

Full Length Research Paper

UREA BASED INCLUSION COMPOUNDS OF CEFIXIME TRIHYDRATE FOR THE IMPROVEMENT OF PHARMACEUTICAL CHARACTERISTICS

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ABSTRACT

Cefixime Trihydrate (Poorly water soluble drug), when prepared as solid dispersion showed improved solubility and dissolution. So the main purpose of this investigation was to increase the solubility and dissolution rate of Cefixime Trihydrate by the preparation of its solid dispersion with urea using solvent evaporation method. Physical mixtures and solid dispersions of Cefixime Trihydrate were prepared by using urea as water-soluble carrier in various proportions (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 by weight), by employing solvent evaporation method. The drug release profile was studied and it was found that the dissolution rate and the dissolution parameters of the drug from the physical mixture as well as solid dispersion were higher than those of the intact drug. FT- IR spectra revealed no chemical incompatibility between drug and urea. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC) and Powder X-Ray Diffraction (PXRD).

Keywords: *Cefixime Trihydrate; Urea; Solvent Evaporation Method; Solid dispersion.*

INTRODUCTION

The solubility of many drugs is often a limiting factor for their applicability. Therefore, the solubility enhancement of these compounds is an important task in pharmaceutical technology, because it leads to better bioavailability and to more efficient application, connected with a diminished environmental stress. The solubility enhancement of poorly soluble compounds can be induced by changes in temperature, solvation properties using different cosolvent compositions, and by inclusion compound formation.

Urea inclusion compounds have attracted

considerable attention over the past few years because of their interesting and dynamic physicochemical properties [1-3]. Although these compounds have been known for a long time [4-6], there is still considerable interest in the inclusion phenomenon varying from the complex structural behavior to basic intermolecular interactions. These inclusion compounds are conveniently considered to consist of two distinct, although not independent, host and guest substructures [7-8]. The host substructure consists of an approximately hexagonal framework of hydrogen bonded urea with open, essentially infinite, parallel, non-intersecting tunnels (approximately diameter 5.5-5.6 Å) which completely enclose guest molecules. The guest substructure consists of guest molecules arranged in periodic repeat distance which is approximately equal to the length of guest molecule in the type of linear conformation that it must adopt in order to fit

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within the confined space available inside the tunnel [9-10].

Cefixime Trihydrate ((6*R*,7*R*)-7-[2-(2-Amino-4-thia-zolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid, 7²-(*Z*)-[O-(carboxymethyl) oxime] trihydrate) (Figure 1). Molecular weight = 507.50 as the trihydrate. Chemical Formula is C₁₆H₁₅N₅O₇S₂·3H₂O. It is used to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. One of the major problems with this drug is its poor solubility in biological fluids that results into poor bioavailability after oral administration. It shows erratic dissolution problem in gastric and intestinal fluid due to its poor water solubility. Rate of absorption and/or extent of bioavailability for such insoluble drug are controlled by rate of dissolution in gastrointestinal fluids [11]. The peak plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) depend upon extent and rate of dissolution of drug respectively. The effort to improve the dissolution and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development. Hence it was aimed to enhance the aqueous solubility and dissolution rate of Cefixime Trihydrate by forming inclusion complex with urea and their physico-chemical properties were investigated.

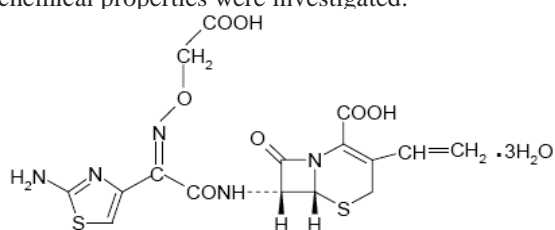


Figure 1: Chemical structure of Cefixime Trihydrate

MATERIALS AND METHODS

Materials

Cefixime Trihydrate was generous gift from FDC Limited, Mumbai. Urea and stearic acid (Analytical

Grade) were purchased from Qualikems Fine Chemicals Pvt. Ltd., New Delhi and CDH Lab Reagent, New Delhi respectively. All other chemical reagents were of analytical grade and were used without any further purification.

Methods

Preparation of urea inclusion compounds of Cefixime Trihydrate with RAE

Cefixime Trihydrate (0.1 g) was dissolved in 20 mL of methanol containing 0.5 g of urea by gentle heating. Stearic acid (0.1 g) was then incorporated into the above solution, resulting in immediate formation of fine crystals. After keeping the solution at room temperature for 3-4 h, crystals were separated by vacuum filtration, dried and stored in suitable containers [12-14].

Characterization of urea inclusion compounds

Fourier Transform Infrared Spectroscopy

All prepared samples were subjected to FTIR spectroscopic studies to determine drug-carrier interaction. FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using Fourier Transform IR spectrophotometer (Perkin Elmer, RXI FTIR System). Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm⁻¹ and the resolution was 2 cm⁻¹.

Differential scanning calorimetric studies

Differential scanning calorimetry (DSC) measurements were carried out on a scanning calorimeter (DSC Q10 V9.0 Build 275, Universal V4.1D TA Instruments). The instrument was calibrated using indium as standard. Samples (5-10 mg) were placed in sealed aluminium pans and heated from 70°C to 250°C at a rate of 10°C/min under nitrogen atmosphere (60 ml/min), with empty pan as reference.

X-Ray Diffraction Studies

The powder x-ray diffraction (XRD) was performed by X'pert Pro with Spinner PW3064 using Ni-filtered, Cu-K α radiation, a voltage of 45 kV, and a current of 40 mA with a scintillation counter. The instrument was operated in the continuous scanning speed of 4°/min over a 2 θ range of 5°C to 40°C.

Determination of the minimum ratio of RAE and NNAE (Normally Non-Adductible Endocyte) for the formation of co-inclusion compounds with urea

The minimum amount of RAE required for adduction of Cefixime Trihydrate per unit quantity of urea was determined by the modified Zimmerschied calorimetric method [6,12] based on measurement of temperature rise following addition of increments of RAE to a methanolic solution of

urea containing excess of drug. Hence, 1.0 g Cefixime Trihydrate and 5 g urea dissolved in 20 mL of methanol were taken. Increments of 0.25 g RAE were successively addition. A plot of temperature versus amount of RAE revealed the minimum amount of RAE utilized in the formation of co-inclusion compounds of Cefixime Trihydrate and RAE in urea [6].

Preparation of urea inclusion compounds containing varying amounts of Cefixime Trihydrate and RAE

A number of urea-Cefixime Trihydrate-RAE co-inclusion compounds containing varying amounts of Cefixime Trihydrate and RAE were prepared using the relative proportions of RAE to Cefixime Trihydrate listed in Table 1.

Table 1. Content uniformity in different Cefixime Trihydrate inclusion compounds (SF3)

Product	RAE : Drug : Urea	Percent drug claimed
SF3.1	0.65 : 1 : 5	96.7 \pm (0.6)
SF3.2	0.8 : 1 : 5	97.2 \pm (0.6)
SF3.3	1 : 1 : 5	98.7 \pm (0.7)
SF3.4	1.2 : 1 : 5	97.1 \pm (0.6)
SF3.5	1.4 : 1 : 5	96.4 \pm (0.8)

Data are mean \pm s.d. for 3 randomly drawn samples of inclusion compounds. RAE, Rapidly Adductible Endocyte.

Assay procedure

Cefixime Trihydrate was estimated at 230 nm using UV spectrophotometer (Systronics Double Beam Spectrophotometer 2202). Standard curve for the estimation was prepared in phosphate buffer pH 6.8 in concentration range of 2-30 μ g/ml. In this concentration range good linearity was observed with the correlation coefficient (R^2) 0.9965. The graph obeyed the Beer-Lambert's law in the selected concentration range.

Drug Content

Solid dispersions equivalent to 100 mg of Cefixime Trihydrate were weighed accurately and dissolved in a suitable quantity of phosphate buffer pH 6.8. The solutions were filtered and drug content was determined at 230 nm by UV spectrophotometer (Systronics Double Beam Spectrophotometer 2202) after suitable dilution.

Dissolution rate studies

The dissolution study was performed using a USP XXIV type II dissolution test apparatus in 900 mL of pH 6.8 phosphate buffer, maintained at 37.0 \pm 0.5°C and stirred at 100 rpm. The quantity of

Cefixime Trihydrate (100 mg) and of inclusion compounds SF3.2 and SF3.3 containing an amount of drug equivalent to 100 mg was added to the dissolution medium. At predetermined time intervals (2, 5, 10, 15, 20 and 30 min); 5 mL of the samples were withdrawn with volume replacement. After filtration, concentration of Cefixime Trihydrate was determined spectrophotometrically at 230 nm. All experiments were conducted in triplicate.

RESULT AND DISCUSSION

The present study explored the formation of urea-drug adducts as a means to increase the dissolution rate of Cefixime Trihydrate. A normally non-adductible endocyte, Cefixime Trihydrate was incorporated into urea adduct in the presence of a suitable RAE (stearic acid). The minimum proportion of RAE required to form the adduct was determined and the physicochemical properties of the resulting adducts were investigated. Finally, it was shown that the complex significantly enhances the dissolution rate of Cefixime Trihydrate.

Fourier Transform Infrared Spectroscopy

FTIR studies were carried out for urea alone as well as co-inclusion complexes (Figure 2 and 3). In the absence of guest molecule, urea crystallizes in a tetragonal arrangement showing characteristics peaks at; 3418.7 cm^{-1} and 3335.8 cm^{-1} for N-H stretching, 1621.8 cm^{-1} for C-O stretching and 1460.6 cm^{-1} and 1150.6 cm^{-1} for C-N stretching. A characteristic peak at 787.1 cm^{-1} was also observed in tetragonal urea. Whereas in the presence of suitable size guest molecule, urea assumes the hexagonal arrangement around the guest, the combination producing a denser structure than that of the tetragonal arrangement. Hence, in co-inclusion complexes of urea with Cefixime Trihydrate the major tetragonal peaks of urea changes to hexagonal peak values. N-H stretching peaks at 3418.7 cm^{-1} and 3335.8 cm^{-1} got changed to 3352.8 cm^{-1} and 3216.3 cm^{-1} respectively. C-N stretching peaks at 1460.6 cm^{-1} and 1150.6 cm^{-1} got changed to 1458.7 cm^{-1} and 1160.8 cm^{-1} respectively. The tetragonal peak at 787.1 cm^{-1} got changed to 791.0 cm^{-1} . The presence of hexagonal peaks confirmed the formation of co-inclusion complexes for Cefixime Trihydrate.

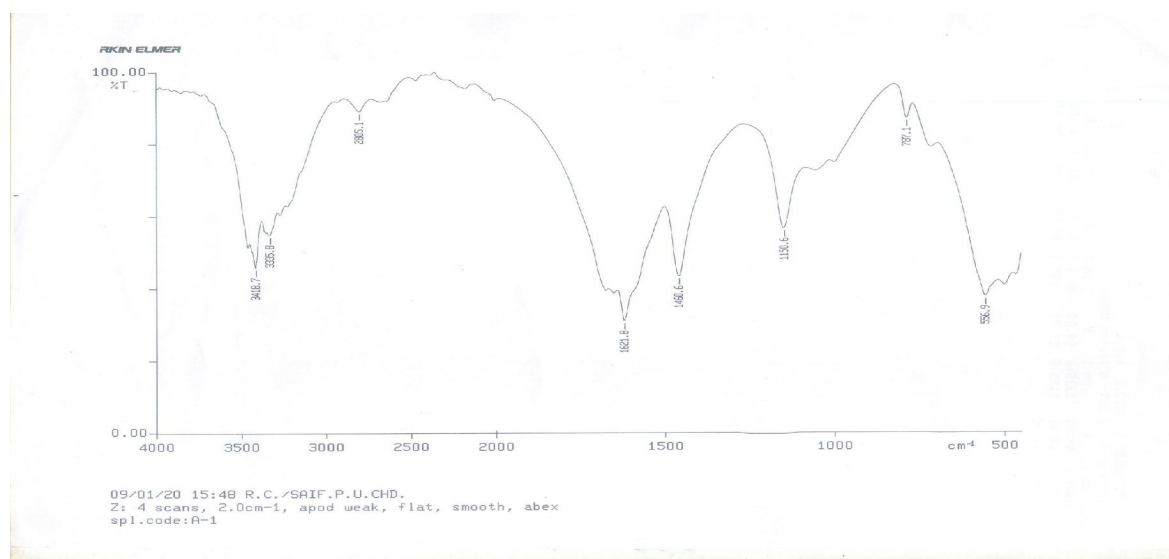


Figure 2: FTIR Spectra of Urea.

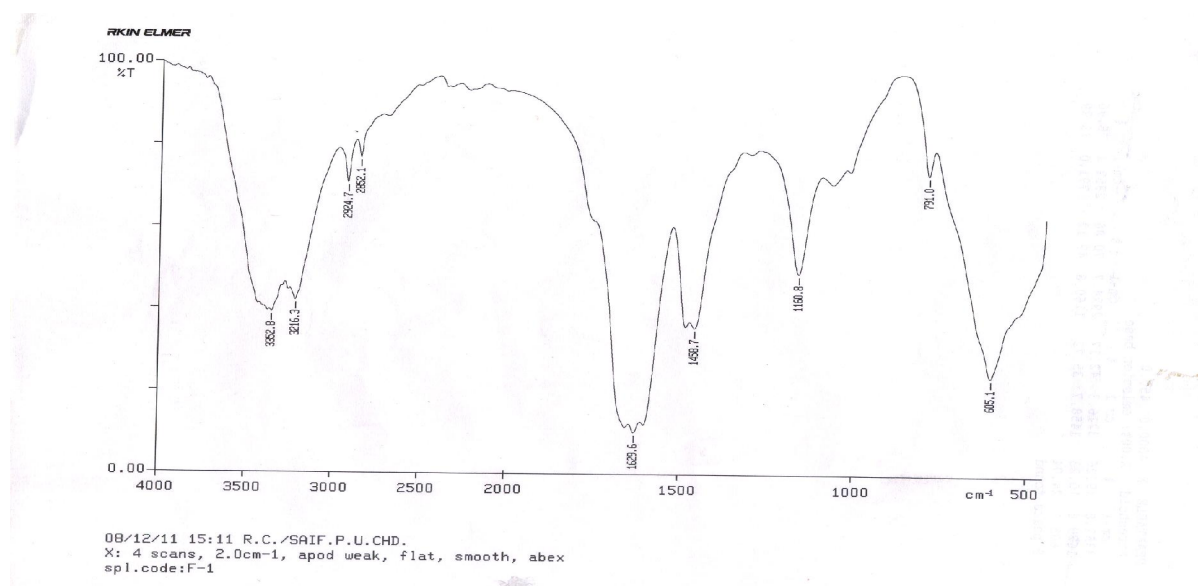


Figure 3: FTIR Spectra of Cefixime Trihydrate Inclusion Compound (SF3.3).

Differential Scanning Calorimetric Studies

The DSC thermograms obtained for Cefixime Trihydrate and inclusion compounds (SF3) crystals are shown in Figure 4 and 5. The thermogram of the drug shows characteristic endotherm corresponding to the melting point of the crystalline drug (i.e. 220.6°C). The thermogram of the inclusion compound does not show a peak in this region,

implying inclusion of the drug into the urea lattice. Further, the thermogram exhibits two endothermic events, a characteristic of the hexagonal form of complexed urea [14-15]. The first step involves the collapse of the hexagonal form of the urea inclusion compound to yield the guest moiety and tetragonal solid urea, while the second step involves melting of tetragonal urea and drug.

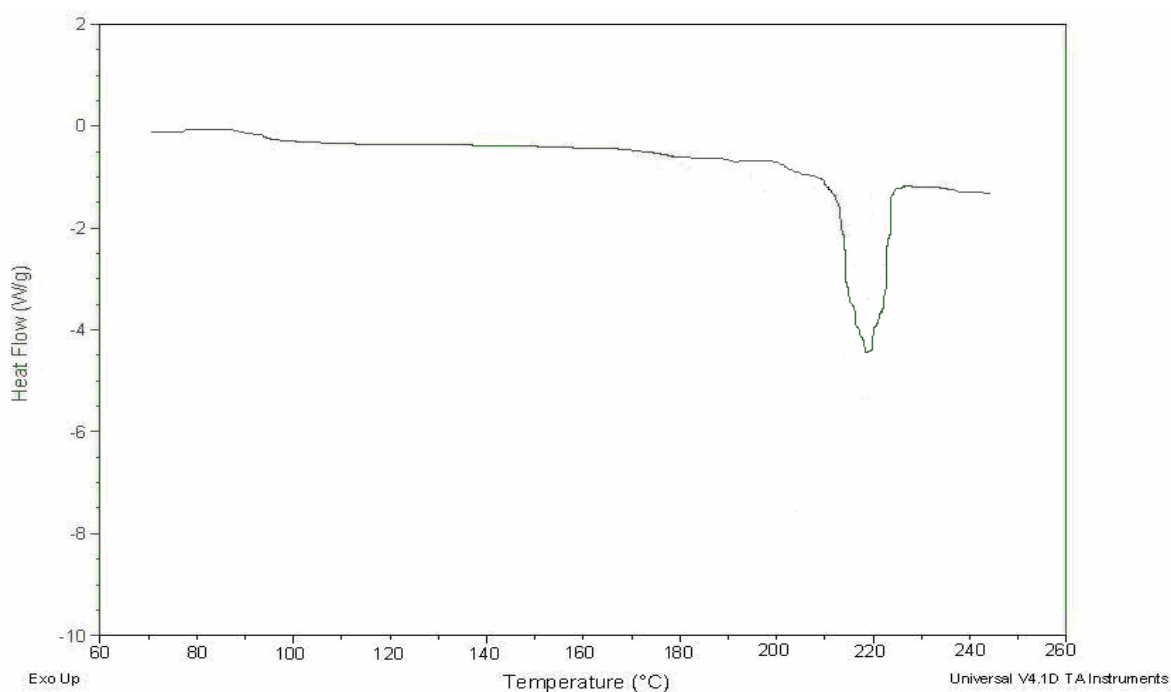


Figure 4: DSC Thermogram of Cefixime Trihydrate

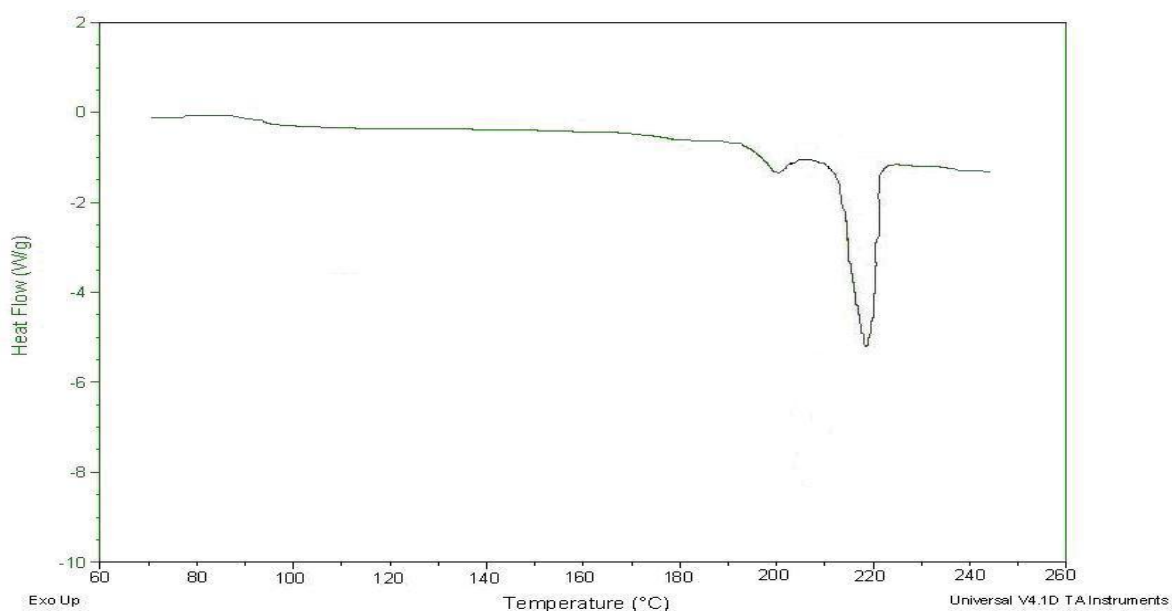


Figure 5: DSC Thermogram of Cefixime Trihydrate Inclusion Compound (SF3.3).

X-Ray Diffraction Studies

The X-ray powder diffraction pattern confirmed the results of DSC analysis (Figure 6). Diffractive peaks relevant to crystalline Cefixime Trihydrate were not detectable in inclusion compound product, indicating that the guest molecules were trapped and isolated from one another in the honeycomb

network of urea and do not contribute to the crystal structure except for slight distortions of the hexagonal channels caused by bulky guests. The diffractogram of hexagonal urea was characteristically distinguishable from that of the pure tetragonal form of urea, indicating a change in the crystalline form of urea.

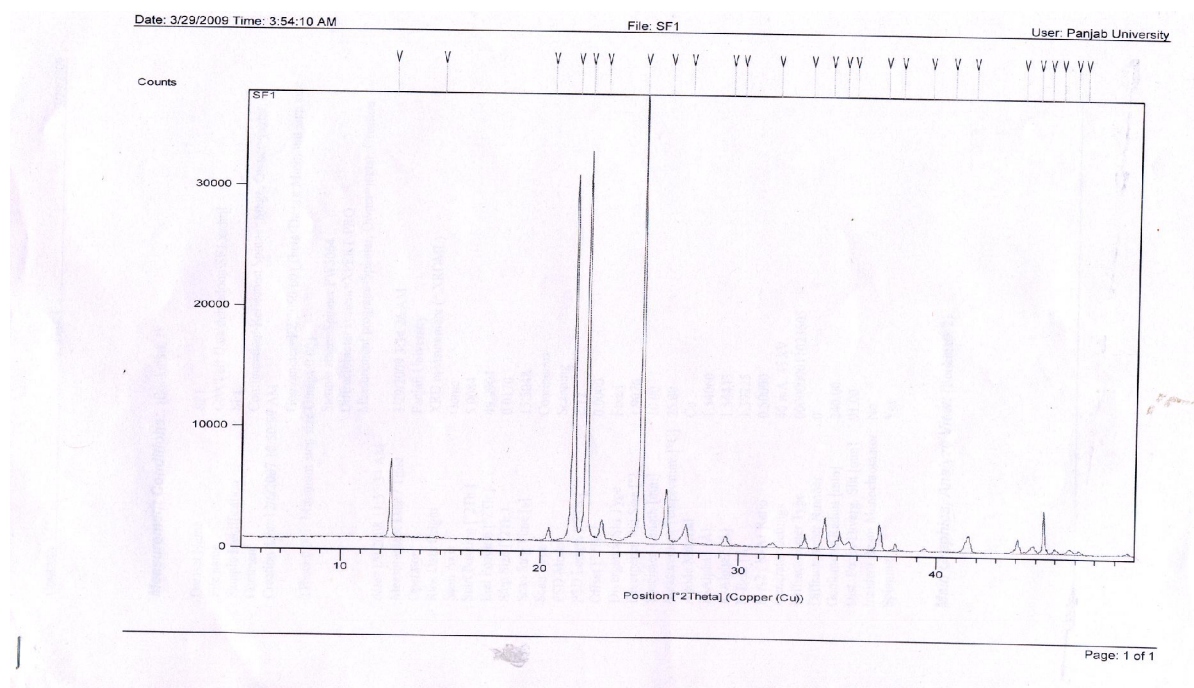


Figure 6: XRD Diffractogram of Cefixime Trihydrate Inclusion Compound (SF3.3).

Minimum ratio of RAE and NNAE for inclusion of NNAE in urea

The increase in temperature on addition of successively increments of stearic acid to a methanolic solution of urea and Cefixime Trihydrate was plotted. The curve demonstrated the following sequence of events: an initial temperature rise, followed by an intermediate final temperature, subsequent temperature rise and then achievement of a final temperature. The minimum amount of RAE required for adduction of Cefixime Trihydrate in urea was calculated from the point of intersection of the lines of extrapolation of the initial rate of temperature rise and intermediate final temperature. The second stage temperature rise is due to displacement of NNAE with RAE, as evidenced by the fact that the overall temperature rise is similar to that of RAE alone^[6]. The minimum ratio of RAE to drug for adduction of Cefixime Trihydrate in urea was determined to be 0.61:1.

Drug content

The drug content data for different inclusion compounds containing varying RAE to drug ratios are presented in Table 1. From the experimental

data, it is apparent that the mean drug content for different inclusion compounds is not significantly different.

Dissolution Studies

Figure 7 shows the dissolution profiles plotted from the experimental values of pure Cefixime Trihydrate and its urea inclusion compounds SF3.2 and SF3.3. The extent of pure Cefixime Trihydrate released was found to be comparatively low, with dissolution of ~17% of the content in 5 min. On the other hand, co-inclusion of the drug in urea provided instantaneous dissolution of ~100% within 5 min for both inclusion compounds. Thus Cefixime Trihydrate complexation in urea led to a 5.8 fold increase in the initial dissolution. The improvement in the dissolution rate of drug from inclusion compounds is in agreement with the results of complex characterization, which indicate that the drug is present in the amorphous form. The amorphous nature of the drug in urea compounds led to an increase in the dissolution rate. When such a system is exposed to an aqueous dissolution medium, the urea lattice dissolves, resulting in the release of the included drug at molecular level.

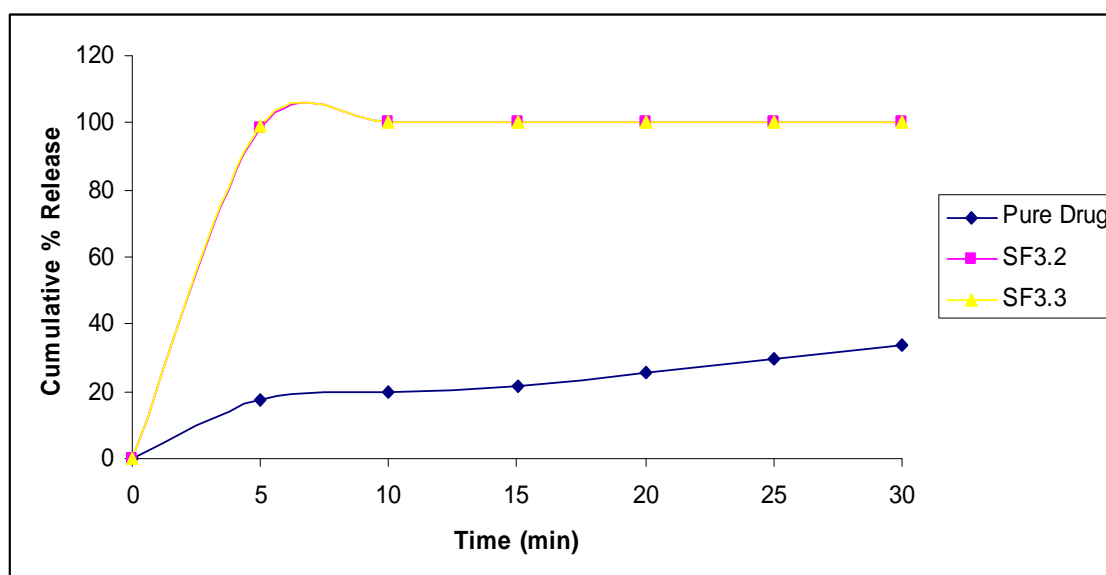


Figure 7: Dissolution profiles of Cefixime Trihydrate drug and Cefixime Trihydrate-RAE-urea co-inclusion compounds containing varying proportions of drug and RAE (♦, Cefixime Trihydrate; ▲, SF3.3; ■, SF3.2).

CONCLUSION

The formation of co-inclusion compounds of Cefixime Trihydrate in urea in the presence of a suitable RAE was studied. The higher dissolution rate displayed by inclusion compounds may imply enhanced oral bioavailability of the drug. The inclusion compounds were also found to show good content uniformity. The overall process of urea inclusion complex formation involves relatively simple preparation steps, reduced processing cost, minimal energy consumption and short processing time. Urea inclusion compounds of Cefixime Trihydrate in the presence of a suitable RAE may be a promising alternative for formulation of potent poorly soluble drugs into immediate release products.

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