International Journal of Current Pharmaceutical Research
Vol 2, Issue 2, 2010

Research Article

UREA BASED INCLUSION COMPOUNDS OF CEFPODOXIME PROXETIL FOR THE IMPROVEMENT OF PHARMACEUTICAL CHARACTERISTICS

S.C. ARORA*[1], P.K. SHARMA[2], RAGHUVEER IRCHHAIYA[3], ANURAG KHATKAR[1], NEERAJ SINGH[1] AND JAGBIR GAGORIA[1]

[1] R.K.S.D. College of Pharmacy, Kaithal, Haryana, India, [2] Dept. of Pharmaceutical Technology, MIET, Meerut, Uttar Pradesh, India

[3] Institute of Pharmacy, Bundelkand University, Jhansi, Uttar Pradesh, India. E mail: scarora_1952@rediffmail.com

Received 18 Dec 2009, Revised and Accepted 05 Jan 2010

ABSTRACT

Cefpodoxime Proxetil is a hydrophobic molecule that is practically insoluble in aqueous media and exhibits an exceedingly slow intrinsic dissolution rate. The present study was emphasized on improving the solubility and dissolution rate of drug by forming inclusion complex with urea. In the present study, Cefpodoxime Proxetil was successfully included in urea together with a suitable rapidly adductible endocyte (RAE). Formation of the urea inclusion compound was confirmed by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies. The modified Zimmerschied calorimetric method was used to estimate the minimum amount of RAE required for adduction of Cefpodoxime Proxetil in urea.

Keywords: Cefpodoxime Proxetil; Urea; Adduct; Inclusion compounds.

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°A) which completely enclose guest molecules. The guest substructure consists of guest molecules arranged in periodic repeat distance whih is approximately equal to the length of guest molecule in the type of linear conformation that it must adopt in order to fit within the confined space available inside the tunnel [9-10].

Cefpodoxime Proxetil (1-[(isopropoxycarbonyl)oxy] ethyl ester of (*Z*)-7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid) (Figure 1) is the orally active ester prodrug of third generation Cephalosporin. Cefpodoxime Proxetil is used orally for the treatment of mild to moderate respiratory tract infections, uncomplicated gonorrhea and urinary tract infections. 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 Cefpodoxime Proxetil by forming inclusion complex with urea and their physico-chemical properties were investigated.

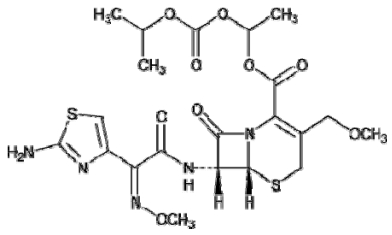

Fig. 1: Chemical structure of Cefpodoxime Proxetil

MATERIALS AND METHODS

Materials

Cefpodoxime Proxetil 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 Cefpodoxime Proxetil with RAE

Cefpodoxime Proxetil (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 transforms 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 150°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-Kα 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 2θ 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 Cefpodoxime Proxetil 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 Cefpodoxime Proxetil 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 Cefpodoxime Proxetil and RAE in urea [6].

Preparation of urea inclusion compounds containing varying amounts of Cefpodoxime Proxetil and RAE

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

Table 1: Content uniformity in different Cefpodoxime Proxetil inclusion compounds (SF3)

Product	RAE : Drug : Urea	Percent drug claimed
SF3.1	0.65 : 1 : 5	95.2 ± (0.7)
SF3.2	0.8 : 1 : 5	97.8 ± (0.5)
SF3.3	1 : 1 : 5	98.1 ± (0.4)
SF3.4	1.2 : 1 : 5	97.2 ± (0.7)
SF3.5	1.4 : 1 : 5	96.8 ± (0.6)

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

Assay procedure

Cefpodoxime Proxetil was estimated at 232 nm using UV spectrophotometer (Systronics Double Beam Spectrophotometer 2202). Standard curve for the estimation was prepared in 15% v/v methanolic phosphate buffer pH 6.8 in concentration range of 2-30 µg/ml. In this concentration range good linearity was observed with the correlation coefficient (R^2) 0.9987. The graph obeyed the Beer-Lambert's law in the selected concentration range.

Drug Content

Solid dispersions equivalent to 100 mg of Cefpodoxime Proxetil were weighed accurately and dissolved in a suitable quantity of methanolic phosphate buffer pH 6.8. The solutions were filtered and drug content was determined at 232 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 ± 0.5°C and stirred at 100 rpm. The quantity of Cefpodoxime Proxetil (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 Cefpodoxime Proxetil was determined spectrophotometrically at 232 nm. All experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The present study explored the formation of urea-drug adducts as a means to increase the dissolution rate of Cefpodoxime Proxetil. A normally non-adductible endocyte, Cefpodoxime Proxetil 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 Cefpodoxime Proxetil.

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 Cefpodoxime Proxetil 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 3421.1 cm^{-1} and 3224.3 cm^{-1} respectively. C-N stretching peaks at 1460.6 cm^{-1} and 1150.6 cm^{-1} got changed to 1466.6 cm^{-1} and 1074.2 cm^{-1} respectively. The tetragonal peak at 787.1 cm^{-1} got changed to 791.3 cm^{-1}. The presence of hexagonal peaks confirmed the formation of co-inclusion complexes for Cefpodoxime Proxetil.

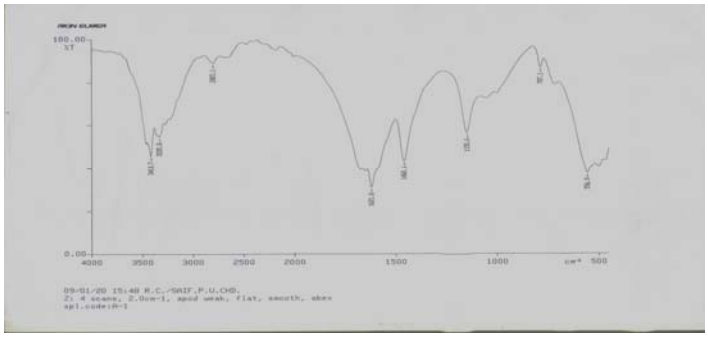

Fig 2: FTIR spectra of urea.

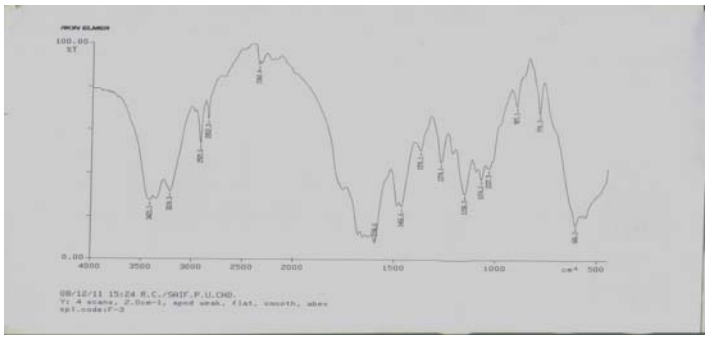

Fig. 3: FTIR Spectra of cefpodoxime proxetil inclusion compound (SF3.3).

Differential scanning calorimetric studies

The DSC thermograms obtained for Cefpodoxime Proxetil 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. 126.8°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.

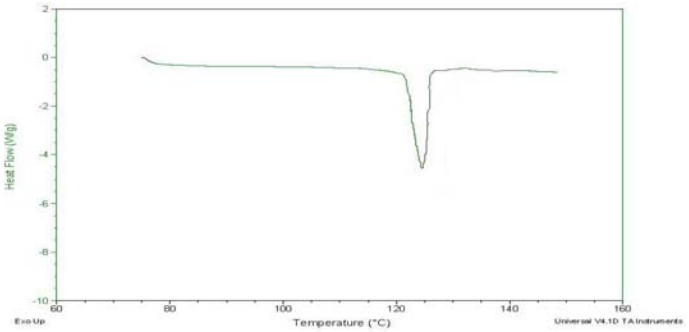

Fig. 4: DSC thermogram of cefpodoxime proxetil

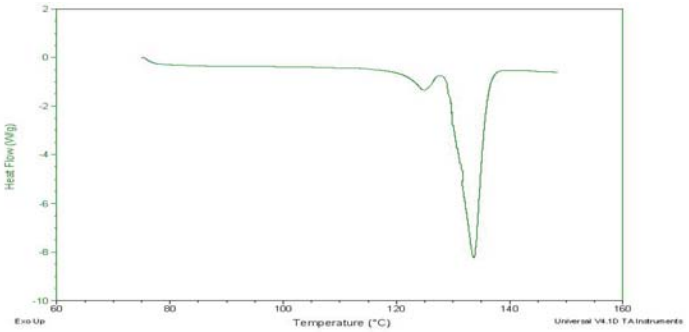

Fig. 5: DSC thermogram of cefpodoxime proxetil inclusion compound (SF3.3).

X-ray diffraction studies

The X-ray powder diffraction pattern confirmed the results of DSC analysis (Figure 6). Diffractional peaks relevant to crystalline Cefpodoxime Proxetil 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.

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 Cefpodoxime Proxetil 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 Cefpodoxime Proxetil 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 Cefpodoxime Proxetil in urea was determined to be 0.64:1.

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.

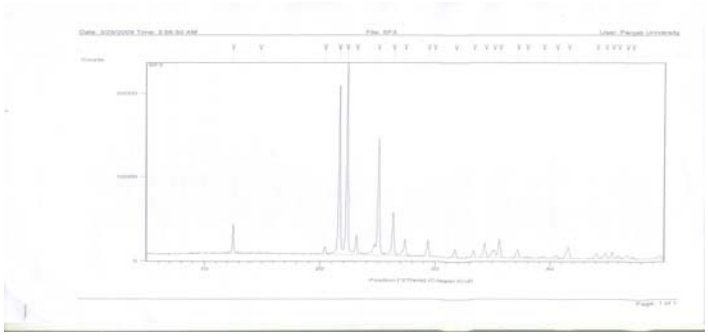

Fig. 6: XRD diffractogram of cefpodoxime proxetil inclusion compound (SF3.3).

Dissolution studies

Figure 7 shows the dissolution profiles plotted from the experimental values of pure Cefpodoxime Proxetil and its urea inclusion compounds SF3.2 and SF3.3. The extent of pure Cefpodoxime Proxetil 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 Cefpodoxime Proxetil 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.

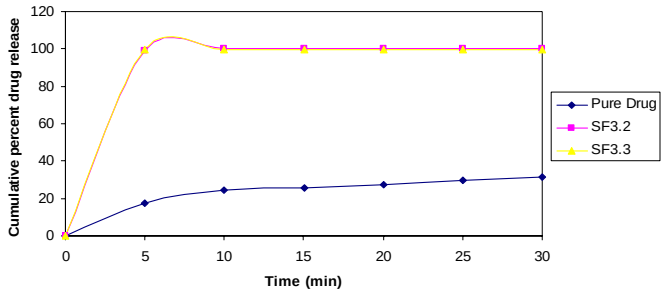

Fig.7: Dissolution profiles of cefpodoxime proxetil drug and cefpodoxime-RAE-urea co-inclusion compounds containing varying proportions of drug and RAE (♦, Cefpodoxime Proxetil; ▲, SF3.3; ■, SF3.2).

CONCLUSION

The formation of co-inclusion compounds of Cefpodoxime Proxetil 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 Cefpodoxime Proxetil in the presence of a suitable RAE may be a promising alternative for formulation of potent poorly soluble rugs into immediate release products.

ACKNOWLEDGEMENT

Authors would like to thank FDC Limited, Mumbai for the generous gift of Cefpodoxime Proxetil.

REFERENCES

1. K. Takemoto and N. Sondo: In J.W. Atwood, J.E.D. Davis, and D.D. MaeNicol (eds.), Inclusion Compounds, Academic Press, London (1984), pp. 47-67.
2. K.D.M. Harris: Phase Trans. 76, 205 (2003).
3. R. Bishop and I.G. Dance: Topics Curr. Chem. 149, 139 (1989).
4. O. Reddlich, C.M. Gable, A.K. Dunlop, and R.W. Millar: J. Am. Chem. Soc 72, 4155 (1950).
5. A.E. Smith: Acta Crystalogr: 5, 224 (1952).
6. W.J. Zimmerschied, R.A. Dinnerstein, A.W. Weitkemp, and R.F. Marschner: Ind. Eng. Chem 42, 1300 (1950).
7. K.D.M. Harris and J.M. Thomas: J. Chem. Soc. Faraday Trans. 86, 2985 (1990).
8. W. Schlenk: Justus Leibigs Ann. Chem. 565, 204 (1949).
9. D. Swern: Ind. Eng. Chem. 47, 216 (1955).
10. Reynolds, J.E.F., Eds., In; Martindale; The Extra Pharmacopoeia, 29th Edn., The Royal Pharmaceutical Society of Great Britain, London, 1993, 295.
11. Madan, A.K., Grover, P.D. (1993) A process for preparing microcapsules for low dose drugs. Indian Patent 182549, 20 January.
12. Madan, A.K. (1994) Microencapsulation of low dose drugs, PhD Thesis, IIT Delhi.
13. Bajaj, V., Madan, A.K. (1994) A process for preparation of urea complexes of vitamin E and its esters. Indian Patent 182620, 24 October.
14. McAdie, M.G. (1962) Thermal decomposition of molecular complexes. Can. J. Chem. 25: 1202-1206.
15. Ahmad, J., Freestone, A.J., Hussain, A. (1994) Differential calorimetry studies on urea-carboxylic acid inclusion complexes. J. Inclusion Phenom, Mol. Recognit. Chem. 18: 115-121.