Antibiotic Cefepime with Antacid, Metal Complexation studied by UV Spectrophotometrically in addition to Exploration of Antimicrobial Activity, In-Vitro Demonstration

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Abstract

As a fourth generation of cephalosporins, cefepime shows very superior activity in opposition to gram - negative organisms like Pseudomonas aeruginosa in addition to gram – positive organisms like Staphylococcus aureus. It is very functional in the lower respiratory tract infection reasoned by Influenza, Aureus, Pneumonia as well as Urinary tract infections caused by the E. Coli, skin in addition to skin structure infections reasoned by S. epidermidis in addition to intra-abdominal infection. The principal rationale of present follow a line of the exploration was to search in vitro interactions of the cefepime with key metal salt also antacid to settle on the bioavailability in view of antimicrobial movement of cefepime following drug metal communications at the pH7.4. Cefepime is one of the cephalosporin drugs so as to be exercised to treat numerous different sorts of infections originated by bacteria. Since the existence of compelling the ligand may influence bioavailability of metal in blood and tissues, for that reason with the intention of study the handy interaction of the cefepime with vital elements in attendance in the body. Cefepime has been related with Zn, Mg as an in-vitro examination. Besides, the anti-microbial movement of drug along with the complexes was resolved. It has scrutinized that cefepime interrelates with metal and antacid on the pH 7.4 by plotting various uv spectrophotometric methods. This examine authenticates that there was the interaction between cefepime and metal, antacid which was authenticated by job’s plot technique furthermore by antimicrobial exploration. This was authenticated that region of inhibition of cefepime with Metal in addition to antacid condensed from 16 mm to 13 mm and 14 mm correspondingly. The typical cefepime disk also checked in opposition to Staphylococcus aureus.

Key Words: cefepime, spectrophotometry, antimicrobial action, complexation, job’s plot

Introduction

Cefepime is the indicated for the respiratory tract infections, soft tissue infections, skin in addition to urinary tract infections as well as febrile neutropenia [1]. Cefepime is the chemically 1 – [[(6R, 7R)-7 – [ 2 – (2 – amino – 4 – thiazyl) glyoxylamido] – 2 – carboxy – 8 – oxo – 5 thia – 1 – azabicyclo [4.2.0] oct – 2 – en – 3 – yl] methyl ] – 1 – methyl pyrrolidinium chloride, 72–(Z) – (0 – methylxime) monohydrchloride , monohydrate. This is the white to pale yellow powder extremely soluble in the water with molecular weight (MW) of 571.5 [2]. At this moment drug interface be capable of the simply be distinct as the interaction connecting a medicine in addition to additional substance with intention of the prevent medicine commencing the stage as expected. These correlations may happen by reason of be short of the knowledge regarding the principle ingredients associated in related substances [3].Two medicines are antagonistic at what time their interaction occurs a reduce in special effects of one or else both of medicines. The dissimilar responses of receptor to act of a medicine has effected in number of arrangements, which use expressions such as "partial agonist", "competitive agonist" etc. This is even expected that a lot of authors would mismanage any given arrangement [4] Commonly iron complexes were used in convey of oxygen in human blood as well as tissues. A mature at rest takes 250ml of uncontaminated oxygen for each minute, these oxygen conceded by metal complex convey system recognized heame, alloying oxygen to go away the blood at what time it arrives the tissue [5]. Antibiotic and metal interaction and successfully found there after interaction result. Also, the antimicrobial activity of drug and the metals complexes were determined. This has been seen that the antibiotic interacts along with metal at the pH 7.4. The different essential metal intricate of the many drugs has been synthesized in addition to characterized by the techniques like NMR, UV, atomic absorption, FT-IR as well as elemental analysis. Spectroscopic, IR Spectroscopic, disk diffusion method, Biological assay studies of complexes [6]. On the other hand in this interaction there uses metals complex which are interaction with drug into our body. And have been use there various type of bacteria for finding zone of inhibition. Some paper there uses methanol and ethanol for disk diffusion result clearly showing [7].
Materials & Methods

| S. No | Name                                | Source                                                  |
|-------|-------------------------------------|---------------------------------------------------------|
| 1     | cefepime                            | Gift samples from Renata pharmaceuticals Ltd.           |
| 2     | Zinc Sulphate (Metal)               | Merck Ltd, Mumbai, India                                |
| 3     | Magnesium Hydroxide (Antacid)       | Merck Ltd, Mumbai, India                                |
| 4     | Sodium di-hydrogen phosphate        | USTC, Foys lake, Chittagong, dept. of pharmacy          |
| 5     | Disodium hydrogen phosphate         | USTC, Foys lake, Chittagong, dept. of pharmacy          |
| 6     | Phosphate Buffer                    | USTC, Foys lake, Chittagong, dept. of pharmacy          |

| Name                | Model     | Source                        |
|---------------------|-----------|-------------------------------|
| pH Meter            | P11-211   | Hanna, Romania                 |
| UV spectrophotometer| T80       | PG instrument Ltd, England    |
| Electronic Balance  | AL-204    | Mettler toledo, Switzerland    |
| Pipette             |           | Fischer scientific, Germany   |

Cefepime stock solution 250 millilitre of 1x10\(^{-2}\) Molar was ready by softening 1.386 gm of cefepime solution in the 250 millilitre of the demineralized water (DMW) in a 250 millilitre volumetric flask. The reserve solution was thinned to desired potency by the buffer solution [8].

**Preparation of metal solutions:**

For the grounding of 0.01 Molar metal solution like zinc sulfate hepta hydrate (exactly 0.28754 gm) was evaluated exactly in addition to initiated with the assist of the funnel in a 100 ml volumetric flask, softened in DM water in addition to framework to the mark by the similar solvent. These prime solutions were additional diluted ten creases in the equivalent solvent along with the concluding solutions were 0.0001 M concentration.

**Preparation of antacid solutions:**

For the preparation of 0.01 M antacid solution, Mg(OH)\(_2\) (0.0740 gm) was evaluated accurately in addition to initiated with the facilitate of funnel in 100 millilitre volumetric flask, softened in demineralized water furthermore construct up to mark by the equal solvent. These primary solutions were further diluted ten folds in the same solvent and the final solutions were 0.0001 M concentration.

**Grounding of the buffer solutions:**

To get ready buffer solution 1.76 gram of the disodium hydrogen phosphate were softened in the demineralized water by 2.43 gtam of the solution dihydrogen phosphate in addition to pH was altered to 7.4 as well as volume was completed to 1000 millilitre with the equivalent solution.

**Grounding of the typical curve of the cefepime**

cefepime reserve solution at the pH 7.4 in addition to concentration of the 1x10\(^{-3}\) Molar was inserted in unlike concentrations to the 10 test tubes, to have subsequent concentrations like 9x10\(^{-5}\) Molar, 8x 10\(^{-5}\) Molar, 7x10\(^{-5}\) Molar, 6x10\(^{-5}\) Molar, 5x10\(^{-5}\) Molar, 4x10\(^{-5}\) Molar, 3x10\(^{-5}\) Molar, 2x10\(^{-5}\) Molar, 1x10\(^{-5}\) Molar. Now the solutions were suitably mixed. Then the absorbance values of solutions were established at 515 nm through UV spectrometer [9].

Using Disc Diffusion Process:

Solution of celebrated concentration (3µg/ml) of trial samples are completed through dissolving measured quantity of the trials in calculated amount of solvents. Dried in addition to sterilized filter term paper discs (6 mm as a diameter) are subsequently impregnated with recognized amounts of trial substances by using micropipette. Discs holding the test substances are positioned on the nutrient agar media homogeneously seeded by the test organism, typical antibiotic discs along with blank discs were utilized as positive furthermore negative control. These plates now are kept at the low temperature like 4°C for the 24 hours to permit maximum diffusion. Throughout this time desiccated discs suck up water from surrounding medium furthermore the trial materials dissolve along with spread out of the trial disc. The diffusion happens according to physical law so as to controls diffusion of the molecules during agar gel. Consequently there was a gradual alter of trial substances concentrations in medium adjoining the disc [10].

**Results and Discussions**

From the subsequent Table 3, this can monitor to the absorbance of the cefepime enhances with the enhancing concentration in keeping with Beer Lambert’s equation.
From the above we can observe that the absorbance of cefepime is different when it interacts with Mg(OH)$_2$.

From the Table 5, it can observe that the absorbance of cefepime is different when it interacts with Mg(OH)$_2$.

| Wavelength/nm | Absorbance of Cefepime | Absorbance of Cefepime with Mg(OH)$_2$ |
|---------------|------------------------|---------------------------------------|
| 200           | 0.038                  | 0.544                                 |
| 240           | 0.040                  | 0.777                                 |
| 280           | 0.340                  | 0.663                                 |
| 320           | 0.180                  | 0.324                                 |
| 360           | 0.107                  | 0.183                                 |
| 400           | 0.030                  | 0.093                                 |
| 440           | 0.035                  | 0.136                                 |
| 480           | 0.066                  | 0.148                                 |
| 520           | 0.089                  | 0.170                                 |
| 560           | 0.096                  | 0.179                                 |
| 600           | 0.126                  | 0.190                                 |
| 640           | 0.137                  | 0.194                                 |

Table 5. Combined Spectral analysis of cefepime with ZnSO$_4$.7H$_2$O.

From the Table 6, it can observe that interaction between drug and metal may lead to form complexes which have different light absorption capacity and spectrum pattern is altered. So any alteration and spectrum behavior is regarded as a tool for primary interaction from the spectral studies.

Outcome of the metals on cefepime by Job’s technique of incessant variation:

The molar proportions of complexes of the cefepime by metal salt were calculated approximately through Job’s method. The examined absorbance rates were calculated in the pH 7.4 at diverse concentration like 1x10$^{-5}$ to 9x10$^{-5}$ Molar of cefepime by metal salt. Then Job’s plots at the pH were acquired through plotting absorbance variation against mole portion of drug.

From the Table 7, it can observe that cefepime forms strong 1:1 complexes with zinc sulfate hepta hydrate which is indicated as inverted ‘V’ shaped curve.

| Concentration of cefepime Mx10$^{-5}$ | Absorbance of cefepime A | Concentration of ZnSO$_4$.7H$_2$O Mx10$^{-5}$ | Absorbance of ZnSO$_4$.7H$_2$O B | Absorbance of mixture C | Absorbance difference D=(A+B)-C |
|--------------------------------------|--------------------------|-----------------------------------------------|---------------------------------|-------------------------|--------------------------------|
| 1                                    | 0.573                    | 9                                             | 0.188                           | 0.111                   | 0.650                          |
| 2                                    | 0.581                    | 8                                             | 0.187                           | 0.109                   | 0.659                          |
| 3                                    | 0.595                    | 7                                             | 0.188                           | 0.109                   | 0.674                          |
| 4                                    | 0.604                    | 6                                             | 0.189                           | 0.112                   | 0.681                          |
| 5                                    | 0.617                    | 5                                             | 0.190                           | 0.111                   | 0.696                          |
| 6                                    | 0.624                    | 4                                             | 0.193                           | 0.128                   | 0.689                          |
| 7                                    | 0.631                    | 3                                             | 0.182                           | 0.125                   | 0.688                          |
| 8                                    | 0.640                    | 2                                             | 0.180                           | 0.136                   | 0.684                          |
| 9                                    | 0.645                    | 1                                             | 0.178                           | 0.150                   | 0.673                          |

Table 7. Values of Job’s plot of cefepime with ZnSO$_4$.7H$_2$O.
From the above we can observe that cefepime forms strong 1:1 complexes with Mg(OH)$_2$ which is indicated as inverted ‘v’ shaped curve.

| Cefepime | Cefepime with ZnSO$_4$.7H$_2$O | Cefepime with Mg(OH)$_2$ |
|----------|-------------------------------|--------------------------|
| 0.573    | 0.188                         | 0.091                    |
| 0.581    | 0.187                         | 0.087                    |
| 0.595    | 0.188                         | 0.094                    |
| 0.604    | 0.189                         | 0.097                    |
| 0.617    | 0.190                         | 0.104                    |
| 0.624    | 0.193                         | 0.098                    |
| 0.631    | 0.182                         | 0.093                    |
| 0.640    | 0.180                         | 0.086                    |
| 0.645    | 0.178                         | 0.084                    |

Table 9. Combined absorbance of drug with different metal & antacid:

### Antimicrobial reading

The antimicrobial effectiveness of the trial agents is calculated by their action to avoid the enlargement of microorganisms neighboring discs which provides clear precinct of inhibition. Later than incubation, the antimicrobial actions of the trial materials were concluded through measuring diameter of zones of the inhibition inside millimeter through a crystal clear mm scale. The trial samples were examined in opposition to Staphylococcus aureus. The typical cefepime disk also checked in opposition to staphylococcus aureus. The consequences of the antimicrobial action, calculated in view of diameter of the zone of the inhibition in the mm were demonstrated in table 10.

| Bacteria Used                       | Standard Disk (Zone of inhibition/mm) | Sample Disk (Zone of inhibition) |
|-------------------------------------|---------------------------------------|----------------------------------|
| Staphylococcus aureus               | 16mm                                  | Cefepime+ZnSO$_4$.7H$_2$O 13mm   |
| Staphylococcus aureus               | 16mm                                  | Cefepime+Mg(OH)$_2$ 14mm         |

Table 10. Diameter of zone of inhibition

Antimicrobial sensitivity testing of cefepime against Staphylococcus aureus after interacting with ZnSO$_4$.7H$_2$O and Mg(OH)$_2$ solution respectively. Now it was proved that zone of the inhibition of the cefepime through Metal and antacid Zn, Mg reduced from 16 mm to 14 mm & 13mm correspondingly due to the metal, antacid and drug interaction.

### Conclusion

Though, there were some limitations in this research work like proper financial support from any side, active pure drug collection was not easy in Bangladesh. Eventually it has been overcome. The sophisticated spectrophotometric technique is easy, straight as well as worthwhile for the fortitude of drug. Commencing this spectral reading, this has been observed that cefepime provides a spiky peak at the 585 nm. At what time Zinc Sulfate furthermore antacid solution, Mg(OH)$_2$ combined with cefepime 1:1 ratio and the strength of peak alters extremely and absorption features are changed due to the interaction although the position of complex do not change. Then antimicrobial viewing of an mediator is crucial to find out its spectrum in opposition to various natures of the pathogenic microorganisms. The Job’s plot have provided the molar percentage of the complexes of cefepime through Zinc Sulfate in addition to antacid solution like Mg(OH)$_2$ designated as inverted ‘v’ shaped curves. These curves can indicate well-built kinetics of the complexation between cefepime by Zinc Sulfate along with antacid solution like magnesium hydroxide. The trial samples were checked in opposition to Staphylococcus aureus. The typical cefepime disk also checked in opposition to Staphylococcus aureus. It was examined that antimicrobial action of the cefepime reduces when it structures complexes through ZnSO$_4$.7H$_2$O in addition to antacid solution like magnesium hydroxide. Thus, through antimicrobial examination it was proved that zone of the inhibition of the cefepime through Metal and antacid Zn, Mg reduced from 16 mm to 13 mm & 14mm correspondingly.

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