

Solubility enhancement of cefixime trihydrate by solid dispersions using hydrotropic solubilization technique and their characterization

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The aqueous solubility of cefixime trihydrate (a water insoluble drug) using different hydrotropic agents was determined and solid dispersions of cefixime trihydrate were prepared by hydrotropic solubilization technique. The drugs content were determined. The aqueous solubility of v was increased many fold in presence of sodium acetate trihydrate as hydrotropic agent. This hydrotropic agent was used to prepare solid dispersion of cefixime trihydrate. Cefixime trihydrate and sodium acetate trihydrate were accurately weighed and taken in a 200 mL beaker. Distilled water 10-15 mL was taken to dissolve hydrotropic agent using heat (48-50 °C). The drug was then added to it and magnetically stirred till whole mass get viscous. The solid dispersions of cefixime trihydrate were characterized by XRD, DSC and IR studies. DSC thermogram, XRD and Infra-Red spectra were studied. Solid dispersions, thus prepared, showed faster release of the drug as compared to pure drug and physical mixture.

Keywords: Cefixime trihydrate. Hydrotropic Solubilization. sodium acetate trihydrate. Hydrotropic solid dispersion

INTRODUCTION

Hydrotrophy is a phenomenon of solubilization, whereby addition of a large amount of secondary solute results in an increase in the aqueous solubility of primary solute in water. This method has been utilized in solubilizing a number of water insoluble drugs. The compounds which have been utilized as solubilizing agents reported in literature are sodium benzoate, urea, nicotinamide, sodium citrate and sodium acetate. Solid dispersion techniques (Saleh, Khordagui, 1985; Rao *et al.*, 2005; Saha *et al.*, 2002; Maheshwari, Indurkhya, 2010; Madhusudhan *et al.*, 2002; Yan *et al.*, 2011; Prasanna, Koppula, 2013) have been used to increase the dissolution, and thereby, the rate of absorption and/

or total bioavailability of poorly water-soluble drugs. The common methods of making solid dispersions are solvent evaporation, fusion, and fusion-solvent methods. The main advantage of hydrotropic solid dispersion (HSD) technique (Kim *et al.*, 2010) is that it completely prohibits the use of organic solvent, thus making the procedure user friendly. The method involves the removal of excess water, if necessary, by evaporation at low temperature.

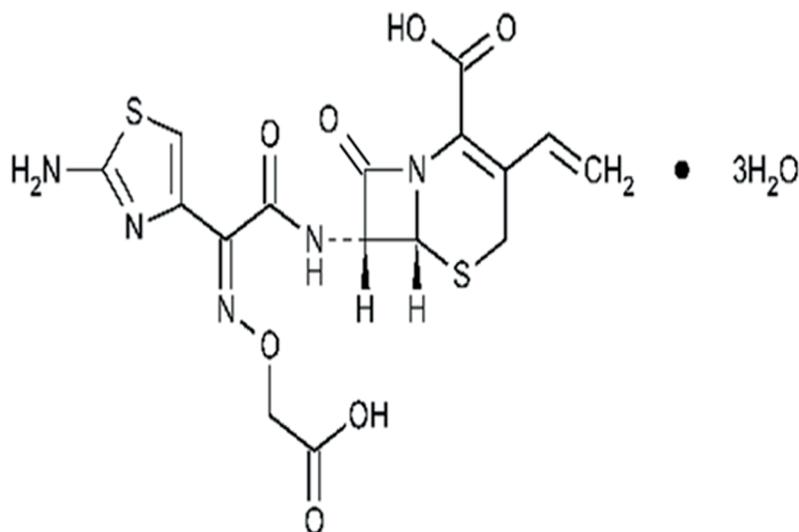
Cefixime trihydrate (Figure 1) is a third generation cephalosporin antibiotic. It works by preventing the synthesis of cell wall which ultimately kills the bacteria. It is used against infections including gonorrhoea, pharyngitis, otitis media, lower respiratory-tract infections such as urinary-tract infections and bronchitis. The absolute bioavailability, as determined of cefixime trihydrate, was found to be 200 mg capsules 48%, 400 mg capsules 40% and an oral solution 52% (Brogden, Richards, 1989). The drug is freely soluble in methanol and dimethyl sulfoxide

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and also to some extent in propylene glycol and glycerin. It belongs to class IV of Biopharmaceutics classification system (BCS) meaning low solubility and low permeability (Dahan, Miller, Amidon, 2009).

The literature reports the estimation of cefixime trihydrate by UV-Visible Spectrophotometric method

(Gadhiya, Bagada, 2013; Shah, Pradhan, Dey, 2013; Selvakumar, Ravichandran, Matsyagiri, 2016) using methanol and water methanol mixture. In the present case the method of Gadhiya *et al.*, (2013) using methanol was used.



Molecular weight 507.50 g/mol

Molecular formula $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$

FIGURE 1 - Chemical structure of cefixime trihydrate.

MATERIAL AND METHODS

Material

Cefixime trihydrate was procured from M/s Yarrow Chem, Mumbai, India. sodium acetate trihydrate (Spectrochem Pvt. Ltd, Mumbai, India), Nicotinamide, Sodium ascorbate, Sodium gluconate, sodium citrate dihydrate (Qualikems Fine Chem Pvt. Ltd, Vadodara, India) and Methanol (Merk Specialities Private Limited, Mumbai, India) were used.

Determination of solubility

Aqueous solubility of cefixime trihydrate (CT) was first determined (Table I). In this process 20 mL of distilled water was taken. Accurately weighted cefixime trihydrate was taken in a container. Measured volume of

water (10 mL) was taken in a small beaker (100 mL) and stirred magnetically. The drug was added in portions till the no more solubility of the drug was there. The stirring was continued for 12 h. The whole assembly was left undisturbed with proper cover for next 24 h. The solution was filtered through Whatman grade 41 in a 100 mL volumetric flask and the volume made up with methanol. Further dilution was accordingly made to achieve concentration (5-25 $\mu\text{g/mL}$) using methanol and the same was analyzed using UV spectrophotometer (UV-1800, Shimadzu Limited, Japan) at 289 nm using regression equation $y = 0.05x + 0.016$.

Enhancement solubility using hydrotropic agents

In the present case sodium gluconate, sodium citrate, sodium acetate trihydrate, citric acid, nicotinamide and dextrose were used as hydrotropic agents. The solution of

these hydrotropic agents was made (10% and 20% w/v) in distilled water. To determine the solubility of cefixime trihydrate in presence of these different hydrotropic agents, the process adopted was same as mentioned above under the heading determination of solubility.

However, in place of distilled water, 10 mL of respective solution of the hydrotropic agents was taken (Table I).

Enhancement ratio in solubility (Table I) was determined using following formula:

$$\text{Enhancement ratio} = \frac{\text{Solubility of drug in hydrotropic solution}}{\text{Solubility of drug in distilled water}}$$

TABLE I - Equilibrium solubility of cefixime trihydrate in different media

Solvent	pH of solvent system	Solubility* (g/100 mL)	Solubility enhancement ratio
Distilled water	7.01	0.0672±0.014	-
10% w/v sodium gluconate solution	5.82	1.7201±0.018	25.59
20% w/v sodium gluconate solution	5.91	5.2242±0.142	77.74
10% w/v tri-sodium citrate solution	8.81	12.2403±0.098	182.14
20% w/v tri-sodium citrate solution	8.71	20.4617±0.124	304.48
10% sodium acetate trihydrate	4.73	42.4012±0.287	630.97
20% sodium acetate trihydrate	4.32	33.3201±0.254	495.83
10% w/v citric acid	2.34	0.1691±0.014	2.51
20% w/v citric acid	2.12	0.1982±0.017	2.94
10% w/v nicotinamide	7.22	5.1601±0.087	76.78
20% w/v nicotinamide	6.71	9.6204±0.098	143.16
10% dextrose	8.43	0.1304±0.012	1.94
20% dextrose	8.51	0.1712±0.015	2.54

*Average of three determinations

Selection of ratios of drug and carrier in Physical Mixture and HSD

Out of all the hydrotropic agents, sodium acetate trihydrate was found to be the best in increasing

solubility of the drug. Thus it was selected for further studies. In this context different ratio of the drug and hydrotropic agent was taken as 1: 2, 1: 4, and 1: 6.

Preparation of hydrotropic solid dispersions of cefixime trihydrate

Accurately weighed cefixime trihydrate (3.3 g) was taken for the preparation of the solid dispersion (1:2). Sodium acetate trihydrate (6.7 g) was accurately weighed and taken in a 200 mL beaker. Distilled water 10-15 mL was added to dissolve hydrotropic agent. Solubilization was effected by heating (48-50 °C). The drug was then added to it and magnetically stirred. The heating was continued for half an hour. The mass was transferred to watch glass and allowed to dry in an oven. The dried mass was scrapped off and powdered in a pestle mortar and shifted through sieve no. 100. The HSD powder was stored in an air-tight glass container. The same way other HSDs were prepared in 1: 4 and 1: 6 ratio of drug: hydrotropic agent.

Physical mixture (PM) of cefixime trihydrate (CT) and sodium acetate trihydrate (SAT)

For the sake of comparison, physical mixture was prepared by trituration in portion (Allen, Povovich, Ansel, 2008) cefixime trihydrate (1.4 g) and sodium acetate trihydrate (8.6 g) and mixed in glass pestle and mortar. The powder was then passed through sieve number 100. The physical mixture was stored in an air-tight glass container.

Determination of drug content in cefixime trihydrate formulations (PM & HSDs)

HSDs/PM containing equivalent to 10 mg of cefixime trihydrate was accurately weighed and transferred to 100 mL beaker and dissolved in a small volume of methanol and transferred to volumetric flask (100 mL) after filtering. The material was transferred quantitatively to the volumetric flask. The solution was further diluted to get a concentration of 10 µg/mL. The absorbance was measured at 289 nm against reagent blank. The results were determined in triplicate (Table II).

TABLE II - Drug contents of physical mixtures and hydrotropic solid dispersions (n = 3)

Drug: Hydrotropic blend	Percent drug content (mean ± S.D.)	
	PM	HSD
CTSAT 1 : 2	-	33.471±0.157
CTSAT 1 : 4	-	20.254±0.108
CTSAT 1 : 6	14.243±0.097	14.312±0.178

PM - physical mixture; HSD - hydrotropic solid dispersion; SD – standard deviation; CTSAT – cefixime trihydrate sodium acetate trihydrate

Powder X-ray diffraction studies of formulated HSD and PM

The x-ray diffractions (XRD) of the powders of CT, PM and solid dispersion were studied on X'pert Pro (PANalytical, Netherland) using Ni-filter and CuK α 1 radiation with Spinner PW3064. A voltage of 45 kV and 40 mA current was applied with a scintillation counter. The samples were scanned by the XRD instrument a range of 5° to 80°.

Differential scanning calorimetry (DSC):

The DSC studies of CT, PM and solid dispersion were performed on DSC Q 20 (TA Instruments USA). The samples (4 mg) were weight accurately and sealed in aluminium pan. The sealed pan of both the samples and reference were placed in a heating cell and heated to 25 °C-300 °C at a rate of 10 °C/min with purging of nitrogen.

Fourier transform infrared spectroscopy (FTIR):

The FTIR studies of CT, PM and solid dispersion were carried out using FTIR Spectrophotometer (Schimadzu, IRAffinity-1, Japan). All samples were scanned in the region of 4000 to 400 cm⁻¹ wavenumber.

Dissolution rate studies

Dissolution rates of CT, PM (1: 6 ratios) and HSD containing drug: hydrotropic blend of 1: 2, 1:4 and 1: 6

ratios were studied using dissolution rate test apparatus (USP XXIV Type II). To perform dissolution rate studies, the CT, PM and HSD equivalent to 100 mg drug were weighted accurately. The dissolution studies were performed by using phosphate buffer solution (pH 7.2) as dissolution medium at 50 rpm and temperature of 37 ± 0.5 °C. Samples (5 mL) of dissolution medium were withdrawn at predetermined time intervals at the same time 5 mL of fresh buffer was added after each withdrawal. The samples were analyzed after suitable dilution with methanol at 289 nm wavelength. The dissolution studies were taken in triplicate and results were calculated as an average.

The percentage dissolution efficiency (%DE) of pure drug, PM and HSD is defined as the ratio of area under the dissolution curve up to a definite time (t) to the area of the rectangle for 100% dissolution in that time. It is calculated by the following equation (Khan, 1975):

$$DE_T = \frac{\int_0^T y_t - dt}{y_{100} \cdot T},$$

where y_t is the percentage of drug dissolved at any time t, y_{100} denotes 100% dissolution, and the integral represents the area under dissolution curve between time 0 and T in minutes. The time T in this study was 90 min.

RESULT AND DISCUSSION

The results of the solubility data showed that the solubility of cefixime trihydrate gets increased synergistically by hydrotropy. Its solubility increased more than 630 times in presence of hydrotropic agent (Sodium acetate trihydrate).

XRD diffraction spectra (Figure 2) were recorded for cefixime trihydrate (CT), physical mixture of CT with sodium acetate trihydrate and solid dispersion of CT with hydrotropic agent in ratio of 1:6. XRD spectra of cefixime trihydrate showed five distinct peaks at 2θ of 5.94, 7.59, 9.06, 15.16 and 19.78. The XRD spectra of physical mixture and solid dispersion of CT with sodium acetate trihydrate depicted characteristic peaks at 2θ of 8.96 and 29.74 with 100% of relative intensity, respectively. The disappearance of the peak at 9.0 in solid dispersion indicates the transformation of cefixime trihydrate to anhydrous form as reported by Kitamura *et al.*, (1990). Thus, the result exhibited that cefixime

trihydrate did not undergo transformation to amorphous form, but was present in crystalline form.

DSC thermogram (Figure 3) of cefixime trihydrate shows an endothermic peak at 107.8 °C suggesting the removal of water from the cefixime trihydrate. DSC thermogram also exhibited exothermic decomposition of the dehydrated solid at 187.3 °C. The presence of exothermic peak at 257.9 °C suggested the melting of cefixime with decomposition. These results are found to be well correlated with previous studies indicating the melting of cefixime trihydrate decomposition over a range of 218-255 °C (Okeke, Srinivasan, Brittain, 2008). DSC thermogram of solid dispersion of cefixime trihydrate with sodium acetate trihydrate showed a sharp endothermic peak at 65.3 °C, which can be correlated to the melting of sodium acetate trihydrate (Jin X *et al.*, 2014). The DSC thermogram of solid dispersion showed an exothermic peak at 186.7 °C and 257 °C which corresponded to the cefixime trihydrate. The absence of endothermic peaks at 107 °C suggests the anhydrous nature of cefixime present in solid dispersion with sodium acetate trihydrate, which was seen in XRD studies.

The FTIR spectra (Figure 4) of CT, PM and solid dispersion of CT were taken. Pure cefixime trihydrate showed- NH stretching of the hydrogen -bonded amide group, primary amine (NH_2) peak at 3392.4 cm^{-1} , CH_3 (C-H stretch) at 2974.2 cm^{-1} , β -lactam peak (C=O stretch) at 1772.5 cm^{-1} , amide (C=O stretch) at 1637.5 cm^{-1} and 1591.2 cm^{-1} , oxime (C-N stretch) 1533.4 cm^{-1} , N-O stretch 1375.2 cm^{-1} and 1338.6 cm^{-1} . The IR spectrum of the PM and HSD depicted the superimposition pattern of CT and SAT by little shifting of the peaks and decreased peak intensity. The FTIR spectrum of HSD showed a weak vibration peak at 3419.7 cm^{-1} which has been observed as an O-H stretching. The peak at 1772.5 cm^{-1} in pure drug, which is due to β -lactam ring C=O stretching, got shifted to 1747 cm^{-1} in the HSD whereas the peak at 1734.2 cm^{-1} due to carbamate C=O stretching mode in pure drug was missing in HSD indicating the bond between the drug and the hydrotropic agent.

The dissolution profiles of CT, PM and solid dispersions in phosphate buffer (pH 7.2) are shown in Figure 5 and Table III. The cumulative percentage drug dissolved in 15 min was found to be 11.58% and 26.847% for pure drug and PM, respectively. The result suggested that presence of hydrotropic agent in physical mixture lead to improve the wetting of CT and hence, increase the dissolution rate. The dissolution rate of CT was significantly enhanced by HSDs. Cumulative

percentage drug dissolved in 5 min was found to be 71.54%, 92.45% and 100% for HSDs in ratio of 1:2, 1:4 and 1:6, respectively. The result also exhibited significant

enhancement of dissolution rate upon increasing the ratio of hydrotropic agent from 1:2 to 1:6.

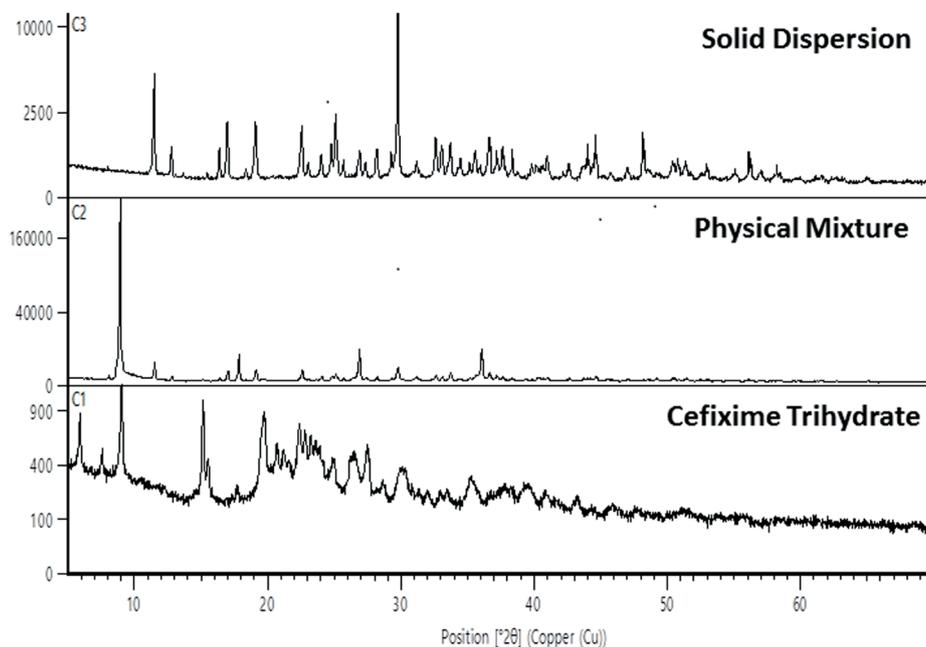


FIGURE 2 - C1. X-ray diffraction spectra of cefixime trihydrate. C2. X-ray diffraction spectra of physical mixture. C3. X-ray diffraction spectra of solid dispersion.

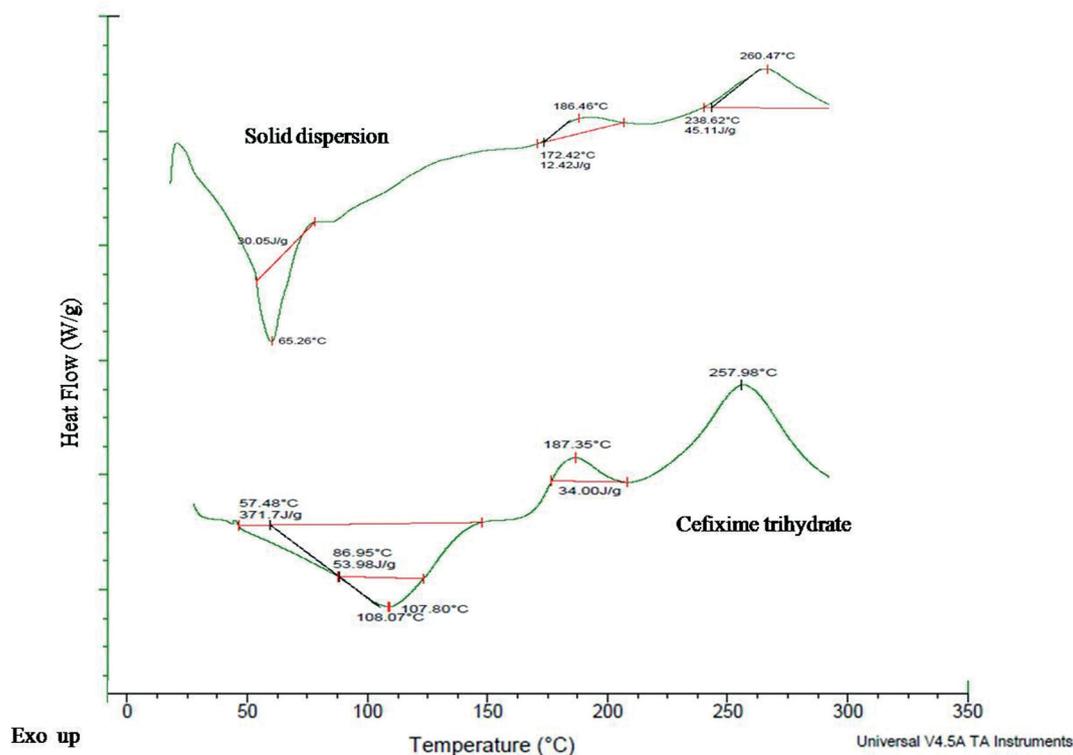


FIGURE 3 - DSC curve of cefixime trihydrate and DSC curve of solid dispersion.

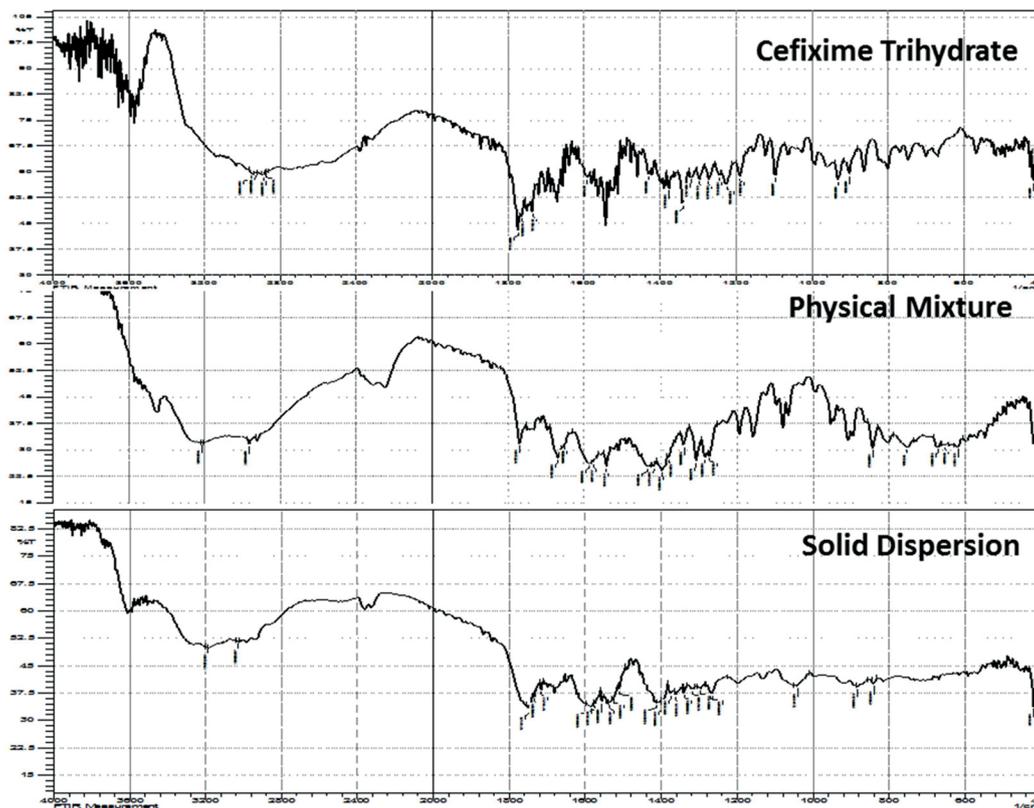


FIGURE 4 - IR spectra of cefixime trihydrate, PM, Solid dispersion.

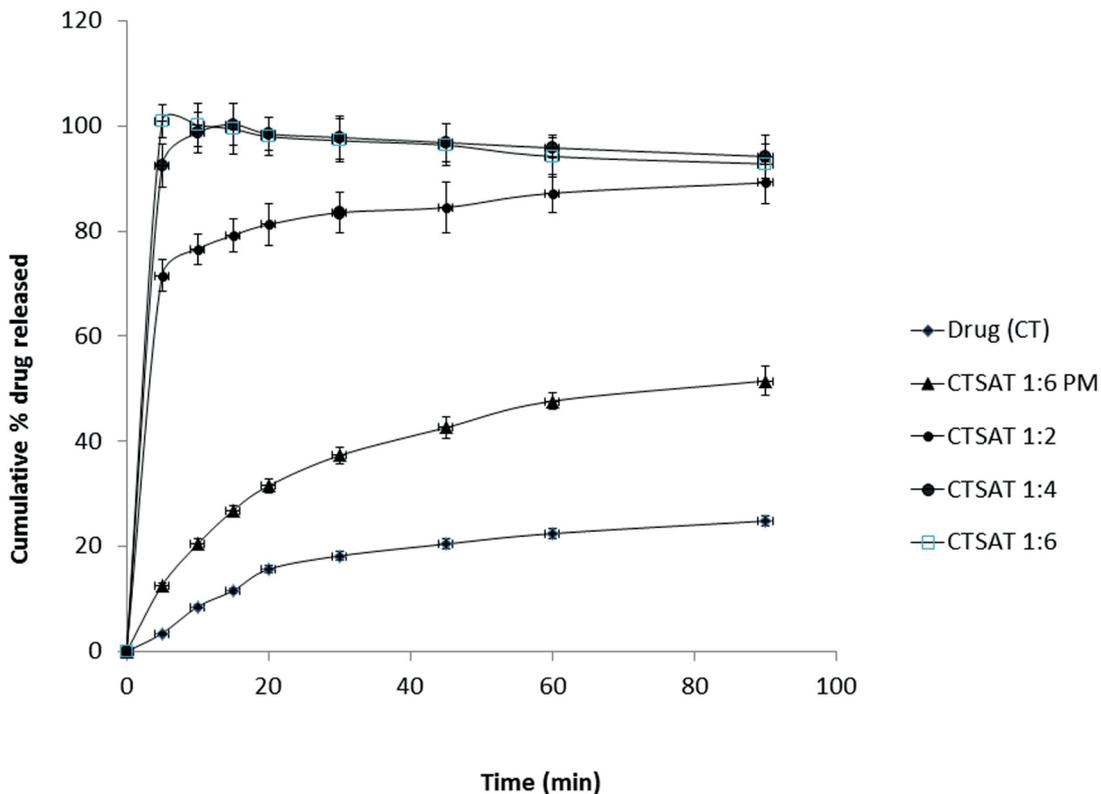


FIGURE 5 - Dissolution profiles of pure drug CT, CTSAT 1:6 PM, CTSAT 1:2, 1:4 and 1:6 HSD in Phosphate buffer pH 7.2.

TABLE III - Dissolution profile of pure drug, CTSAT 1:6 PM, CTSAT 1:2, 1:4 and 1:6 HSD in Phosphate buffer pH 7.2 (n=3)

Cumulative percentage drug dissolved (Mean \pm SD)					
Time (min)	Drug (CT)	CTSAT 1:6 PM	CTSAT 1:2	CTSAT 1:4	CTSAT 1:6
0	0	0	0	0	0
5	3.452 \pm 0.251	12.583 \pm 0.508	71.542 \pm 3.087	92.451 \pm 4.061	100.903 \pm 3.078
10	8.526 \pm 0.412	20.421 \pm 1.056	76.528 \pm 2.871	98.652 \pm 3.874	100.102 \pm 4.098
15	11.586 \pm 0.578	26.847 \pm 0.987	79.207 \pm 3.078	100.274 \pm 4.034	99.418 \pm 4.782
20	15.657 \pm 0.781	31.524 \pm 1.247	81.243 \pm 4.085	98.523 \pm 3.089	98.012 \pm 3.647
30	18.214 \pm 0.807	37.294 \pm 1.471	83.519 \pm 3.846	97.806 \pm 4.064	97.208 \pm 4.065
45	20.476 \pm 1.021	42.628 \pm 2.047	84.514 \pm 4.907	96.842 \pm 3.678	96.351 \pm 3.981
60	22.457 \pm 0.972	47.649 \pm 1.547	87.205 \pm 3.643	95.841 \pm 2.045	94.213 \pm 4.025
90	24.851 \pm 0.986	51.498 \pm 2.805	89.214 \pm 4.059	94.205 \pm 4.067	92.802 \pm 3.754

CT- cefixime trihydrate; PM - physical mixture; HSD - hydrotropic solid dispersion; SD – standard deviation; CTSAT – cefixime trihydrate sodium acetate trihydrate

The improved dissolution rate of CT from HSDs could be attributed to the transformation of one crystalline form to another form, in addition to increasing wetting of CT in presence of hydrotropic agent and contact between the drug and the carrier. The rapid dissolution of CT from solid dispersions may be attributed to a decrease in the crystallinity of drug and its molecular and colloidal dispersion in the hydrophilic carrier matrix.

The percentage dissolution efficiency (%DE90) at 90 min was calculated to compare the relative performance of pure drug, PM and solid dispersion. It appears as a better parameter than drug percentage released for comparison because it includes both rate and extent of release. The %DE90 of pure drug, PM and solid dispersion 1:2, 1:4 and 1:6 was found to be 18.13%, 38.73%, 81.75, 93.74 and 93.44 respectively. The solid dispersion showed enhancement in dissolution rate from pure drug as %DE90 increases from 18.13% to 93.74%.

CONCLUSION

Hydrotropic solid dispersion of cefixime trihydrate was prepared with SAT using solvent evaporation method. Solid dispersion of cefixime trihydrate (1:4 and 1:6 ratio) showed fast release of drug as compared to pure drug and physical mixture. Thus, a better absorption and a quick onset of action is expected when these HSD would be administered in formulation orally. The proposed method would be safe, convenient and economical.

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