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IMPROVEMENT IN SOLUBILITY OF CEFIXIME TRIHYDRATE BY HYDROTROPIC METHOD

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Keywords:

Cefixime trihydrate, Piperazine, Sodium benzoate, Solubility studies, Solid dispersion, Dissolution rate

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ABSTRACT: Background: Solubility is an important boundary to obtaining the needed drug concentrations in systemic circulation for pharmacological response to be shown. In today's time, poor water solubility is the crucial issue faced with developing new chemical entities. **Objective:** Cefixime trihydrate (CT) is an oral third-generation cephalosporin antibiotic used to treat bacterial diseases. It has an oral bioavailability of 40-50% and belongs to the BCS class-IV. This study aims to boost the solubility of poorly aqueous soluble anti-bacterial drug cefixime trihydrate (CT) by the hydrotropic solubilization technique. **Methods:** Hydrotropy is one of the solubility improvement techniques that enhance the solubility to many folds with hydrotropes. Sodium benzoate (SB) and piperazine (PP) are the hydrotropes that were selected for the preparation of solid dispersion to improve the solubility of cefixime trihydrate. Thus, prepared solid dispersions were evaluated for percentage yield, drug content, saturation solubility and *in-vitro* dissolution studies. **Results:** The result showed increased solubility and *in-vitro* drug release of CT compared to the pure drug. The solubility of cefixime trihydrate was enhanced 6 times by using two hydrotropes. **Conclusion:** In this work, it was concluded that the use of two hydrotropes gave an effective and safe approach to the solubility enhancement of CT. Hence, we can say that hydrotropic techniques can be used to improve the solubility of cefixime trihydrate.

INTRODUCTION: Improving the solubility of the poorly aqueous soluble drug is one of the major current difficulties in the pharmaceutical sciences. The bioavailability of the drug depends on the dissolution rate and solubility, which can affect the drug's therapeutic activity. Various factors affect the solubility of a drug *i.e* temperature, molecular size, pressure, polymorph form, pH of solvent, nature of solute and solvent, porosity, *etc*.

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Multiple techniques are used to improve the dissolution and solubility of poorly soluble drugs: solid dispersion, co-solvents, nanosuspension, salt formation, surfactants, micronization, self-emulsifying, and hydrotropic [1]. Cefixime trihydrate is an oral third-generation cephalosporin antibiotic used to treat gonorrhea and urinary tract infections. CT has low solubility and dissolution profile which is a key parameter for its low bioavailability.

The Chemical structure of cefixime trihydrate is shown in **Fig. 1**. In this work, we focussed on increasing the solubility of CT by hydrotropic solubilization technique [2]. Hydrotropy is well-known process of increasing the dissolution and bioavailability of poorly soluble drugs.

The term hydrotropic was firstly given by Neuberg Carl A. in 1916. Hydrotropes act as hydrophilic carriers and the phenomenon done through this to achieve solubility can call as hydrotropic. It can be understood as 'solubilization' phenomenon whereby the addition of a large amount of the second solute increases the aqueous solubility of another solute''. Some examples of hydrotropes are citric acid, urea, sodium acetate, sodium citrate, sodium benzoate, piperazine, *etc*. Using one hydrotrope at a high concentration may be toxic, while a blend of hydrotropes allows the reduction. The major advantages of this method are that it is highly selective, and there is no need for chemical modifications. But it has some disadvantages also; if we use an excessive number of hydrotropic agents, then toxicity may arise [3, 4].

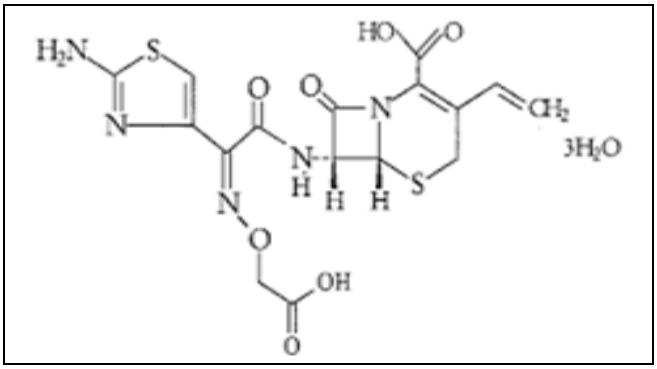

FIG. 1: STRUCTURE OF CEFIXIME TRIHYDRATE

MATERIALS AND METHODS:

1. Materials: Cefixime trihydrate drug sample was supplied as a gift sample by Mankind Pharma, Poanta, Sodium benzoate, piperazine, potassium, dihydrogen phosphate, and disodium hydrogen phosphate were purchased from Central Drug House, Mumbai, India. And all other chemicals were of analytical reagent grades.

1.2 Pre-Forulatory Studies:

1.2.1 Determination of Melting Point: The melting point was determined using a capillary tube with the help of a melting point apparatus. The drug was filled in a capillary tube, welded from one end, and then kept in the melting point apparatus until the drug melted. When the drug completely melted, temperature was noted as the melting point [5, 6].

1.2.2 Study of Solubility of Cefixime Trihydrate in Different Hydrotropes and Selection of Hydrotropes: Sodium benzoate, piperazine, tannic acid, and citric acid were used as a hydrotrope. An approximate solubility determination was employed to select the best hydrotropes for cefixime trihydrate. The solubility of the CT drug was checked in different hydrotropes individually (sodium benzoate, tannic acid, citric acid and piperazine). The individual hydrotropes were taken and mixed with a fixed amount of distilled water in a beaker. Then, an excessive amount of pure drug sample was added to a beaker containing hydrotropic solution. Then place the solution over the magnetic stirrer for 24 hrs. After 24 hrs equilibrium state was achieved, then filters of the solution and filtrate were obtained and diluted the solution if needed and observed the absorbance in the U.V at 287 nm against blank solution and the selection of hydrotropes by using the formula given below [7, 8].

Solubility Enhancement Ratio = Solubility of drug in hydrotropic solution

Solubility of drug in water.

1.3.3 Fourier Transform Infrared Spectroscopy (FTIR): The IR spectroscopy was conducted through the FTIR spectrophotometer. The CT sample was combined with KBr (200-400mg). Then it was compressed in between the discs with the execution of pressure by hydraulic pressure for up to 5 min. after the light was then passed through pellets. The resolution was 1 $cm^{-1,}$ and the range of scanning was 4000-40 cm^{-1} [9].

2.3 Preparation of Cefixime Trihydrate Solid Dispersion using mixed Hydrotropes: The solvent evaporation method was used to formulate the solid dispersion by using hydrotropic agents. In this process, the drug and selected hydrotropes are mixed in the different ratios in a beaker with distilled water. The temperature should be maintained between (80-85 °C). The selected hydrotropes is taken and added to water then slowly drug added to the beaker then put the beaker into a magnetic stirrer, and the magnetic bead is dropped in the beaker, and the temperature should be maintained for the optimum stirring procedure should be continued until the semisolid mass is obtained. Then, the semisolid mass is spread on several watch glasses and placed in an oven, and the temperature should be maintained between (60-65 °C). Triturate with the mortar pestle, and pass it

through sieve no after drying. 100. The prepared solid dispersion (F1-F4) was stored in a desiccator for further evaluation [10, 11].

2.5 Evaluation of Formulated Batches (F1-F4):

2.5.1 Solid-state Characterization: The FTIR, XRD, DSC was conducted for the best-optimized formulation. The best formulation was tested according to the % drug release and the solubility of this formulation. FTIR spectrum was done to specify the drug and identify any impurities in the sample taken for the study. XRD was performed to check the phase behavior of the formed solid. The samples were scanned in the range of 5° (2θ) to 90° (2θ). DSC was done to check the effect of temperature on the formulation [11, 12].

2.5.2 Determination of Percentage Yield: The percentage yield of the prepared CT hydrotropic solid dispersions was calculated to determine the loss of ingredients during the preparation. It is also an important parameter to check the efficiency of the preparation method. It was calculated by using a formula given below [13].

Percentage yield = Practically obtained weight of product / Theoretically weight of formula ×100

2.5.3 Determination of Drug Content: The amount of CT in the solid dispersion sample was determined at 287 nm using a double beam U.V spectrophotometer. Solid dispersion was equivalent to 10mg of cefixime trihydrate and then dissolved in 10 ml methanol. The concentration of cefixime trihydrate in the solution was determined through the formula given below [14, 15].

Drug content = Practical amount / Theoretical amount × 100

2.5.4 Saturation Solubility: To evaluate the increase in the solubility of cefixime trihydrate, the excess amount of solid dispersion of CT (approximately 50mg) was added to 100ml of methanol. Then the beaker should be placed over the magnetic stirrer for 24hrs after 24 hrs. The samples were then filtered, suitably diluted and determined at 287 using a double beam spectrophotometer [15, 16].

2.5.5 *In-vitro* Drug Release: The *in-vitro* drug release was done through the "USP Paddle Type II apparatus". Dissolution flask containing 900ml of 0.1 HCL and the temperature should be maintained in between 37℃±0.5℃. With rotation at 50 rpm 5 ml of the dispersion was taken and replaced with the 5 ml of same quantity of fresh dissolution medium. Each sample was filtered and the amount of CT dissolved was analyzed spectro-photometrically at 287 nm using 0.1 HCL as a blank solution 17.

RESULTS AND DISCUSSION

3.1 Pre-formulation Analysis of Cefixime Trihydrate:

3.1.1 Melting Point: The melting point of cefixime was found to be 220℃.

3.1.2 Cefixime Trihydrate Solubility in Selected Hydrotropes: The solubility of CT was observed to be 0.068mg/ml in distilled water. The Solubility and solubility enhancement ratio of Cefixime trihydrate is given in **Table 1**. So, according to the results of the solubility enhancement ratio, the solubility of cefixime trihydrate was observed in the following order: Piperazine > sodium benzoate> tannic acid > citric acid. The two hydrotropes were selected (PP and SB) for further research works; these two hydrotropes have the highest solubility among the others.

TABLE 1: SOLUBILITY AND SOLUBILITY ENHANCEMENT RATIO

S. no.	Hydrotropes 20%(w/v)	Solubility in(mg/ml)	Solubility enhancement ratio(mg/ml)
1.	Sodium benzoate	1.09	16
2.	Tannic acid	0.36	5
3.	Citric acid	0.198	3
4.	Piperazine	3.9	57

3.1.3 Fourier Transform Infrared (FTIR) Spectroscopy: FTIR studies were done to identify the drug and check its purity. The characteristic peaks of CT as shown in **Fig. 2.** The various bands were obtained, showing the presence of the functional group. The -OH group stretching vibration were observed at 3680-57, 3293-11cm^{-1}, -NH stretching at 3534-74cm^{-1}, C-H stretching at 2919-25cm^{-1}, C-O stretching at 1669-32cm^{-1} peak.

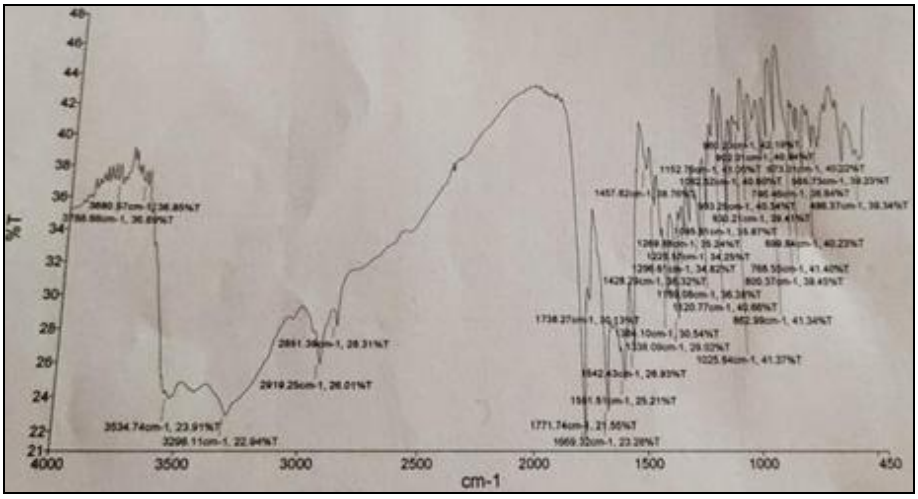

FIG. 2: FTIR SPECTRUM OF CEFIXIME TRIHYDRATE

3.2 CT Hydrotropic Solid Dispersion: Different formulations of cefixime trihydrate hydrotropic solid dispersion (F1, F2, F3, and F4) were prepared in different ratios using the hydrotropic blend of sodium benzoate and piperazine. Solid dispersion was prepared by the method of solvent evaporation method. The selected dose of CT was 100mg, and the value hydrotropes were selected according to their ratio, as shown in **Table 2**. Different formulations with different ratios are shown in **Fig. 3.**

TABLE 2: FORMULATION OF CEFIXIME TRIHYDRATE SOLID DISPERSION WITH HYDROTROPIC BLEND SOLUTION

Formulation	Solid dispersion ratios (Drug: hydrotropic blend)	Hydrotropic blend (Sodium benzoate: Piperazine)
F1	1:2:1	2:1
F2	1:1:2	1:2
F3	1:4:2	4:2
F4	1:2:4	2:4

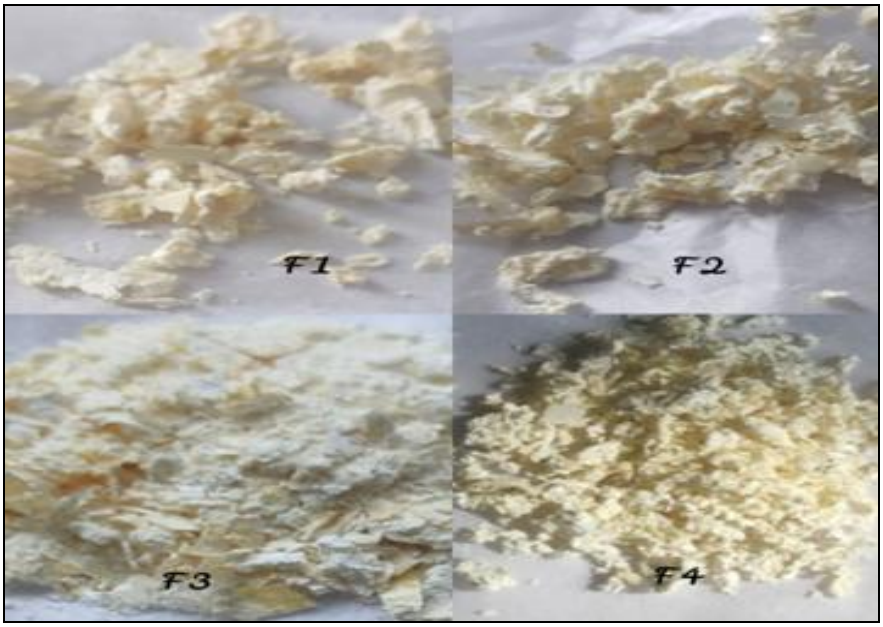

FIG. 3: DIFFERENT FORMULATION IMAGES OF PREPARED SOLID DISPERSION

3.3 Evaluation of Formulated Batches:

3.3.1 Fourier Transform Infrared (FTIR) Spectroscopy: FTIR spectroscopy's infrared spectra of CT solid dispersion were studied using KBR disc.

The FTIR spectrum of CT solid dispersion is shown in the given **Fig. 4**. The main peaks were similar and well- identified in the performed FTIR spectra of F4 formulation.

It was disclosed that there were no differences in positions of absorption bands; only slight changes are observed, hence confirming the absence of interactions in the middle of cefixime trihydrate and two hydrotropes.

The physical changes arise because of a change in the drug's crystalline form, which was answerable for the enhancement of solubility of cefixime trihydrate.

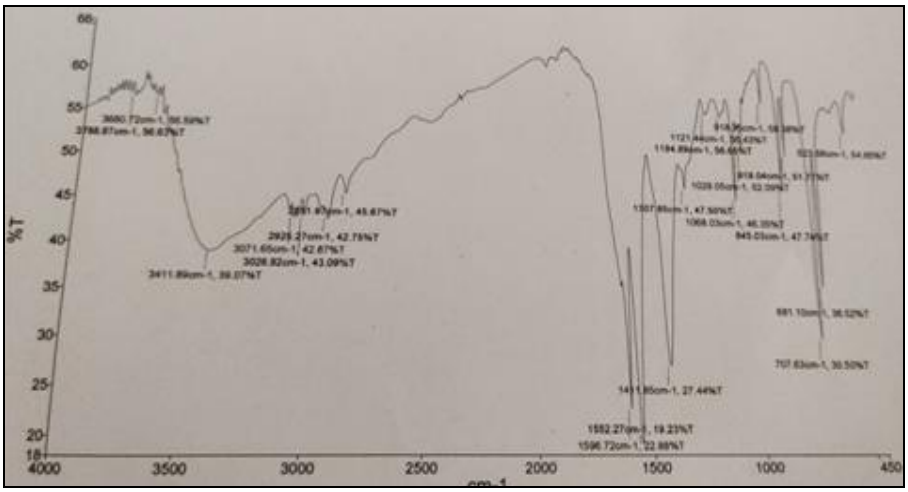

FIG. 4: FTIR SPECTRA OF A MIXTURE CEFIXIME TRIHYDRATE, SODIUM BENZOATE AND PIPERAZINE

3.3.2 Differential Scanning Calorimetry: The DSC of formed solid dispersion of F4 formulation is shown in **Fig. 5**.

Generally, the DSC thermograms help in predicting the intermolecular interaction between the compound through a shift in the sharpness of peak and intensity of thermograms.

DSC shows a little sharp endothermic fusion peak near 218 °C, which corresponds to the melting point of cefixime trihydrate.

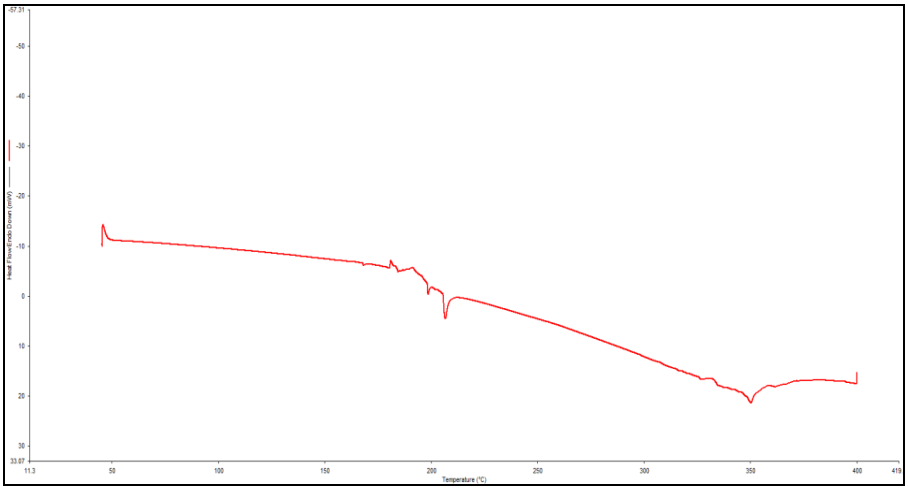

FIG. 5: DSC OF MIXTURE OF CEFIXIME TRIHYDRATE, SODIUM BENZOATE, AND PIPERAZINE

3.3.3 X-ray Diffraction: The diffraction pattern of solid dispersion of the F4 formulation is shown in **Fig. 6.**

The F4 formulation diffractogram showed a decrease in the sharp peak, indicating the drug's conversion to its amorphous form. XRD of optimized F4 formulation showed broadening of peaks indicating the phase convert from crystalline to amorphous form.

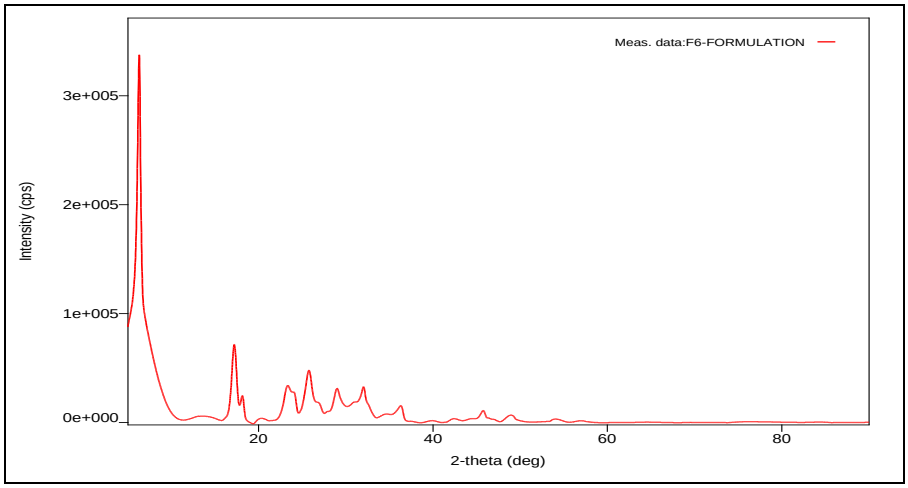

FIG. 6: XRD OF MIXTURE OF CEFIXIME TRIHYDRATE, SODIUM BENZOATE AND PIPERAZINE

3.3.4 Percentage Yield and Drug Content: The formulations' percentage yield and drug content were determined through the mentioned formula in the procedure, and the results are presented in **Table 3.**

TABLE 3 PERCENTAGE YIELD AND DRUG CONTENT OF VARIOUS FORMULATIONS

Formulation	% Yield	Drug content
F1	90.75±0.12	88.50±0.05
F2	91.57±0.01	90.24±0.02
F3	95.62±0.01	93.32±0.10
F4	96.85±0.02	95.10±0.2

3.3.5 Saturation Solubility of Various Formulations: The saturation solubility of various prepared cefixime trihydrate solid dispersions using hydrotropes.

The result of saturation solubility studies and solubility enhancement is given in **Table 4**. All solid dispersion shows higher saturation solubility as compared with pure drug solubility.

Pure drug (CT) showed 0.068mg/ml of saturation solubility. Solubility enhancement was calculated by using the formula mentioned previously.

The graph of saturation solubility of various formulations is shown in **Fig. 7.**

TABLE 4: SATURATION SOLUBILITY AND SOLUBILITY ENHANCEMENT OF DIFFERENT FORMULATIONS

Formulations	Saturation solubility (mg/ml)	Solubility enhancement
F1	0.232	3.4
F2	0.280	4.11
F3	0.425	6.64
F4	0.464	6.8

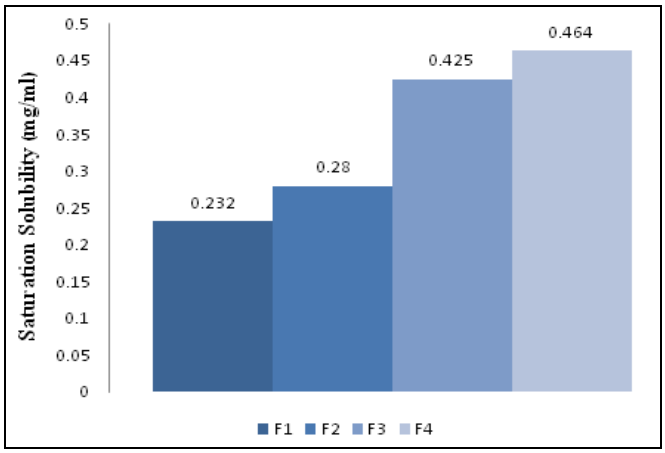

FIG. 7: SOLUBILITY STUDIES OF VARIOUS FORMULATIONS

3.3.6 *In-vitro* Drug Release: Cefixime trihydrate was having a low solubility and absorption rate. Solid dispersion was the technique used to enhance the drug solubility and thus ultimately increase the dissolution characteristics.

The *in-vitro* drug release was done through "USP Paddle Type II apparatus". Dissolution flask containing 900ml of 0.1 HCl and the temperature should be maintained between 37°C ± 0.5°C with rotation at 50 rpm 5 ml of the dispersion was taken and replaced with the 5 ml of the same quantity of fresh dissolution medium.

Each sample was filtered, and the amount of CT dissolved was analyzed spectrophotometrically at 287 nm using 0.1 HCl as a blank solution.

The *in-vitro* dissolution results of cefixime and solid dispersion batch F4 are given in **Fig. 8**. The drug release results are given in **Table 5.**

TABLE 5: DRUG RELEASE OF VARIOUS FORMULATIONS

Time (min)	Pure drug	F1	F2	F3	F4
5	2.42±0.251	25.53±0.45	28.08±0.05	39.56±0.23	41.87±0.80
10	6.08±0.520	36.42±0.32	40.10±0.87	51.43±0.49	54.04±0.24
15	10.20±0.653	41.20±0.08	45.32±0.34	57.23±0.12	60.34±0.51
30	16.45±0.209	50.27±0.76	53.74±0.64	62.54±0.38	66.70±0.67
45	18.28±0.12	61.12±0.91	60.61±0.04	70.82±0.09	73.20±0.37
60	21.54±0.76	69.15±0.21	76.12±0.44	85.04±0.19	90.42±0.41

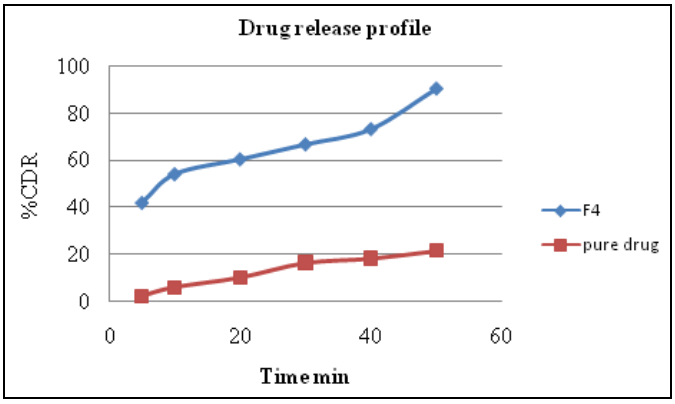

FIG. 8: DISSOLUTION PROFILE OF PURE DRUG AND F4 (SOLID DISPERSION HYDROTROPIC SOLUTION)

Cefixime trihydrate was chosen as a drug for its solubility enhancement. It is a BCS class IV drug with low solubility and low permeability. Thehydrotropes were used to enhance the solubility of the hydrophobic drug. The solubility of Cefixime trihydrate determines in different hydrotropes. Sodium benzoate and piperazine were selected amongst all. Sodium benzoate (16 mg/ml) and piperazine (57mg/ml) show the drug's highest solubility. So, these two hydrotropes were used for further research work. Solid dispersion was prepared in a different ratio using a blend of selected hydrotropes and F4 formulation, which produces the maximum solubility and maximum drug release, among the others. Then F4 formulation was selected for further evaluation of drugs such as, FTIR, DSC and XRD.

CONCLUSION: It was found that Cefixime trihydrate solubility was enhanced 6 times by using these hydrotropes. Two hydrotropes were selected amongst others which show the highest solubility in the drug. Through this research work, we concluded that hydrotropes can be a safe, simple, accurate and effective measure to enhance the dissolution rate and the bioavailability of drugs without any chemical modification. Solid dispersions in different ratios were prepared by the solvent evaporation method, which increases the solubility of the drug. F4 was chosen for further evaluation, showing the maximum solubility enhancement and drug release amongst other formulations. The solubility and dissolution studies have shown the possibility of improving the solubility of cefixime trihydrate by the hydrotropic method.

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CONFLICTS OF INTEREST: The authors declare that there is not any conflict of interest.

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