International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.8, No.1, pp 05-10, 2015

Selection of excipients for the formulation of Ceftriaxone sodium loaded chitosan Nanoparticle through drug-excipient compatibility testing

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Abstract: Ceftriaxone (CFTX) sodium is a semisynthetic antibiotic that can effectively treat several types of bacterial infections. Ideal formulation is considered appropriate when no interactions drug-excipient or excipient-excipient occur. In this strategy, devising a quick and accurate method to evaluate and choose the best excipients for stable dosage forms constitute, a real achievement in the pre-formulation stage. Recently by the application of thermal analytical techniques of the drug-excipient compatibility stage of development of solid dosage form has increased enormously. The intention of the present work was to study the compatibility of Ceftriaxone drug substance with the excipients employed in colon target release capsule preformulation by adopting the Thermo gravimetric analysis (TGA) study and Fourier transform Infra red spectrophotometric study (FTIR). Based on the TGA results Ceftriaxone was found to be compatible with Chitosan and Sodium tri polyphosphate. FTIR was used as supportive techniques for the analyses.
Keywords: FTIR, DGA, Ceftriaxon, chitosan.

Introduction

Ceftriaxone (CFTX) sodium is a semisynthetic antibiotic that can effectively treat several types of bacterial infections. CFTX is chemically known as, (Z) -7-[2-(2-aminothiazol-4-yl) -2-methoxyiminoacetyl amido] -3-[(2,5-dihydro-6- hydroxy-2-methyl- 5-Oxo-1,2,4-triazin-3-yl) thiamethyl] -3-cephem-4-carboxylic acid, disodium salt, CFTX is a β-lactamase-resistant cephalosporin with an extremely long serum half-life. The beta lactam moiety of CFTX binds to caboxypeptidase, endopeptidase, transpeptidase, in the bacterial cytoplasmic membrane. These enzymes are involved in cell wall synthesis and cell division. By binding these, CFTX results in the formation of defective cell walls and cell death[1]. CFTX is used for various clinical condition such as Lower Respiratory Tract Infections, Acute Bacterial Otitis Media, Skin And Skin Structure Infections, Urinary Tract Infections Uncomplicated Gonorrhea Pelvic Inflammatory Disease Bacterial Septicemia Bone And Joint Infections Intra-Abdominal Infections Meningitis[2]. The dose will be vary according to the severity of diseased conditions. Markedly available formulation- Injection, powder for solution 500 mg (3.6 mEq of sodium/g) - Injection, powder for solution 1 g (3.6 mEq of sodium/g)

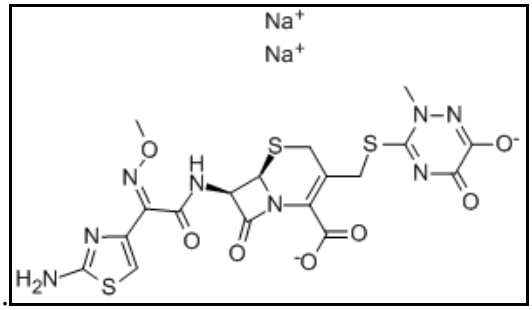

Fig-1 Chemical structure of ceftriaxone sodium

In recent years, it has become more and more evident that the development of new drugs alone is not sufficient to ensure progress in drug therapy. A promising strategy to overcome these problems involves the development of suitable drug carrier systems. Solid nanoparticles were introduced at the beginning of the 1990s, as an alternative to solid nanoparticles, emulsions and liposomes in cosmetic and pharmaceutical preparations[3-4]. Chitosan, the amino polysaccharide copolymer of 1,4 D-glucosamine and N-acetyl glucosamine is derived from chitin by alkaline59,60 or enzymatic deacetylation[5].A formulation is considered appropriate when no interactions drug excipient or expient- expient occur. The poor cellular penetration of the antibiotic was attributed to its high molecular weight (661.6) as well as its hydrophilicity (log P −0.6) (11–16). Efforts have been made to increase its oral absorption. One attempt aimed at increasing its functional lipophilicity through the formation of ion pairs by coupling with positively charged bile acids[6].Thermal analysis is one of the most frequently used instrumental techniques on pharmaceutical researches to solve technological problems in the pre formulation stages of solid dosage forms[7].In this sense devising a quick and accurate method to test and select the best excipients for stable dosage forms constitute a real achievement in the preformulation stage[8-9] .The aim of this work was to evaluate the compatibility between Ceftriaxone sodium and some pharmaceutical excipient, using Themo anlytical technique(TGA) and Fourier transform infrared spectroscopy (FTIR).

Materials and Methods

Ceftriaxone sodium, chitosan (MW= 60–90 kDa; degree of deacetyla- tion 85%) and sodium tripolyphosphate (TPP) were purchased from Sigma Aldrich, USA. All other chemicals were used analytical grade.

Melting point

A capillary tube was taken and it was filled with the help of Bunsen burner. Then this capillary tube which was filled with the drug was placed in a melting point viewer and degree at which the drug gets melted down was considered as the melting point of the drug.

Solubility profile of Ceftriaxone sodium in different solvents (at 25°C)

Solubility of the drug is predicted by dissolving 1 gm of the drug in proportions of 1 ml, 10 ml, 30 ml and 100 ml of the proposed solvents. So, according to the dilution or dissolving property the solubility was predicted by measuring the absorbance by using UV-Visible Spectroscopy method.

UV–visible spectroscopy

The UV–visible spectra were obtained from UV–visible spectrophotometer, Shimadzu UV-1800 model, Japan. Ceftriaxone sodium stock solution (10mg/ ml) was prepared. Aliquots were withdrawn and making concentration of 5 ; 10 ; 15; 20; 25 mg/ml. Absorbance was taken at 257nm. (Table 1)

FT-IR analysis

The FT-IR spectra of the samples were analyzed using a Perkin-Elmer, FT-IR spectrophotometer, USA within the range of 4000–400 cm−1. Each5 mg of drug, chitosan and tri sodium polyphosphate was mixed with 100 mg of KBr and compressed into pellet using hydraulic press. All spectra were corrected against the reference spectrum of KBr pellet.

Thermogravimetric analysis (TGA)

A Perkin-Elmer Model of TGA-7 thermo gravimetric system with a microprocessor driven temperature control unit and a TA data station was used. The mass of the samples was generally in the range of 2–3 mg. The sample pan was placed in the balance system equipment and the temperature was raised from 25 to 800 ◦C at a heating rate of 10 ◦C per minute with the nitrogen flow rate of 50 cm3/min. The mass of the sample pan was continuously recorded as a function of temperature.

Result and Discussion

Melting point: Melting point was found to be 179° C which confirms the identification of drug[10]

Solubility: Freely soluble in water at P^H 1.2, 5.5, 6.8, 7.4, sparingly soluble in methanol, very slightly soluble in Ethanol Aceton and Octanol.at 25°C. [11]

Selection of analytical wave length and calibration of standard curve

The diluted stock solution was scanned for maximum wavelength and it was found to be 257 nm, which was selected as the maximum wavelength for UV-Visible Spectroscopy.[12]

Standard curve for ceftriaxone Sodium:

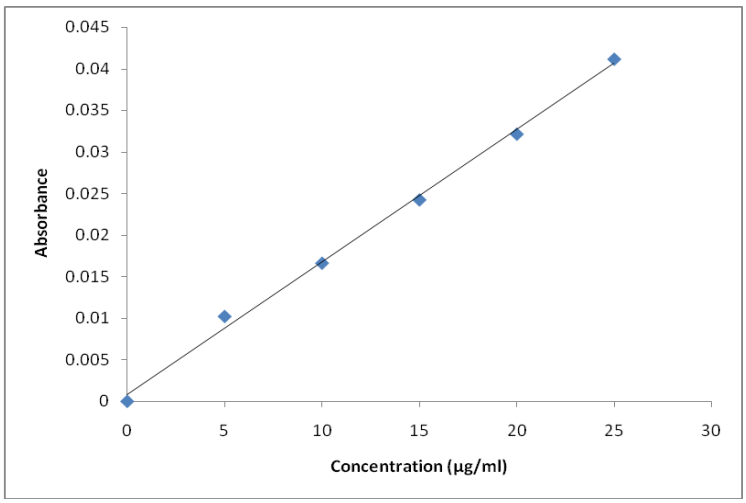

Fig-2 UV-Visible Spectroscopy

Table-1

Slope	0.001593
Regression coefficient	0.99682

Table-2

Concentration (µg/ml)	**Absorbance**
0	0
5	0.0102
10	0.0166
15	0.0242
20	0.0321
25	0.0411

Fourier Transformed Infrared Spectroscopy Analysis.

FTIR spectrum of the prepared nanoparticles revealing the chemical interaction between the components. All the ingredients were studied for compatibility between them. For that purpose infrared spectra of individual polymer (Fig-4) were compared with infrared spectra of drug polymer complex (Fig-5). FTIR studies for Ceftriaxone showed characteristic peaks at 3432.7 cm-1 (N-H stretching mode of H-bonded amide group), 1741 cm-1 (β-lactam C=O stretching vibrations) and 1592 cm-1 oxime C=N stretching vibrations). The

spectra for Ornidazole revealed peaks at 3258.14 cm-1 (O-H stretching vibrations),1536 cm-1(asymmetric NO2 stretching vibrations) and the C=O stretching mode at 1741 cm-1. The spectrum of pure chitosan (Fig-4) exhibited an amine deformation peak at 1600cm-1 and amide I carbonyl stretch at 1643cm-1. The peak for chitosan at 898 cm-1 is assigned to the saccharide structure [13,14].The IR spectral interpretation shows that the spectra obtained from the formulation (Fig-5) matches with original spectra of drug. Similarly characteristic peaks, for the polymers were also noticed in the formulation spectrum. There was no change of any characteristic peaks which confirms that the absence of chemical interaction between the drug and polymers.

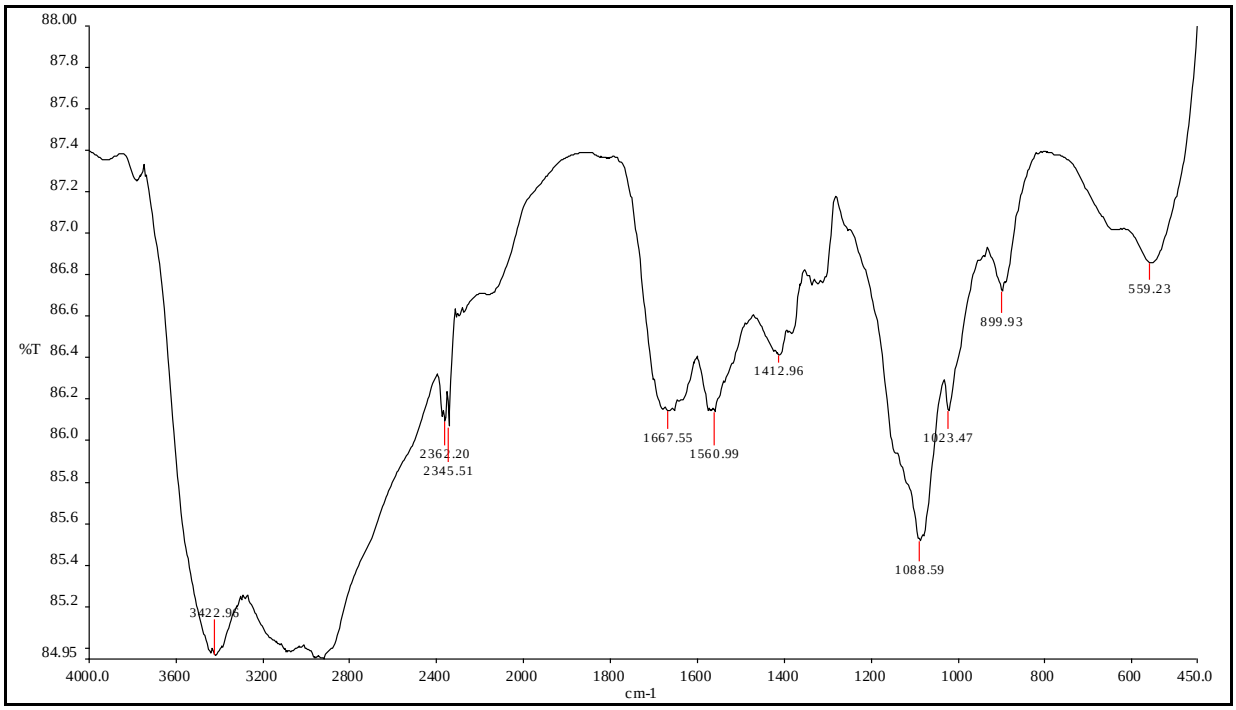

Fig-3 FTIR –Ceftriaxone Sodium

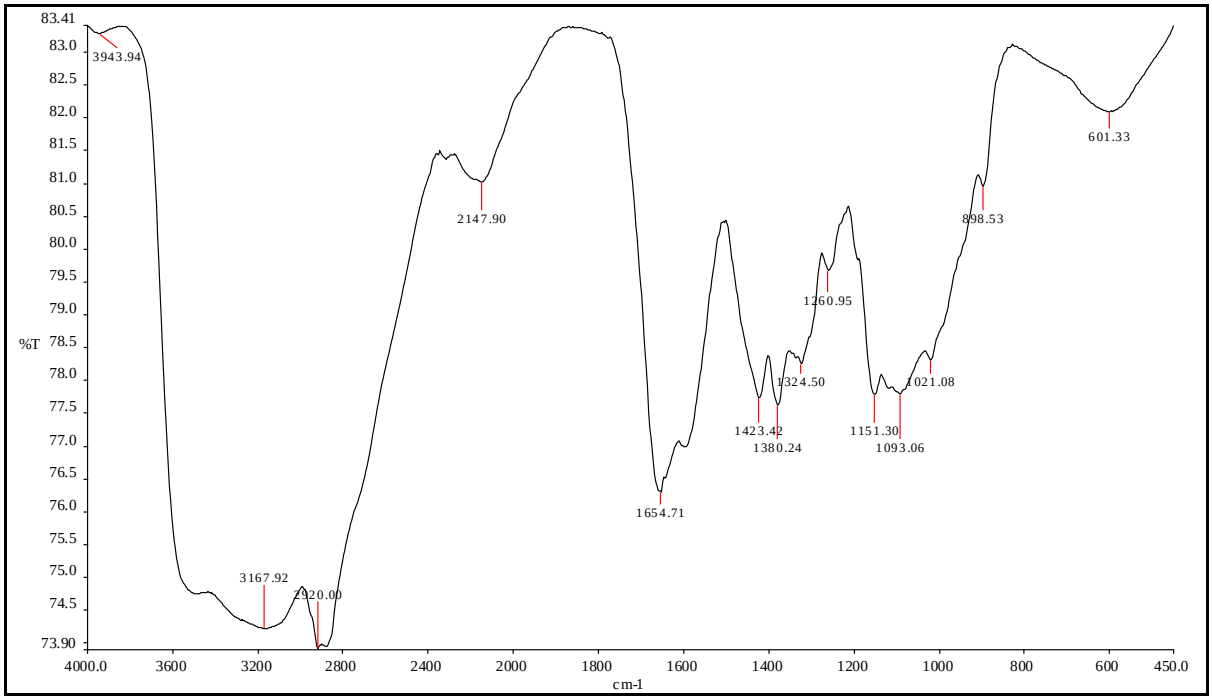

Fig- 4 FTIR-Chitosan

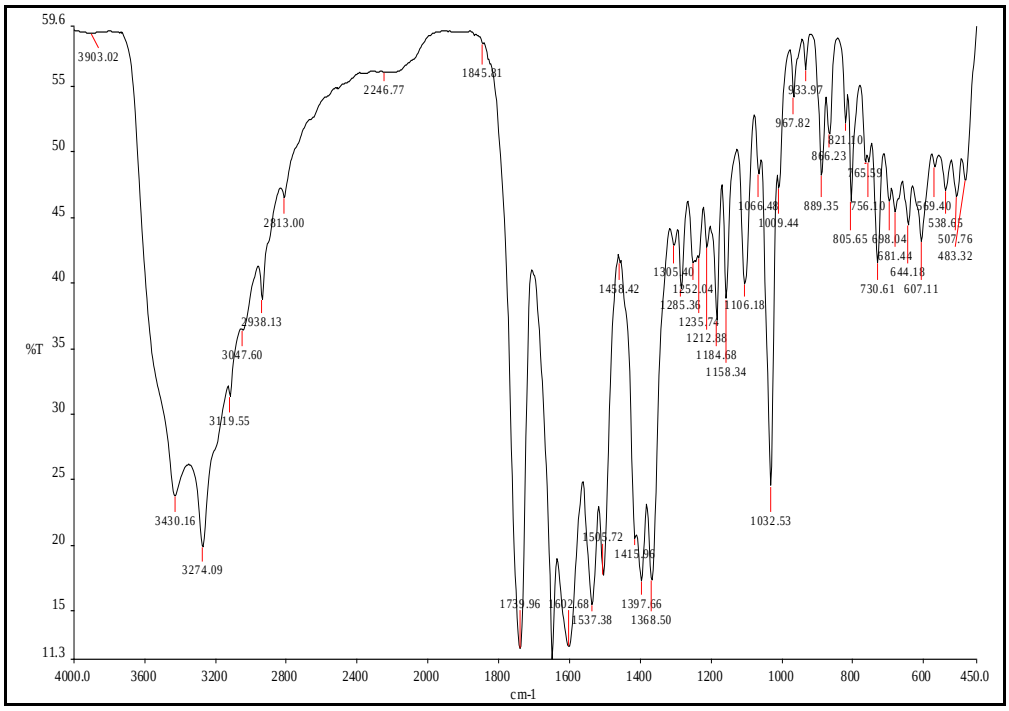

Fig-5 FTIR-Ceftriaxone sodium Chitosan Complex

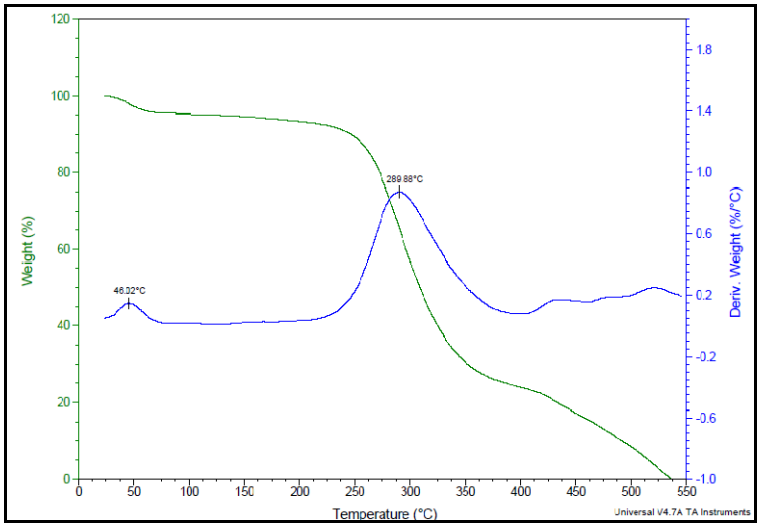

Fig-6 Thermo gravimetric Analysis

Fig- 6 shows the thermal analysis of drug combined with excipients. The Thermo gravimetric TGA is a technique in which, upon heating a material, its weight increases or decreases[15]. TGA measures a sample's weight as it is heated or cooled in a furnace. TGA decomposition information can be used to predict the useful product lifetimes of some polymeric materials. The sample is heated at three or more different heating rates. The use of the different heating changes the time scale of the decomposition event. Thermo gravimetric analysis (TGA) is a simple analytical technique which is used to study the thermal stability of the sample and their weight loss at different temperatures[16]. It also confirms the successful loading of CFXT within chitosan nano particle. We observed a four step decomposition pattern on Ceftriaxone loaded chitosan nano particle (Fig. 6). Initially, weight loss was observed at 58.63˚C, due to the release of water molecules. The second step in the curve weight loss at146.93˚C indicating the decomposition of CS and the third step was observed at 297.15˚C with the weight loss could be due to the decomposition of both CS .Finally the fourth step of decomposition was examined at635˚C of about 14.34% which might be due to the decomposition of pure ceftriaxone. By comparing the thermogram of ceftriaxone and chitosan nano particle, we confirmed the loading of ceftriaxone sodium within chitosan nano particle.

Conclusion:

The present study confirms that there is no chemical interaction between drug and excipient. From the results of FTIR and DSC methods, it is proven that FTIR and DSC are fast screening tools to check compatibility in early stages of a pre formulation process. Based on our results, all excipients were found to be compatible ceftriaxone sodium. It is conclude that the selected excipients can be further used for formulating ceftriaxone sodium chitosan coated nanoparticle

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