Complexation and Interaction Study of Antibiotic Cefixime with Essential Metals by Spectrophotometric Method

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Citation: Rubel MD, Akij MDS and Islam MDS. Complexation and interaction study of antibiotic cifixime with essential metals by spectrophotometric method (2019) Edelweiss Pharma Analy Acta 1: 14-17.

Abstract
This research work designates of interaction and complexation studies of Cefixime with essential metal. Cefixime involved the third generation drug of penicillin. In vitro analysis, Cefixime must be interacted with metal like Mg²⁺ and Mn²⁺. At pH 7.4, this study was done in different ratios of cefixime with metal and antacid both at room temperature 25°C. By this study, it is investigated that drug Cefixime is complexed with metal as well as antacid which is confirmed by jobs plot. This experiment was carried out by using ultra violet spectrophotometer. The microbial sensitivity test is important to know whether there is any change in the effectiveness of Cefixime after the interaction with metals. There was a remarkable change in the effectiveness of Cefixime and its complexes. This research work confirms that there was interaction between Cefixime with Metals like Mg²⁺ and Mn²⁺ which was confirmed by Jobs plot method by spectrophotometric assay.

Keywords: Cefixime, Complexation, Interaction, Jobs Plot.

Introduction

Drug-drug, drug-metal interaction is a common phenomenon. A drug interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agent. These unwanted and unforeseen interactions are adverse and undesirable but there are other interactions that can be beneficial and valuable, such as the deliberate co-prescription of antihypertensive drugs and diuretics in order to achieve antihypertensive effects possibly not obtainable with either drug alone. The mechanisms of both types of interaction, whether adverse or beneficial, are often very similar [1].

There are different types of drug interactions: Drug-drug interaction, Drug-herbal interaction, Food-drug interaction etc. Drug interactions are complex and chiefly unpredictable. A known interaction may not occur in every individual. This can be explained because there are several factors that affect the likelihood that a known interaction will occur.

Zinc is an important co-factor for several enzymatic reactions in the human body, vitamin B12 has cobalt atom and its core, and hemoglobin contains iron. Like Cu, Mn, Se, Cr, Mo are all trace elements, which are important in the human diet. Another subset of metals include those used in therapeutically in medicine, Al, Bi, Au, Ga, Li and Ag are all part of medical armamentarium [2-4].

Humans need a certain amount of certain metals to function normally. Most metals are used as cofactors or prosthetics in enzymes, catalyzing specific reactions and serving essential roles. Anemia symptoms are caused by lack of a certain essential metal. Anemia can be associated with malnourishment or faulty metabolic processes, usually caused by a genetic defect. The metal complexes can be utilized for the transport of selected organic chemotherapeutic drugs to target organs, or for the decarboxylation of those toxic organic compounds which are able, before or after metabolic activation of reacting with metals or 1:1 complexes.

It is emphasized that degree to which metal ions interact in vivo should employ the conditional constants which take into account competition from other ions specially Ca²⁺, H⁺ and OH⁻. The genotoxic consequences of the virus chemical factors involved in chelation, along with examples; kinetics, stabilization or oxidation state, lipophilicity, the mixed ligand formation, are discussed. Cefixime is a semi-synthetic, moderate spectrum of penicillin group of antibiotic.

Cefixime is an antibiotic that is used for the treatment of a variety of bacterial infections, skin and urinary tract infections, pneumonia, and strep throat. It binds to one of the penicillin binding proteins which inhibit the final transpeptidation step of the peptidoglycan synthesis in the bacterial cell wall, thus inhibiting biosynthesis and arresting cell wall assembly resulting in bacterial cell death. Cefixime is a broad spectrum antibiotic and is commonly used to treat bacterial infections of the ear, urinary tract, and upper respiratory tract [5-10].
Materials and Methods

In this study, all the chemical substances, reagents used here were pure and were kept under sorted under suitable conditions.

**Preparation of stock solution:** In this study, 250 ml of 1×10⁻² stock solution of Cefixime was measured by 0.16902 gm of Cefixime in 250 ml of demineralised water in a 250 ml volumetric flask. This solution was further diluted to expected concentration by using buffer solution.

**Preparation of metal solution:** In this study, 0.1M metal solution, Magnesium sulphate hepta hydrate, MgSO₄·7H₂O (0.24648gm) was measured perfectly as well as the last solution were 0.01 M concentration.

**Preparation of buffer solution:** In this study, for the preparation of buffer solution, firstly 8.06 gm of Na₂H₂PO₄ was mixed in demineralized water with 1.05 gm of NaH₂PO₃ and then pH 7.4 was confirmed [12].

**Preparation of standard curve of Cefixime:** In this study, Cefixime stock solution at pH 7.4 and concentration 1×10⁻⁵M was mixed in different concentrations like: 9×10⁻⁵M, 8×10⁻⁵M, 7 ×10⁻⁵M, 6×10⁻⁵M, 5×10⁻⁵M, 4×10⁻⁵M, 3×10⁻⁵M, 2×10⁻⁵M, 1×10⁻⁵M. The absorbance volume of the solutions was determined at 256 nm by UV spectrometer [13].

| No | Name                           | Source                                                |
|----|--------------------------------|-------------------------------------------------------|
| 1  | Cefixime                       | Gift samples from alivon laboratories ltd             |
| 2  | Magnesium sulfate              | Merck ltd, Mumbai, India                              |
| 3  | Manganese sulfate              | 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        |

**Table 1:** List of chemicals and reagents.

All the equipment and instruments used throughout the study are given in the following table along with their source.

| Name                        | Model       | Source                        |
|-----------------------------|-------------|-------------------------------|
| PH meter                    | PH-211      | Hanna, Romania                |
| Electronic balance          | AL-204      | Mettler toledo, Switzerland   |
| Micropipette                |             | Fischer scientific, Switzerland |

**Table 2:** List of instruments and equipment.

From the above Table, we can observe that the absorbance of Cefixime increases with increasing concentration according to Beer Lambert's law.

| Mx10⁻⁵ | Absorbance |
|--------|------------|
| 1      | 0.051      |
| 2      | 0.068      |
| 3      | 0.102      |
| 4      | 0.118      |
| 5      | 0.135      |
| 6      | 0.184      |
| 7      | 0.202      |
| 8      | 0.237      |
| 9      | 0.272      |

**Table 3:** Standards curve of Cefixime.

Results and Discussion

From the above table we can observe that the absorbance of Cefixime varies at different wavelength.

| Wavelength /nm | Absorbance of Cefixime | Absorbance of Cefixime+MgSO₄·7H₂O |
|----------------|-------------------------|----------------------------------|
| 200            | 1.6                     | 1.31                             |
| 210            | 0.88                    | 0.95                             |
| 220            | 0.66                    | 0.92                             |
| 230            | 0.26                    | 0.88                             |
| 240            | 0.63                    | 0.63                             |
| 250            | 0.8                     | 0.54                             |
| 260            | 0.94                    | 0.5                              |
| 270            | 0.66                    | 0.38                             |
| 280            | 0.54                    | 0.031                            |
| 290            | 0.008                   | 0.008                            |

**Table 4:** Absorbance of Cefixime at different wavelength.

From the above table we can observe that the absorbance of Cefixime is different when it interacts with MgSO₄·7H₂O due to drug metal interaction.

| Wavelength/nm | Absorbance of Cefixime | Absorbance of Cefixime+MnSO₄·H₂O |
|---------------|-------------------------|----------------------------------|
| 200           | 1.6                     | 0.89                             |
| 210           | 0.88                    | 0.85                             |
| 220           | 0.66                    | 0.64                             |
| 230           | 0.26                    | 0.53                             |
| 240           | 0.64                    | 0.78                             |
| 250           | 0.8                     | 0.63                             |
| 260           | 0.94                    | 0.33                             |
| 270           | 0.66                    | 0.2                              |
| 280           | 0.54                    | 0.046                            |
| 290           | 0.008                   | 0.014                            |

**Table 5:** Spectral analysis of Cefixime with MgSO₄·7H₂O.

From the above table we can observe that the absorbance of Cefixime is different when it interacts with MnSO₄·H₂O.

This table shows that absorbance of cefixime is quite different from absorbance of Cefixime and metal complexes. The intensity of the peak of Cefixime changes remarkably i.e. absorption characteristics are altered due to interaction but the position of the compound does not shift. Interaction between drug and metal may lead to form complexes which have different light absorption capacity and spectrum pattern is altered.

Effect of metals on Cefixime by Jobs method of continuous variation: The molar ratios of the complexes of Cefixime with metal salts were estimated by jobs method of continuous variation. The observed absorbance values were measured in pH 7.4 at various concentrations (1×10⁻⁵ to 9×10⁻⁵M) of Cefixime and metal salts at 2310 nm.
The Jobs plots at pH 7.4 were obtained by plotting absorbance difference against the mole fraction of the drug which is presented in the following table.

| Concentration of Cefixime M×10^-5 | Absorbance of Cefixime A | Concentration of MnSO4.H2O M×10^-5 | Absorbance of MnSO4.H2O B | Absorbance of mixture C | Absorbance difference D=(A+B)-C |
|------------------------------------|--------------------------|-----------------------------------|---------------------------|------------------------|------------------------------|
| 1                                  | 0.052                    | 9                                 | 0.07                      | 0.044                  | 0.078                        |
| 2                                  | 0.069                    | 8                                 | 0.073                     | 0.049                  | 0.093                        |
| 3                                  | 0.103                    | 7                                 | 0.079                     | 0.057                  | 0.125                        |
| 4                                  | 0.119                    | 6                                 | 0.085                     | 0.062                  | 0.142                        |
| 5                                  | 0.136                    | 5                                 | 0.135                     | 0.068                  | 0.203                        |
| 6                                  | 0.185                    | 4                                 | 0.112                     | 0.061                  | 0.235                        |
| 7                                  | 0.203                    | 3                                 | 0.102                     | 0.126                  | 0.179                        |
| 8                                  | 0.238                    | 2                                 | 0.057                     | 0.157                  | 0.138                        |
| 9                                  | 0.273                    | 1                                 | 0.013                     | 0.188                  | 0.098                        |

Table 7: Values of job plot of Cefixime and MnSO4.H2O.

From the above table we can observe that Cefixime forms strong 1:1 complexes with manganese Sulfate mono hydrate which is indicated as ^ shaped curve which indicates confirm interaction and complexation with drug and metal.

| Concentration of Cefixime M×10^-5 | Absorbance of Cefixime A | Concentration of MnSO4.H2O M×10^-5 | Absorbance of MnSO4.H2O B | Absorbance of mixture C | Absorbance difference D=(A+B)-C |
|------------------------------------|--------------------------|-----------------------------------|---------------------------|------------------------|------------------------------|
| 1                                  | 0.052                    | 9                                 | 0.206                     | 0.079                  | 0.179                        |
| 2                                  | 0.069                    | 8                                 | 0.195                     | 0.073                  | 0.192                        |
| 3                                  | 0.103                    | 7                                 | 0.187                     | 0.083                  | 0.213                        |
| 4                                  | 0.119                    | 6                                 | 0.183                     | 0.056                  | 0.246                        |
| 5                                  | 0.136                    | 5                                 | 0.177                     | 0.018                  | 0.295                        |
| 6                                  | 0.185                    | 4                                 | 0.113                     | 0.040                  | 0.258                        |
| 7                                  | 0.203                    | 3                                 | 0.098                     | 0.072                  | 0.229                        |
| 8                                  | 0.238                    | 2                                 | 0.053                     | 0.097                  | 0.194                        |
| 9                                  | 0.273                    | 1                                 | 0.020                     | 0.129                  | 0.164                        |

Table 8: Values of job plot of Cefixime and MnSO4.H2O.

From the above table we can observe that Cefixime forms strong 1:1 complexes with manganese Sulfate mono hydrate which is indicated as ^ shaped curve which indicates confirm interaction and complexation with drug and metal.

| Cefixime | Cefixime+MgSO4.7H2O | Cefixime+MnSO4.7H2O |
|----------|---------------------|---------------------|
| 0.052    | 0.044               | 0.079               |
| 0.069    | 0.049               | 0.073               |
| 0.103    | 0.057               | 0.083               |
| 0.119    | 0.062               | 0.056               |
| 0.136    | 0.068               | 0.018               |
| 0.185    | 0.061               | 0.04                |
| 0.203    | 0.126               | 0.072               |
| 0.238    | 0.157               | 0.097               |
| 0.273    | 0.188               | 0.129               |

Table 9: Combined absorbance of drug with different metal.

The above table shows that the absorbance of Cefixime differs from the absorbance of Cefixime + MgSO4.7H2O and Cefixime + MnSO4.7H2O due to interaction and complexation with antibiotic and metals.

Conclusion

In this research work, the interaction of an important antimicrobial drug, Cefixime and MgSO4.7H2O and also Cefixime, MnSO4.H2O at 7.4 by a variety of physical method like inspection of spectral behavior, Jobs method of continuous variation.

From spectral study, it has been observed that Cefixime gives a sharp peak at 256 nm. When MgSO4.7H2O and MnSO4.H2O salt mixed with Cefixime at 1:1 ratio, the intensity of the peak changes remarkably specifically absorbance decreases sharply.

Thats why absorption characteristics are altered due to interaction but the position of the compound does not shift at all. The Jobs plot has given the molar ratio of complexes of Cefixime and MgSO4.7H2O and also Cefixime, MnSO4.H2O. At pH 7.4 Cefixime forms strong 1:1 complexes with metals MgSO4.7H2O and MnSO4.H2O indicated as ^ shaped curves.

These curves indicate strong kinetics of complexation between Cefixime with MgSO4.7H2O and Cefixime with MnSO4.H2O. When drug individually act with metals MgSO4.7H2O and MnSO4.H2O curve of their absorbance are verify.

By this research work, it helps in the study of selection the best dosage form for better treatment which can be justified by the future in vivo analysis. And definitely very important in adjusting the effective dose and dose ranges.

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