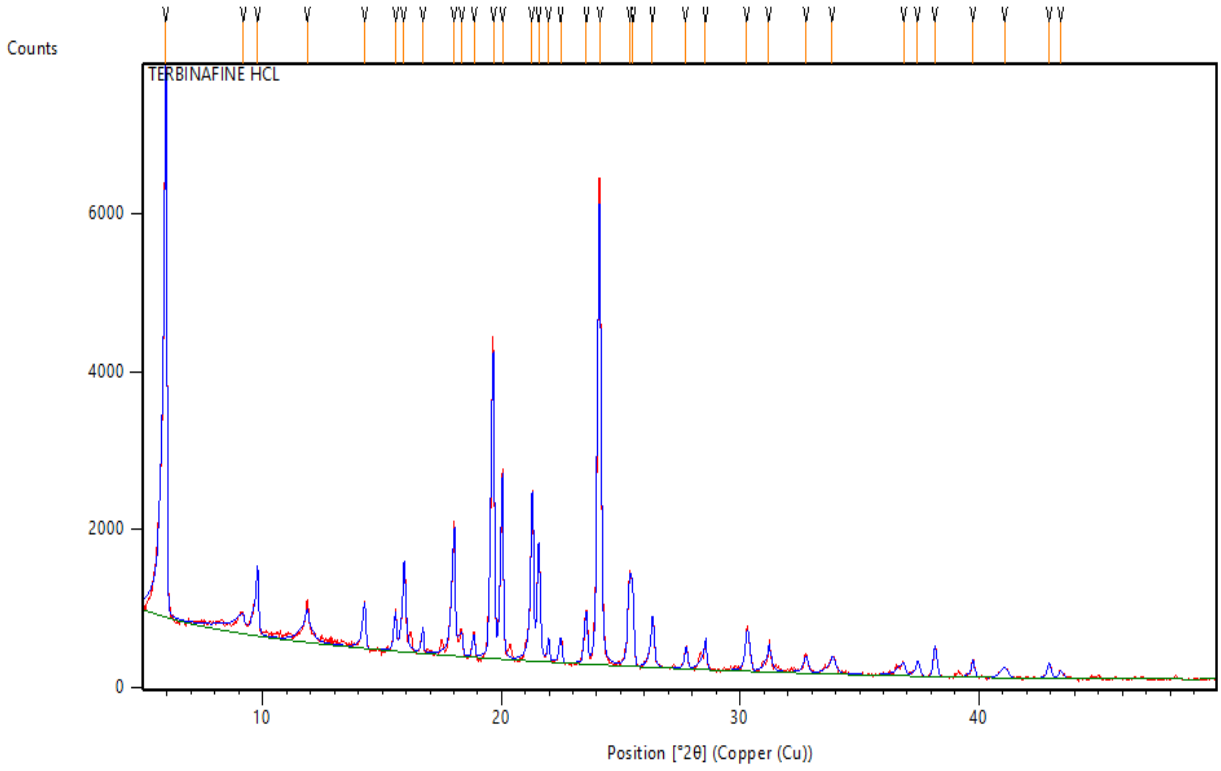
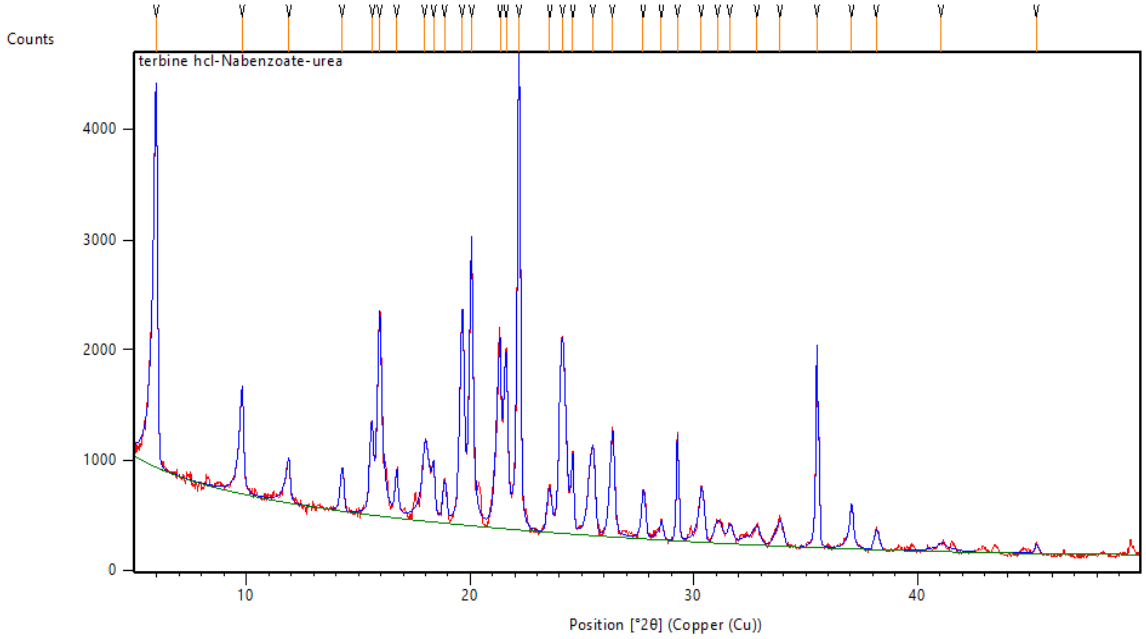


Figure 7: XRPD of Terbinafine hydrochloride+sodiumbenzoate+urea



Scanning Electron Microscopy (SEM)

SEM studies were carried out to determine the surface morphology of the physical mixture containing the drug and the hydrotropic blends.

The study revealed that there was a slight change observed from

Figure 8: Scanning electron microscopy of terbinafine hydrochloride

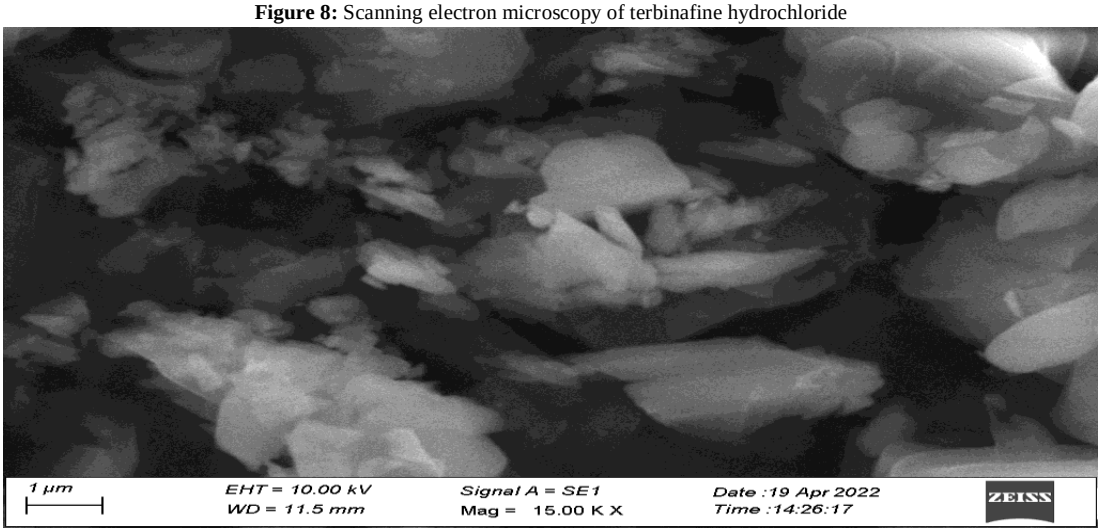
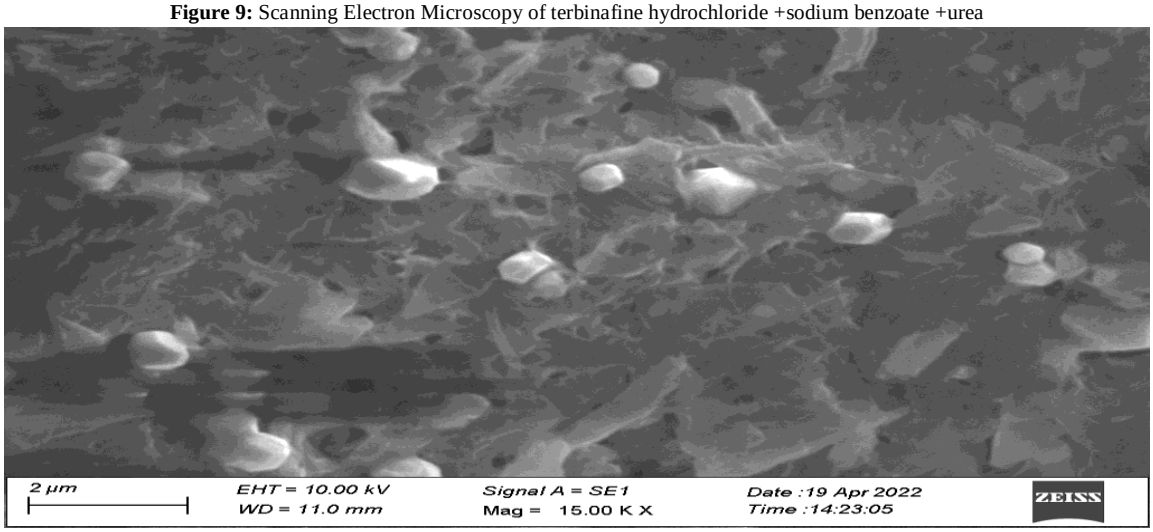


Figure 9: Scanning Electron Microscopy of terbinafine hydrochloride +sodium benzoate +urea



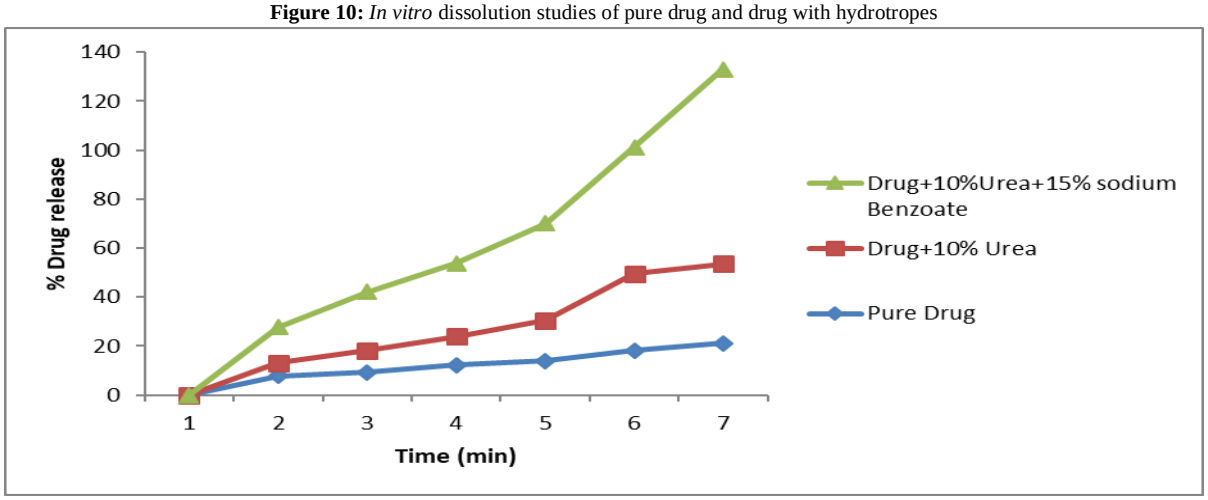
crystalline to amorphous form as it possesses a highly porous nature which results in penetration of water molecules resulting in rapid drug dissolution. The SEM images and particle size distributions and its morphology of the physical mixtures were presented in Figure 8-9. The physical mixture was found to be flaky in shape with a narrow particle size distribution. Upon further magnification, the physical mixture in form of rods with smooth and uniform surfaces

Invitro Dissolution Studies

The dissolution studies of terbinafine hydrochloride and the selected hydrotropes reveals that the dissolution rate was increased for the selected hydrotropes as shown in Figure 10. Similar to solubility studies maximum dissolution rate was found at 10% urea and 10% urea +15% sodium benzoate. Whereas pure terbinafine hydrochloride shows 21.06 of drug release at 120 minutes due to the poor wetting of drug molecule by water. It was observed that about 1.53, 3.77-fold increase was observed in dissolution was determined for 10% urea and 10% urea and 15% sodium benzoate respectively in 120 minutes.

However, in case of drug +urea combinations, drug with urea and sodium benzoate mixture the drug release was observed to be 32.25% and 79.59 % respectively owing to increased wetting of drug molecules.

Figure 10: *In vitro* dissolution studies of pure drug and drug with hydrotropes



CONCLUSION

Poor solubility of drug may result in low bioavailability and thus less therapeutic action. Similarly, terbinafine hydrochloride also has a poor solubility profile and with the oral bioavailability 70%-80%. The FTIR results revealed that are is no interactions between the hydrotropes and the drug. The DSC analysis revealed that there are no interactions between the drug terbinafine hydrochloride and selected hydrotropic blends. The XRD analysis revealed that there is change of form from crystalline to amorphous. Surface morphology of the physical mixture was determined by using SEM indicated a change in crystalline to amorphous form with a highly in porous nature, which led to the rapid penetration of water resulting in rapid and increase in drug dissolution.

ACKNOWLEDGEMENTS

The authors would like to thank the Department of Science and Technology – Fund for Improvement of Science and Technology Infrastructure in Universities and Higher Educational Institutions (DST-FIST), New Delhi for their infrastructure support to our department.

Conflicts of interest:

The authors declare no conflict of interest in this study.

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How to cite this article

Raagul Seenivasan, Sriram Suresh Iyer, Venkatesh Prasath Narayanasamy, Vijayaraghavan Krishnan,Micah Isaac Anand, Dhandapani Nagasamy Venkatesh, 2023. Solubility enhancement of terbinafine hydrochloride by hydrotropic technique. Journal of medical pharmaceutical and allied sciences, V 12 - I 1, Pages - 5596 – 5603. DOI: 10.55522/jmpas.V12I1.4067.