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# *In-Vitro* Interaction of Cefpodoximeproxetil with Different Essential Metal, Antacids and Investigation of Antimicrobial Activity

MD. Shahidul Islam*[1], Nobina Akter[1]
[*1]Assistant Professor, Department of Pharmacy, University of Science & Technology Chittagong (USTC)
[1]Department of Pharmacy, University of Science and Technology Chittagong
Email address: [*1]s_i_liton@yahoo.com

***Abstract*—** *The research work comprises of interaction studies of cefpodoximeproxetil with essential metals and investigation of antimicrobial activity of cefpodoximeproxetil. Cefpodoximeproxetil is included among the cephalosporins drug class which is active against a wide range of gram positive and negative bacteria.Since the presence of compelling ligand may affect the bioavailability of a metal in the blood or tissues, therefore in order to study the probable interaction of cefpodoximeproxetil with essential and trace elements present in the body. Cefpodoximeproxetil has been interacted with Mg $(OH)_2$ (magnesium hydroxide), $CaCO_3$ (calcium carbonate) antacids and Zn metal salts in vitro. All the reaction conditions were simulated to natural environment. Also the antimicrobial activity of the drug and the complexes were determined. There is a effect of pH on drug metal complexation. It has observed that cefpodoximeproxetil interacts with metal on a PH 7.4, the stability constant of these complexes were determined in order to evaluate their possible in vivo implications. In order to investigate the number of metal &antacid involved in the complexion with cefpodoximeproxetil complexes were elucidated by exploiting various spectrophotometric methods. The ultraviolet studies of these complexes were carried out and compared. Here due to interaction of both cefpodoximeproxetil with metal & antacid, it is shown that the standard absorbance of cefpodoximeproxetil is quite different from the absorbance of mixture of both drug-metal & drug-antacid. Otherwise, in antimicrobial study we have seen the same thing that is due to their interaction the antimicrobial effect or activity of cefpodoximeproxetil is reduced. The standard zone of inhibition of cefpodoximeproxetil is 17mm but since cefpodoximeproxetil is interacted with metal[$ZnSO_4.7H_2O$] & antacid [$Mg(OH)_2$], [$CaCO_3$] it is reduced into 14mm, 10mm, 13mm.*

## I. INTRODUCTION

A drug interaction is a situation in which a substance (usually another drug) affects the activity of a drug when both are administered together. This action can be synergistic (when the drug's effect is increased) or antagonistic (when the drug's effect is decreased) or a new effect can be produced that neither produces on its own. Typically, interactions between drugs come to mind (drug-drug interaction). However, interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and medicinal plants or herbs (herb-drug interactions). People taking antidepressant drugs such as monoamine oxidase inhibitors should not take food containing tyramine as hypertensive crisis may occur (an example of a drug-food interaction). These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances.[1] When the interaction causes an increase in the effects of one or both of the drugs the interaction is called a synergistic effect. An "additive synergy" occurs when the final effect is equal to the sum of the effects of the two drugs (Although some authors argue that this is not true synergy). When the final effect is much greater than the sum of the two effects this is called enhanced synergy. This concept is recognized by the majority of authors, although other authors only refer to synergy when there is an enhanced effect. These authors use the term "additive effect" for additive synergy and they reserve use of the term "synergistic effect" for enhanced synergy. The opposite effect to synergy is termed antagonism. Two drugs are antagonistic when their interaction causes a decrease in the effects of one or both of the drugs.[2], [3] Both synergy and antagonism can both occur during different phases of the interaction of a drug with an organism, with each effect having a different name. For example, when the synergy occurs at a cellular receptor level this is termed agonism, and the substances involved are termed *agonists*. On the other hand, in the case of antagonism the substances involved are known as inverse agonists. The different responses of a receptor to the action of a drug has resulted in a number of classifications, which use terms such as "partial agonist", "competitive agonist" etc. These concepts have fundamental applications in the pharmacodynamics of these interactions. The proliferation of existing classifications at this level, along with the fact that the exact reaction mechanisms for many drugs are not well understood means that it is almost impossible to offer a clear classification for these concepts. It is even likely that many authors would misapply any given classification. [4] It is possible to take advantage of positive drug interactions. However, the negative interactions are usually of more interest because of their pathological significance and also because they are often unexpected and may even go undiagnosed. By studying the conditions that favor the appearance of interactions it should be possible to prevent them or at least diagnose them in time. The factors or conditions that predispose or favor the appearance of interactions include [5] Old age, Polypharmacy,Genetic factors etc. Drug dependent factors: [6] Narrow therapeutic index, Steep dose-response curve, Saturable hepatic metabolism etc. Cefpodoximeproxetil is a broad spectrum



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third-generation cephalosporin, which reveals potent antibacterial activity against both Gram-positive and Gram-negative bacteria, and high stability in the presence of beta-lactamases. Low concentrations of cefpodoxime inhibit most respiratory pathogens [7]. This drug has very good in-vitro activity against Enterobacteriaceae, Hemophilus spp. and Moraxella spp., including beta-lactamase producers and many strains resistant to other oral agents. It also has activity against Gram-positive bacteria, especially against streptococci. It has no activity against enterococci. It is well tolerated and is one of the first third-generation cephalosporin's to be available in oral form [8].

## II. Material and Methods

All the chemicals used here were analytical grade and were sorted under optimum storage conditions. The experimental mixtures and solutions were prepared in standard volumetric flasks about one hour prior to recording the data.

*Preparations of Stock Solution*

Cefpodoximeproxetil solution 250 ml of $1\times10^{-2}$ was prepared by dissolving 0.8735 gm of cefpodoximeproxetil in 250 ml of demineralized water in a 250 ml volumetric flask. The stock solution was diluted to desired strength by buffer solution.

*Preparation of Metal Solutions*

For the preparation of 0.1M metal solution, Zinc sulfate hepta hydrate (0.0287gm), antacids like Magnesium hydroxide (0.058531gm) and Calcium carbonate (0.1000 gm) were weighted accurately and introduced with the help of funnel in 100 ml volumetric flask separately, dissolved in demineralised water and make up to the mark with the same solvent. These primary solutions were further diluted ten folds in the same solvent and the final solutions were 0.01 M concentration.

*Preparation of Buffer Solution*

To prepare buffer solution 1.76 gm of disodium hydrogen phosphate was dissolved in demineralized water with 2.43 gm of sodium di hydrogen phosphate and pH was adjusted to 7.4 and the volume was made to 1000 ml with the same solution.

*Preparation of standard curve of cefpodoximeproxetil*

Cefpodoximeproxetil stock solution at pH 7.4 and concentration of $1\times10^{-5}$ M was added in different concentrations to ten test tubes, to have the following concentrations: $9\times10^{-5}$M, $8\times10^{-5}$M, $7\times10^{-5}$M, $6\times10^{-5}$M, $5\times10^{-5}$M, $4\times10^{-5}$ M, $3\times10^{-5}$M, $2\times10^{-5}$M, $1\times10^{-5}$M.

The solutions were then properly mixed. The absorbance values of the solutions were determined at 235 nm by UV spectrophotometer. As a control of reference sample, phosphate buffer solution of pH 7.4 was used. The standard curve was obtained by plotting the absorbance values against the corresponding concentrations.

*Disc Diffusion Method*

Solution of known concentration (3µg/ml) of the test samples are made by dissolving measured amount of the samples in calculated volume of solvents. Dried and sterilized filter paper discs (6 mm diameter) are then impregnated with known amounts of the test substances using micropipette. Discs containing the test material are placed on nutrient agar medium uniformly seeded with the test microorganism, Standard antibiotic discs and blank discs (impregnated with solvent) are used as positive and negative control. These plates are then kept at low temperature ($4^oC$) for 24 hours to allow maximum diffusion. During this time dried discs absorb water from the surrounding media and then the test materials dissolve and diffuse out of the sample disc. The diffusion occurs according to the physical law that controls the diffusion of molecules through agar gel. As a result there is a gradual change of test materials concentrations in the media surrounding the disc. The plates are then incubated at $37^oC$ for 24 hours to allow maximum growth of the organism. If the test materials have any antimicrobial activity, it will inhibit the growth of the microorganisms and a clear, distinct zone of inhibition will be visualized surrounding the medium. The antimicrobial activity of the test agent is determined by measuring the diameter of zone of inhibition expressed in millimeter. The experiment is carried out more than once and the mean of the readings is required.[9]

*Determination of Antimicrobial Activity by the Zone of Inhibition*

The antimicrobial potency of the test agents is measured by their activity to prevent the growth of the microorganisms surrounding the discs which gives clear zone of inhibition. After incubation, the antimicrobial activities of the test materials were determined by measuring the diameter of the zones of inhibition in millimeter with a transparent millimeter scale.

## III. Results and Discussion

The standard curve was obtained by plotting the absorbance values against the corresponding concentrations.

| **Mx10$^{-5}$** | **Absorbance** |
|---|---|
| 1 | 0.645 |
| 2 | 0.682 |
| 3 | 0.743 |
| 4 | 0.778 |
| 5 | 0.796 |
| 6 | 0.847 |
| 7 | 0.875 |
| 8 | 0.949 |

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

This figure shows that absorbance of cefpodoxime proxetil is quite different from absobance of metal and antacid.

The intensity of the peak of cefpodoxime proxetilchanges remarkably i.e. absorption characteristics are altered due to interaction but the position of the compound does not shift.

Interaction between drug with metal& antacid may lead to form complexes which have different light absorption capacity and spectrum pattern is altered. So any alteration n spectral



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behavior is regarded as a tool for primary interaction from the spectral studies.

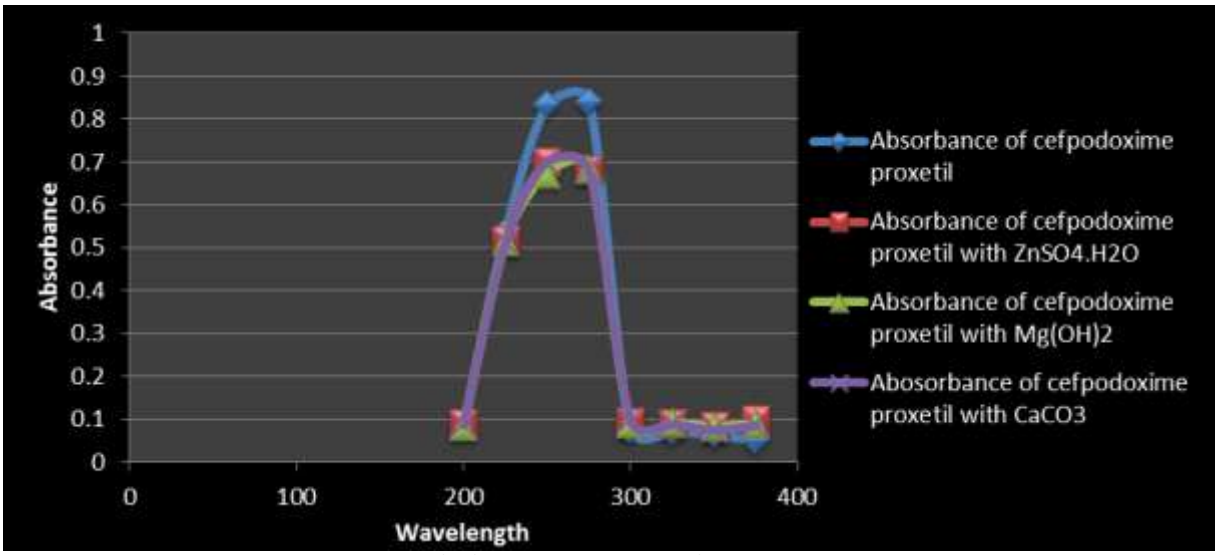
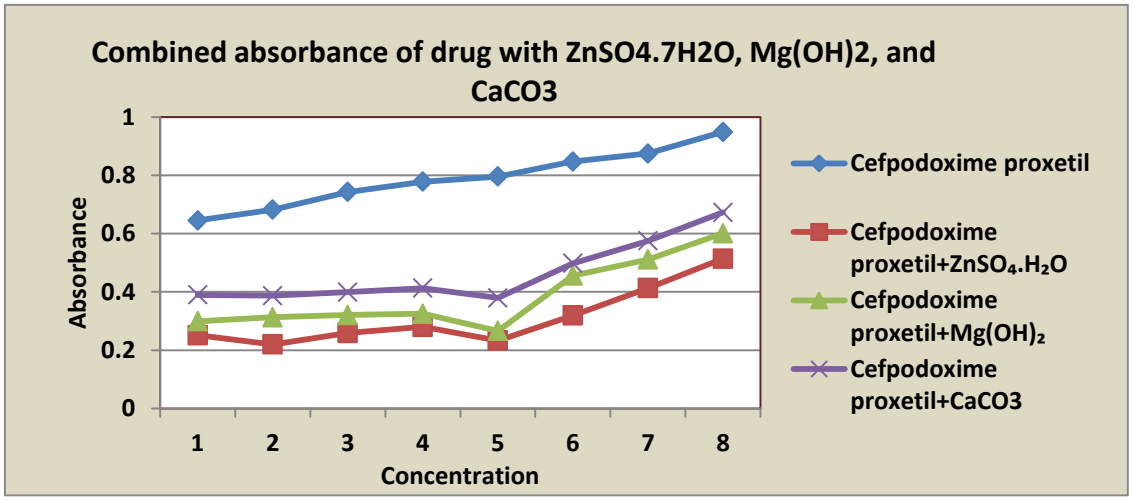



Fig. Combined spectral curve of cefpodoxime proxetil and cefpodoxime proxetil with metal & antacid.

*Job's Plot:*




The above figure shows that the absorbance of Cefpodoximeproxetil differs from the absorbance of Cefpodoxime proxetil+$ZnSO_4.7H_2O$,Cefpodoximeproxetil+$Mg(OH)_2$, Cefpodoxime proxetil+$CaCO_3$.

*Antimicrobial Study:*

The test samples were tested against *Staphylococcus aureus*.The standard ciprofloxacin disk also tested against *Staphylococcus aureus*. The results of the antimicrobial activity, measured in terms of diameter of zone of inhibition in mm are showed in table.

| Bacteria used | Standard disk (zone of inhibition/mm) | Sample disk (zone of inhibition/mm) |
|---|---|---|
| *Staphylococcus aureus* | 17mm | $\frac{\text{Cefpodoximeproxetil} + ZnSO_4.7H_2O}{14\text{mm}}$ |
| *Staphylococcus aureus* | 17mm | $\frac{\text{Cefpodoximeproxetil} + MgSO_4.7H_2O}{10\text{mm}}$ |
| *Staphylococcus aureus* | 17mm | $\frac{\text{Cefpodoximeproxetil} + CaCO_3}{13\text{mm}}$ |

## IV. CONCLUSION

In the present work, the interaction of an important antimicrobial drug, Cefpodoximeproxetil with Zinc Sulfateheptahydrate, Magnesium hydroxide, and Calcium carbonate at 7.4 by a variety of physical method like inspection of spectral behavior, Job's method of continuous



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variation. From spectral study, it has been seen that Cefpodoximeproxetil gives a sharp peak at 335 nm. When Zinc Sulfate heptahydrate, Calcium carbonate and Magnesium hydroxide mixed with ciprofloxacin at 1:1 ratio, the intensity of the peak changes remarkably (absorbance decreases) i.e. absorption characteristics are altered due to interaction but the position of the compound do not shift. The antimicrobial screening of an agent is essential to ascertain its spectrum against various types of pathogenic organisms. the susceptibility of organism (bacteria in this case) to antimicrobial agents can be measured In vitro by a number of techniques among which the disk diffusion method using different concentration of the agents absorbed on material filter paper disks, is widely acceptable for the preliminary evaluation of antimicrobial activity. Job's plot has given the molar ratio of complexes of Cefpodoximeproxetil and Zinc Sulfate heptahydrate, Calcium carbonate and Magnesium hydroxide. At pH 7.4Cefpodoximeproxetilforms strong 1:1 complexes with zinc Sulfate heptahydrate, Calcium carbonate and Magnesium hydroxide indicated as '^' shaped curves. These curves may indicate strong kinetics of complexation between Cefpodoximeproxetil and Zinc Sulfate heptahydrate and Magnesium hydroxide and Calcium carbonate. When drug individually act with Zinc Sulfate heptahydrate, Calcium carbonate and Magnesium hydroxide curve of their absorbance are verify. It is known to us the availability of the drug represents the amount (quantity or concentration) of drug. It helps in the study of selection the best dosage form for treatment. And obviously very important in adjusting the effective dose and dose ranges.

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