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Research Article

Enhancement of *In-Vitro* Dissolution Efficiency of Cefixime Trihydrate Using Natural Polymer by Solid Dispersion Technique.

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ABSTRACT
Solid dispersions (SD) are one of the most effective and promising technique used to improve the solubility of poorly water soluble drugs. This technology is mainly applied to improve the solubility of Class II and Class IV drugs. Cefixime is an oral third generation cephalosporin antibiotic most widely used in the treatment of various infections, which has oral bioavailability of 40-50% and it belongs to the BCS Class IV. Many attempts were made in the past to increase its solubility by preparing its solid dispersions. However, very few literature reports are available where in natural polymers are used for preparation of solid dispersions. In the present work, an attempt was made to increase the solubility of Cefixime by preparing its solid dispersions using natural polymer i.e. guar gum. Solvent evaporation method was used for preparing Solid dispersions with different drug- polymer ratio. The prepared solid dispersions were evaluated for preformulation studies, percentage yield, in-vitro dissolution studies, dissolution efficiency, FTIR, DSC etc. The result obtained from above studies showed that the solubility and dissolution profile of Cefixime solid dispersions were improved as compared to pure drug. Therefore it can be concluded that Solid dispersion technology can be used to improve the solubility of Cefixime.

KEYWORDS
Solid Dispersions, Cefixime, solvent evaporation method, in-vitro dissolution study.

1. INTRODUCTION

The therapeutic efficacy of a drug product intended to be administered by the oral route mainly depends on its absorption by the gastrointestinal tract. However, for a drug substance to be absorbed, it needs to be solubilised. Solubility is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and low permeability. By improving the dissolution profile of these drugs, it is possible to enhance their bioavailability and reduce side effects. Solid dispersions are one of the most successful strategies to improve dissolution rate of poorly soluble drugs. SDs can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties [1]. Solid dispersion is a unique approach which was introduced by Sekiguchi and Obi. In this method, the drug is dispersed in extremely fine state in an inert water soluble carrier in solid state. Number of insoluble drugs has shown to improve their dissolution character when converted to solid dispersion. Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers [2]. A number of freely water soluble materials such as citric acid, succinic acid, bile acids, sterols and related compounds and polymers like polyvinyl pyrrolidone and poly ethylene glycols are used as carrier for solid dispersions. By this approach the dissolution rate and bioavaibility of poorly soluble drugs can be increased [3]. The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drug is increasing.Various hydrophilic carriers such as natural polymers viz. guar gum has been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs [4].

Cefixime is an oral third generation cephalosporin antibiotic which is used in the treatment of gonorrhea, tonsillitis and pharyngitis [5,6]. Cefixime is employed in the treatment of a variety of respiratory tract infections and otitis media [7]. However, the low aqueous solubility and poor dissolution of this drug in gastric fluid affects its rate of absorption, resulting in a low and variable oral bioavailability. Hence, the present study was aimed to increase the solubility and bioavailability of Cefixime using natural polymer i.e. gaur gum. Cefixime solid dispersions were prepared by different techniques viz. physical mixture, solvent evaporation method and kneading method.

2. MATERIALS AND METHODS

Cefixime trihydrate was obtained as generous gift from FDC Limited, Mumbai. All other chemical reagents were of analytical grade.

2.1. Preformulation Studies

The Preformulation studies were carried out for the drug and excipients.

2.2. Preparation of Solid Dispersion

Cefixime trihydrate was mixed with guar gum polymer in ratio of 1:1, 1:2 and 1:3, were later dissolved in an adequate amount of dichloromethane. To obtain solid dispersion of Cefixime Trihydrate: Guar Gum) it was dried in oven for 50 min at 60 degree Celsius. The resultant SDs

was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a sieve number # 60 before packing in an airtight container. These solid dispersions were evaluated for dissolution studies as per the following procedure [8].

2.3. Evaluation of prepared solid dispersions

2.3.1. Percentage yield

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation [9].

$$PY = \frac{\text{PractIcal mass(SD)}}{\text{Theoritical mass (drug+carri)}} \times 100 \quad \text{---Equation 1.}$$

2.3.2. In- vitro dissolution studies

Drug release profilr of different in drug: polymer ratio were obtained by using USP dissolution apparatus using phosphate buffer 7.4 (900 ml) as dissolution medium at 50 rpm. The samples were withdrawn at fixed intervals, diluted suitably with dissolution medium and analyzed spectrophotometrically at 287 nm. The dissolution was evaluated as dissolution efficiency at 180 min [10,11]. The dissolution efficiency (D. E.) of solid dispersion is the area under the dissolution curve of the rectangle described by 100% dissolution in the same time [12].

2.3.3. Calibration curve

2.3.3.1. Calibration curve Alcoholic solution

Accurately weighed solid dispersion of cefixime trihydrate(1:3) (100 mg) was dissolved in 100 ml of dichloromethane to get Stock Solution I (SS I) from which accurately measured 1 ml solution was withdrawn and diluted up to 100 ml with dichloromethane in volumetric flask to get SS II (100µg/ml). The dilutions of 0.5, 01, 1.5, 02, 2.5 and 10µg/ml were prepared. Absorbance of each solution was measured at 287 nm in triplicate by taking dichloromethane as a reference standard. The results were then plotted as a graph of Absorbance vs. Concentration (µg/ml).

2.3.3.2. Calibration curve Phosphate buffer pH 7.4

Accurately weighed solid dispersion of cefixime trihydrate (1:3) (100 mg) was dissolved in 100 ml of PBS 7.4 to get stock solution I (SS I) from which accurately measured 1 ml solution was withdrawn and diluted up to100 ml with PBS 7.4 in volumetric flask to get SS II (100µg/ml). The dilutions of 0.5, 01, 1.5, 02, 2.5 and 10µg/ml were prepared. Absorbance of each solution was measured at 288 nm in triplicate by taking PBS 7.4 as a reference standard. The calibration curve was obtained by plotting Absorbance vs. concentration (µg/ml).

2.3.4. Fourier Transform Infra red spectroscopy (FTIR)

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Shimadzu Corporation (Koyto, Japan) facilty (model - 8400S). Samples were prepared in KBr disks in a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm [13].

2.3.5. Differential Scanning Calorimetry of Cefixime Solid Dispersion (1:3)

The Differential Scanning Calorimetry Study was carried out for cefixime solid dispersion (1:3) drug. The DSC pattern was recorded on a METTLER TOLEDO DSC. Thermograph was

obtained by heating 1–5 mg sample in crimped Aluminum pans at heating rate of 10 ^{0}C/min, from 40 ^{0}C to 220 ^{0}C, in a nitrogen atmosphere (flow rate 40 mL/min) [9,10,11]. Data was analyzed, using STAR-SW 9.20 software.

3. RESULTS AND DISCUSSION

3.1. Preformulation Studies

3.1.1. Physical characterization of drug

They are summarized in following table 1.

Table 1.Physical Characteristics of Cefixime Trihydrate.

Parameters	Observations
Colour	white to light yellow
Odour	Odourless
Taste	Bitter
Melting Point	218-220^{0}C
Angle Of Repose	22.93^{0}C
Bulk Density	0.675 gm/cc
Tapped Density	0.757 gm/cc
Carr's compressibility index	12.56%
Hausner ratio	1.12

3.1.2. Determination of Absorption Maximum (λ max)

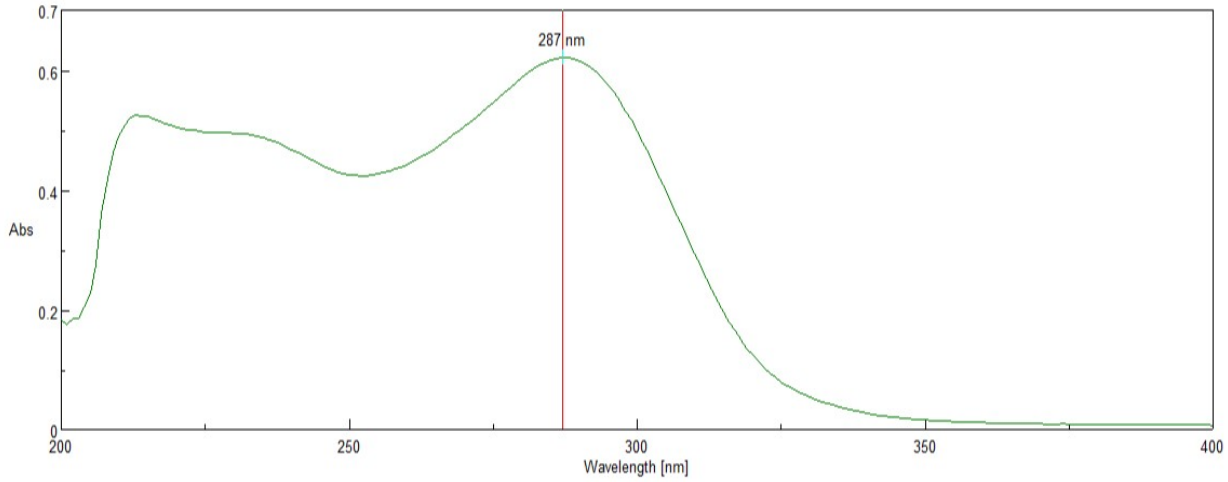

Fig. 1. UV λ max of cefixime trihydrate in phospate buffer pH 7.4- 287 nm.

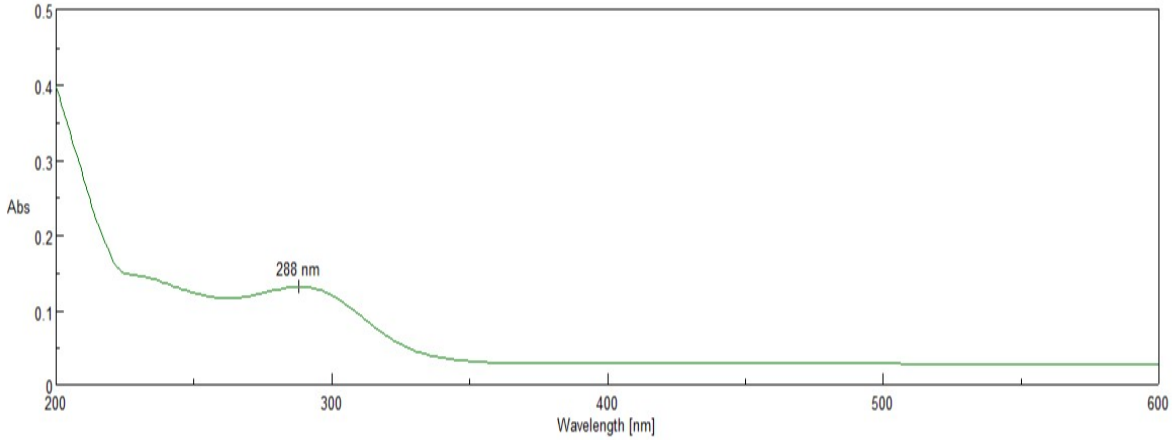

Fig. 2. UV ƛ max of Cefixime trihydrate in Dichloromethane-288 nm.

3.1.3. Determination of Calibration curve

a. Alcoholic solution

The standard calibration curves for Cefixime trihydrate were dtermined in dichloromethane system, the calibration curve have been depicted in figure 3.

The regression value of calibration curves in dichloromethane were found to be 0.993.

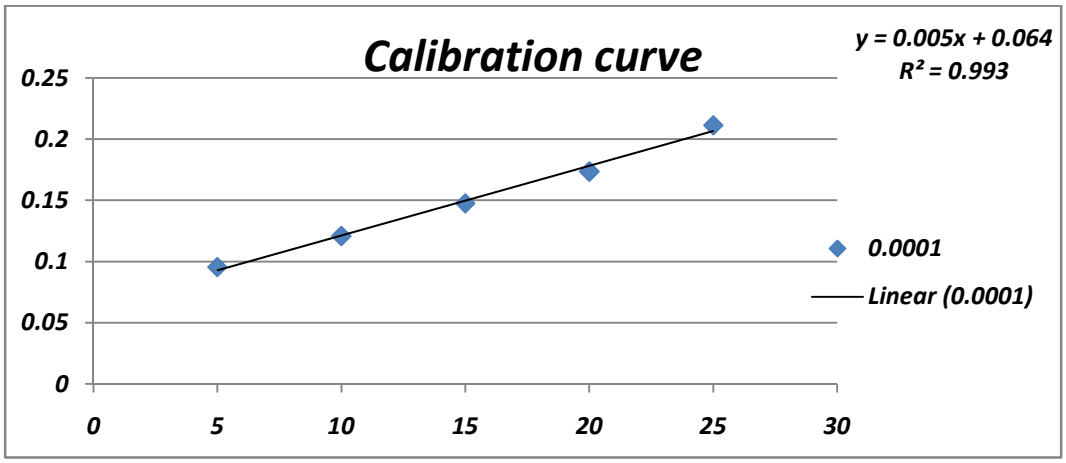

Fig. 3. Calibration curve of Cefixime trihydrate in dichloromethane.

b. Phosphate buffer pH 7.4

The standard calibration curves for Cefixime trihydrate were dtermined in phosphate buffer pH 7.4 system, the calibration curve have been depicted in figure 4.The regression value of calibration curves in phosphate buffer 7.4 were found to be 0.994.

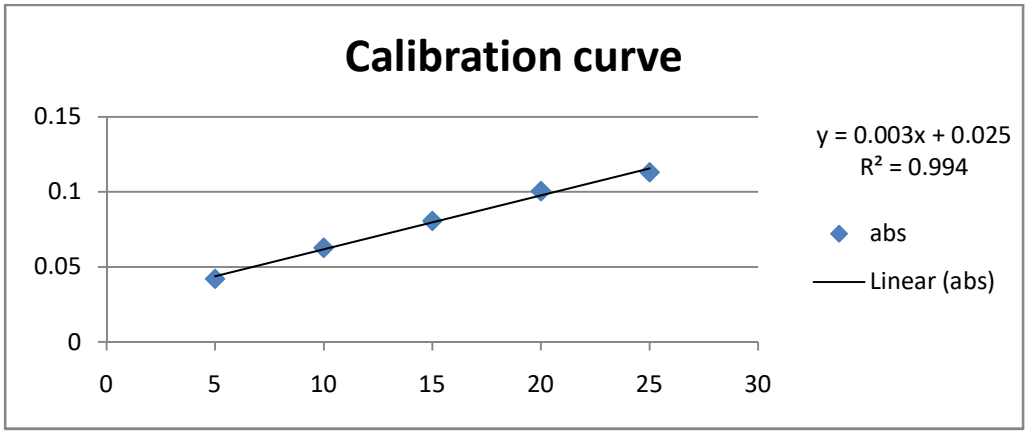

Fig. 4. Calibration curve of Cefixime trihydrate phosphate buffer 7.4.

3.1.4. FTIR Analysis of Cefixime Trihydrate

IR spectra of Cefixime and its solid dispersions are identical. The principle IR absorption peaks of Cefixime solid dispersions (1:3) were observed and found to be identical with the spectra of Cefixime pure drug. Thus, from the spectra it was understood that there was no interaction between Cefixime and the carriers used in the preparation of solid dispersions.

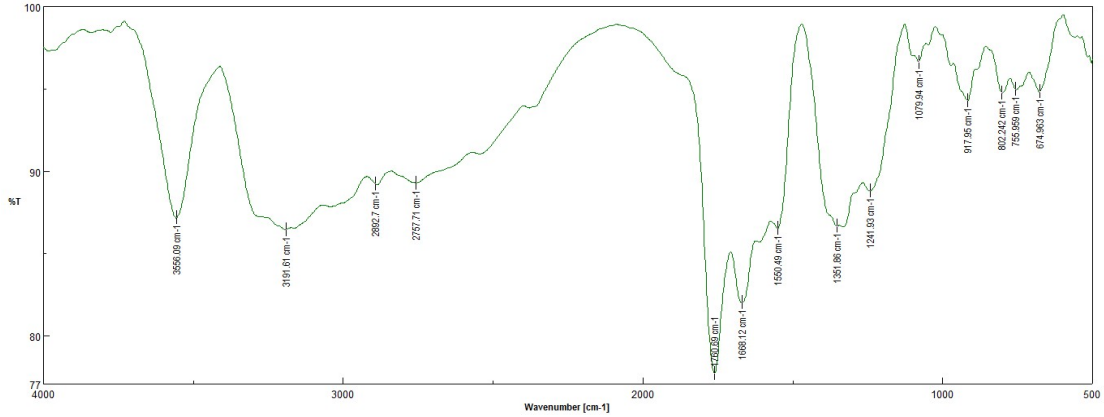

Fig. 5. IR spectra of cefixime trihydrate.

Table 2. IR spectra ranges of Cefixime trihydrate.

Functional group	Absorption range	Pure drug Peak	Type of Vibration
C=O Carbonyl	1670-1820 cm^{-1}	1760.69cm^{-1}	Stretch
NH2 Amine	3400-3500 cm^{-1}	3556.09 cm^{-1}	Stretch
C-N Amine	1080-1360 cm^{-1}	1069.94 cm^{-1}	Stretch
Alcohols (O-H)	3200-3600 cm^{-1}	3556.09 cm^{-1}	Stretch
C=C Alkenes	1640-1670 cm^{-1}	1668.12 cm^{-1}	Stretch

3.1.5. Differential Scanning Calorimetry of Cefixime Trihydrate

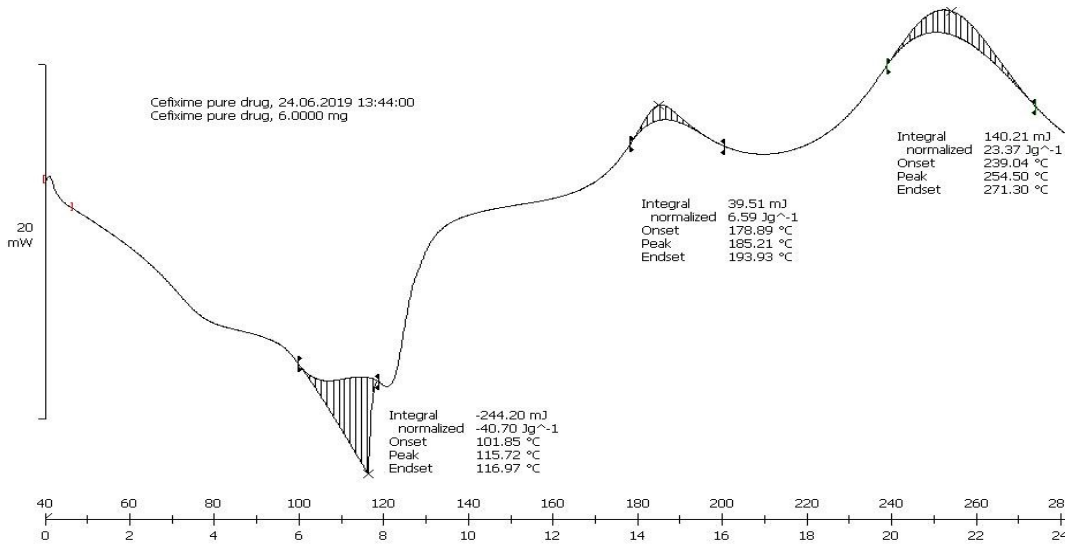

Fig. 6. Differential Scanning Calorimetry of Cefixime Trihydrate.

The melting behavior of pure Cefixime Trihydrate was studied using (DSC; Mettler Teledo star system). The melting endotherm was obtained and Cefixime showed sharp endothermic peak at 116.97 ^{o}c and exothermic peak at 254.50 ^{o}c as depicted in fig.6 . The melting point in the DCS is in the range of the reported melting point which was 216-220^{o}c, thus confirming purity of sample.

3.2. Evaluation of Solid dispersion

3.2.1. Preparation and characterization of amorphous solid dispersion

The appearance of the solid dispersion of cefixime was amorphous in nature and Light brown in colour

3.2.2. Percentage yield

Percentage yield was found to be solid dispersion of cefixime trihydrate (1:1, 1:2, 1:3) are given in the following.

Table 3. Percentage yield of solid dispersions.

Composition Ratio	Percentage yield
dispersion of cefixime trihydrate (1:1)	90%
dispersion of cefixime trihydrate (1:2)	88.33%
dispersion of cefixime trihydrate (1:3)	87.25%

3.2.3. Determination of Calibration curve

a. Alcoholic solution

The standard calibration curves for Solid Dispersion Cefixime trihydrate(1:3) were dtermined in dichloromethane system, the calibration curve have been depicted in figure 7.

The regression value of calibration curves in dichloromethane were found to be 0.998.

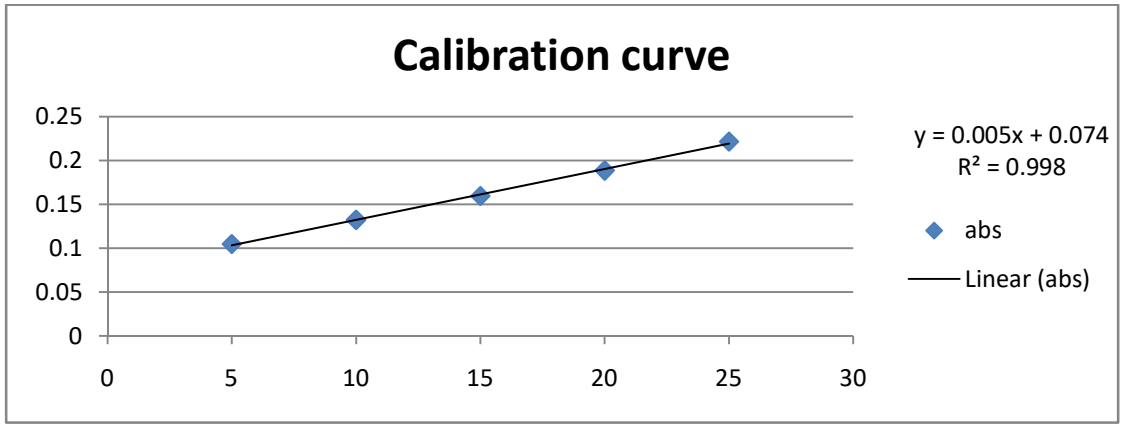

Figure 7.Calibration Curve of SD (1:3) in Dichloromethane by UV spectrometer.

b. Phosphate buffer pH 7.4

The standard calibration curves for Solid dispersion (1:3) Cefixime trihydrate were dtermined in phosphate buffer pH 7.4 system, the calibration curve have been depicted in figure 8.

The regression value of calibration curves in phosphate buffer 7.4 were found to be 0.998.

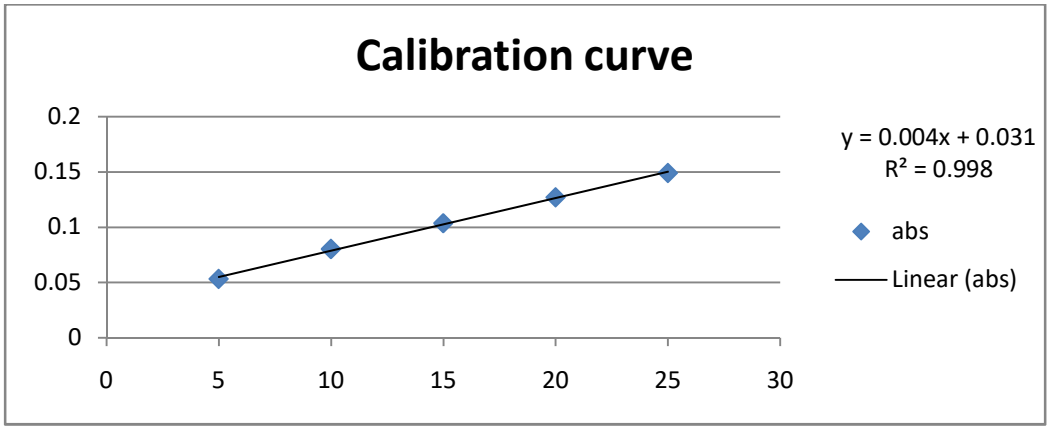

Fig. 8. Calibration Curve of SD (1:3) in Phosphate Buffer 7.4 by UV spectrometer

3.2.4. FTIR of solid dispersion cefixime (1:3):/ compatibility studies

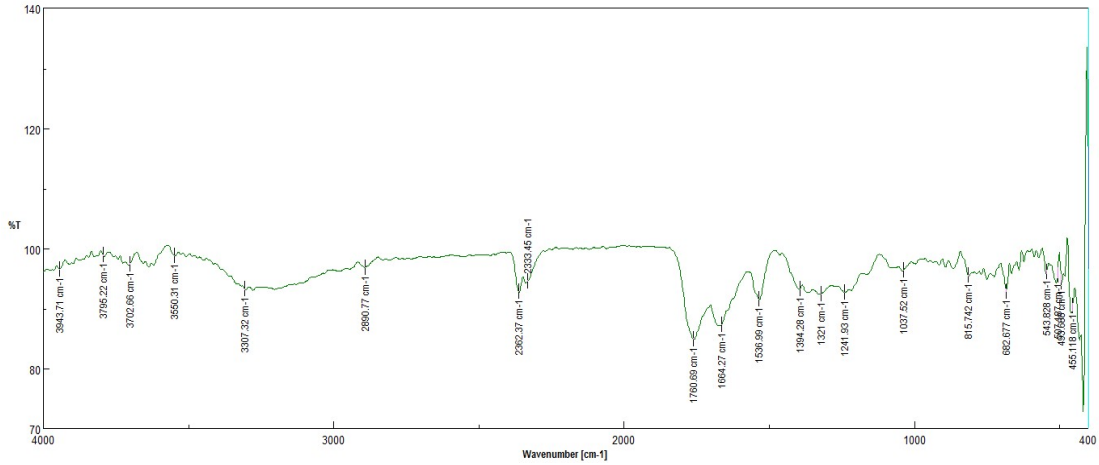

Fig. 9. FTIR of solid dispersion cefixime (1:3).

Compatibility study solid dispersion cefixime trihydrate (1:3) ratio carried out with polymer guar gum to determine possibility of any drug interaction. FTIR spectroscopy shows no evidence of any interaction between drug and interaction. In ftir spectra result, solid dispersion cefixime trihydrate (1:3) ratio if it is stabilized, then offers many fold increase in solubility.

Table 4.IR spectra ranges of solid dispersion cefixime (1:3)

Functional group	**Absorption range**	**Cefixime with gaur gum (1:3) Peak**	**Type of Vibration**
C=O Carbonyl	1670-1820 cm^{-1}	1760.69cm^{-1}	Stretch
NH2 Amine	3400-3500 cm^{-1}	3550.31cm^{-1}	Stretch
C-N Amine	1080-1360 cm^{-1}	1037.52cm^{-1}	Stretch
Alcohols (O-H)	3200-3600 cm^{-1}	3550.31cm^{-1}	Stretch
C=C Alkenes	1640-1670 cm^{-1}	1664.27cm^{-1}	Stretch

3.2.5. Differential Scanning Calorimetry of Cefixime Solid Dispersion (1:3)

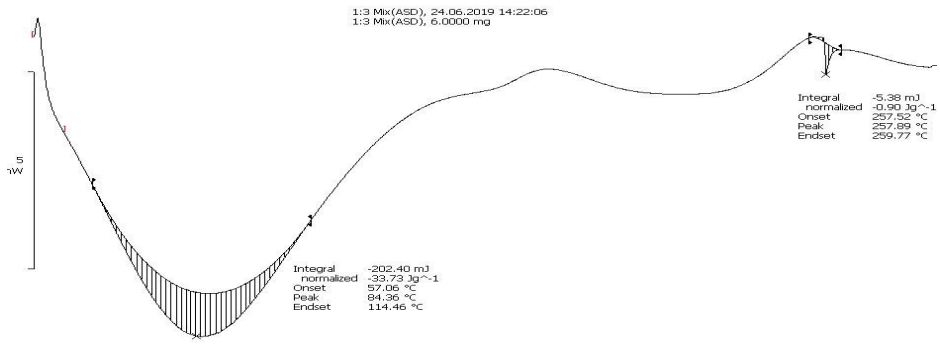

Fig. 10. Differential Scanning Calorimetry of Cefixime Solid Dispersion (1:3).

The solid dispersion 1:3 cefixime prepared with polymer (gaur gum) , were subjected for DSC studies, where in solid dispersion 1:3 of cefixime started melting at 84°C and completed at 257°C. This wide range of melting process suggests that formulation is a product of physical mixture of the polymer (gaur gum) mentioned herein, if it is a reaction product which might have formed during the formulation, it would give rise to short range of melting process , which has not happened in this case. This confirms the drug used in the formulation is in the free state rather than in the chemically reacted form. Drug is freely available to the system whenever administered. One can draw the conclusion that, during the process of formulation in this case also, drug and polymer have not undergone any chemical reaction.

3.2.6. In-Vitro dissolution profile and dissolution efficiency

Table 5. Dissolution efficiency of pure drug and solid dispersion Cefixime trihydrate.

Time in Min	**% dissolution efficiency For Compositions**			
	Pure Drug	**1:1**	**1:2**	**1:3**
00	00	00	00	00
5	34.74	44.52	55.37	78.59
10	34.89	44.64	56.08	79.76
15	35.44	44.91	56.44	80.43
20	36.65	45.40	56.60	81.68
25	37.58	46.57	57.87	82.54
30	38.22	47.71	59.63	83.40
45	39.28	48.40	61.56	86.12
60	41.39	51.12	64.19	87.31
120	43.05	55.07	65.96	89.56
180	44.06	56.52	68.99	91.98

In vitro release studies revealed that there was marked increase in the dissolution rate of drug from all the SDs when compared to pure drug itself. The dissolution efficiency was found to 91.98% with 1:3 ratio compositions after 180 min. The drug release profile depicted in fig.11 confirmed that solubility was enhanced in the drug: polymer ratio of 1:3 as it has higher dissolution rate compared pure drug. All the SDs followed first order kinetics and ‘r’ values suggested that all the SDs followed Higuchi matrix model.

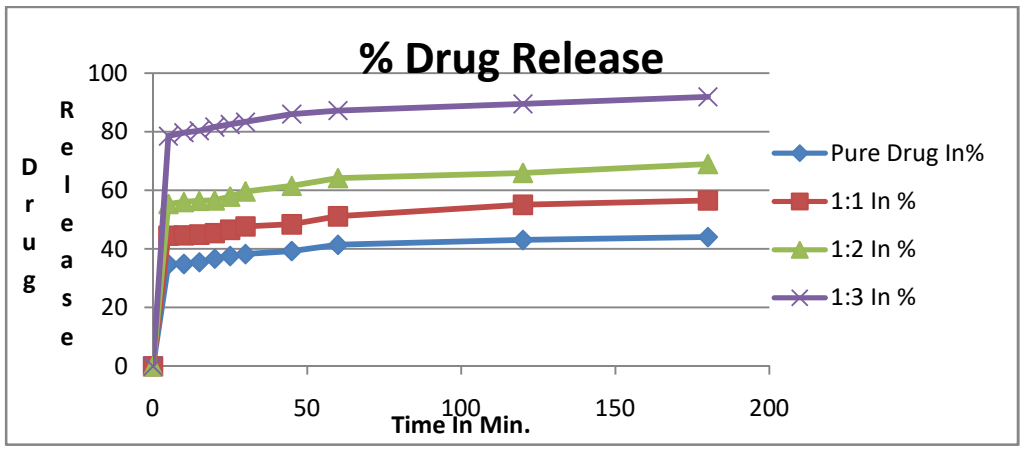

Fig. 11. % of drug release of drug and different (SDs).

4. CONCLUSION

The solid dispersions of Cefixime with the guar gum as carrier were prepared and evaluated. FTIR has shown that there was no interaction between the drug and carrier. The solubility and dissolution studies have shown enhancement in solubility of Cefixime through solid dispersion with natural polymer viz.., guar gum. A maximum increase in dissolution profile was found with Cefixime: guar gum solid dispersion with a weight ratio of 1:3 prepared by solvent evaporation method. Hence it can be concluded that the objectives of solubility and in-vitro dissolution enhancement were achieved successfully.

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