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DEGRADATION STUDIES OF SELECTED FLUOROQUINOLONES

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INTRODUCTION

Fluoroquninolones are a family of broad-spectrum synthetic antimicrobial agents having particular activity against gram-negative organisms especially Pseudomona aeroginosa. These compounds have a fluoro group attached to the central ring system. Nalidixic acid is the parent compound of the group introduced in 1962. They are classified as 1st, 2nd, 3rd and 4th generation fluoroquinolones having nalidixic acid, ciprofloxacin, levofloxacin and moxifloxacin belonging to the classes respectively. These are bactericidals and acts by attacking the DNA gyrase and topoisomerase in gram-negative and –positive bacteria respectively.[1,3] The activity may reduce in acidic media.[4] These are well-absorbed orally and cannot cross BBB, have major adverse effects GIT related however CNS related ADR are severe but rare.[3,5,6] Heterocyclic quinolones stand for diverse biological and chemical reactivity.[7] The Quinolonecarboxylic acids, carboxyquuinoloes, or 4- quinolones are a group of synthetic antibacterials structurally related to nalidixic acid. The term 4- quinolone has been used as a generic name for the common 4-oxo-1, 4-dihydroquinoline skeleton. Under this system nalidxic acid, a napthyridene derivative, is an 8- aza-4 quinolone, cinoxacin, a cinnoline derivative, is a 2-aza-4-quinolone, and pipemidic and piromidic acids, pyridopyrimidine derivatives, 6,8-diaza-4-quinolones.[8]

Studies have been performed regarding the stability of fluoroquinolones[9,14] and other drugs.[15,16] The stability of active pharmaceutical ingredient is determined by applying the process of degradation. ICH has described parameters for forced degradation. In this study different quinolones were exposed to different degradation conditions including acidic, basic and photo conditions.[17,18] Antibiotic residues have been influenced by cooking time and temperature because Stability of antibacterial residues during heating is different.[19]

The degradation of FQs is a health hazard for humans and other living organisms. So a study was conducted on the photochemical degradation process of enrofloxacin (ENR) and ciprofloxacin hydrochloride (CIP), and two marine microalgae.[20] Ciprofloxacin and other fluoroquinolones are commonly used broad-spectrum antimicrobial agents for treating bacterial infections.[21] A study indicated different factors contributing to the degradation of ciprofloxacin like effects of initial concentrations, pH values, different additives and composite pollutants on ciprofloxacin hydrochloride removal using γ irradiation were investigated.[22] In this study two processes were compared which included photolysis and photo-catalysis. Moreover it also caters to a method development for removing antibiotics from water.[23] The degradation has been occurred either in pure water or in the presence of NaOH or NaCl in Photocatalytic and photoelectrocatalytic degradation of the antibacterial fluoroquinolone drug, ciprofloxacin, has been studied in the presence of nanocrystalline titania films supported on glass slides or transparent electrodes.[24] A study indicated that after the different period of implantation (15, 30, 60 and 90 days), that the Alkaline phosphatase (ALP) and Acid phosphatase (ACP) activities showed an excellent osteoinductive property of BG (M)-PVA, that this phenomena decreased with the presence of ciprofloxacin.[25] Loss of antibacterial activity has been reported following irradiation of ciprofloxacin solutions by ultraviolet light.[26] In one study LFX was found to be oxidation sensitive.[27] In order to avoid levofloxacin degradation and retain its pH in an optical preparation a work was done to prolong contact period with ocular exterior.[28] The pH sensitivity of levofloxacin was mentioned in a study in which levofloxacin released from CS/ALG nanoparticles was 71% at pH 7.4 within 7 h. It is a new quinolone antimicrobial agent that exhibits broad-spectrum in-vitro bactericidal activities against gram-positive and gram-negative aerobes.[29] In our present study encompasses the assay and degradation of ciprofloxacin, levofloxacin and moxifloxacin (Figure 2).

MATERIALS AND METHODS

Materials

The fluoroquinolones used were Ciprofloxacin 500mg, Levofloxacin 500mg and Moxiflxacin 400mg. 0.1N NaOH and 0.1 N HCl were accurately prepared. Freshly prepared distilled water was used throughout the study. Glass wares used are volumetric flasks, stirrer, beakers, pipette and measuring cylinder. All glass wares used were made up of Pyrex material. Initially they were

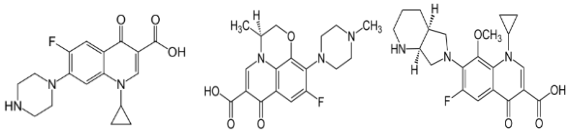
rinsed with chromic acid then with water and finally washed with freshly prepared distilled water.

Instruments

Weighing Balance used for weighing the drug was 'Shimadzu Japan' , pH meter, water bath, UV light and Spectrophotometer 'UV-1601, UV / Visible spectrophotometer, Shimadzu Japan' for the measurement of absorbance of quinolones.

Selection of wavelength detection

The solutions of all the three quinolones were scanned in the range of 200-400nm and was found that ciprofloxacin demonstrated maximum absorbance at 278nm, Levofloxacin at 294 nm and moxifloxacin at 293nm and therefore were selected as the detection wavelengths for the respective drugs.



(a) (b) (c)

Figure 1: (a) ci1profloxacin, (b) levofloxacin and (c) moxifloxacin

Standard Preparation

Individual solutions of the working standards of Ciprofloxacin HCl, moxifloxacin HCl and levofloxacin HCl were prepared by dissolving in 0.1N HCl so as to get the final solution of 5.1 µg/ml, 8.2 µg/ml and 9.8 µg/ml respectively. The absorbance of the standard and the sample solutions were made at 278, 293 and 294 respectively using 0.1 N HCl as blank.

Sample Preparation

Two different brands were used manufactured by the multinational pharmaceutical companies. 20 tablets of each brand of ciprofloxacin were taken, weight and were finely powdered. 251.9 mg of drug each drug was accurately weight and transferred into a 250 ml volumetric flask. 60 ml of 0.1 N HCl was added and sonicated for 30 minutes. The volume was made up with 0.1 N HCl and shake well. The solutions were filtered through Whatman #1 filter paper. 1 ml of the resulting solution was taken in a 200 ml volumetric flask and the volume was made up with 0.1 N HCl and mixed well to get 5 µg/ml. The sample solutions of moxifloxacin and levofloxacin were also prepared in the similar manner by taking 324.5 mg and 682.2 mg of the powdered drug so as to get the final solution of 9.98 µg/ml and 10.6 µg/ml respectively.

Parameters for degradation studies

10 ml of each of the 12 solutions (ciprofloxacin, moxifloxacin and levofloxacin; one standard and three sample solutions) were taken in a beaker in four slots. To study the degradation pattern in acidic pH, 1 N HCl was added to each beaker and the pH was adjusted at 3.0. The beakers were allowed to stand for 10 mins. and the absorbance was determined at 278nm for ciprofloxacin, 293nm for moxifloxacin and 294 nm for levofloxacin. Similarly, 1 N NaOH for added in the another slot of 12 solutions to study the effect of basic medium. The pH was adjusted to 9.0 and the beakers were allowed to stand for 10 mins. The third slot of solutions were placed in the UV light for 30 mins and the absorbance was measured at the respective wavelengths and further 5 readings were taken after every 30 mins intervals. Forth slot solutions were placed in water bath for 30 mins at 85 ^{o}C and then the absorbance were analyzed at their respective wavelengths. The solutions were again placed in the water bath and the absorbances were taken after every 30 mins.

RESULT AND DISCUSSION

The results obtained from the study (Table 1) have indicated that the fluoroquinolone mostly degraded by acidic pH is moxifloxacin. It can be seen that 11.41% of the drug has been degraded. Ciprofloxacin and levofloxacin are not much affected by the acidic medium and only 2% of the drug (in both the cases) has been found to be destroyed. The comparision of the degradation versus the assay has also done to indicate the percentage of drug degraded (Table 2, Figure 2). Basic pH has not affected the levofloxacin much (2.4%) and the mg/tablet left from been decomposed is 376.2 mg, however ciprofloxacin and moxifloxacin are affected 24.7% and 22.4% respectively (Table 3, Figure 3). Levofloxacin has been found to be much degraded by heat i.e. 48.5%. moxifloxacin has degraded by the UV light but to a lesser extent i.e 12.9%.

Table 1: Absorbance of neat solutions and pharmaceutical products of Ciprofloxacin, Levofloxacin and Moxifloxacin

Parameters	Ciprofloxacin	Levofloxacin	Moxifloxacin
Standard solution	0.538	0.864	0.883
Sample 1	0.502	0.854	0.792
Sample 2	0.513	0.891	0.857
Acidic pH	0.491	0.852	0.791
Basic pH	0.378	0.843	0.696
Heat (90 ^{o}C)			
30 mins.	0.491	0.781	0.791
60 mins.	0.485	0.855	0.781
90 mins.	0.477	0.855	0.781

120 mins.	0.477	0.852	0.777
150 mins.	0.476	0.846	0.777
UV light			
30 mins.	0.486	0.774	0.799
60 mins.	0.484	0.458	0.798
90 mins.	0.483	0.453	0.798
120 mins.	0.483	0.451	0.798
150 mins.	0.482	0.451	0.798

Table 2: Degradation VS % Assay of Ciprofloxacin, Levofloxacin and Moxifloxacin

	Ciprofloxacin	Levofloxacin	Moxifloxacin
Assay	107.1	98.6	98.9
Acidic pH	97.74	97.23	88.59
Basic pH	75.24	96.20	77.59
Heat			
30 mins	95.55	88.32	89.48
60 mins	96.34	52.26	89.37
90 mins	96.15	51.69	89.37
120 mins	96.15	51.46	89.37
150 mins	95.95	51.46	89.37
UV light			
30 mins	97.74	89.12	88.59
60 mins	96.54	97.57	87.47
90 mins	94.95	97.57	87.47
120 mins	94.95	97.23	87.02
150 mins	94.75	96.54	87.02

Table 3: Degradation VS % mg/tab of Ciprofloxacin, Levofloxacin and Moxifloxacin

	Ciprofloxacin	Levofloxacin	Moxifloxacin
Assay	535.6	493.1	395.5
Acidic pH	488.7	486.1	354.3
Basic pH	376.2	481.0	311.8
Heat			
30 mins	477.7	441.6	357.92
60 mins	481.7	261.3	357.48
90 mins	480.7	258.4	357.48
120 mins	480.7	257.3	357.48
150 mins	479.7	257.3	357.48
UV light			
30 mins	488.7	445.6	354.3
60 mins	482.7	487.8	349.8
90 mins	474.7	487.8	349.8
120 mins	474.7	486.1	348.0
150 mins	473.7	482.7	348.0

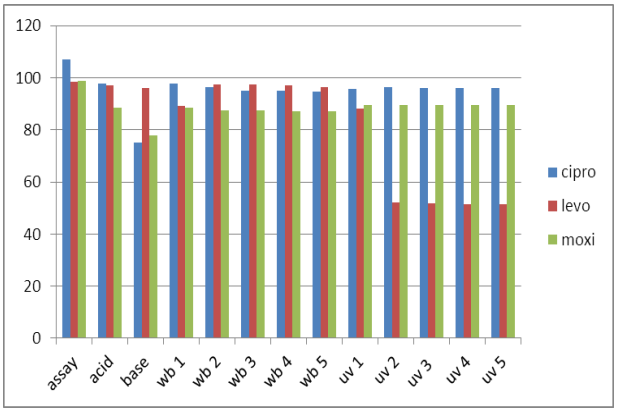


Figure 2: Graphical representation of degradation VS % Assay of Ciprofloxacin, Levofloxacin and Moxifloxacin

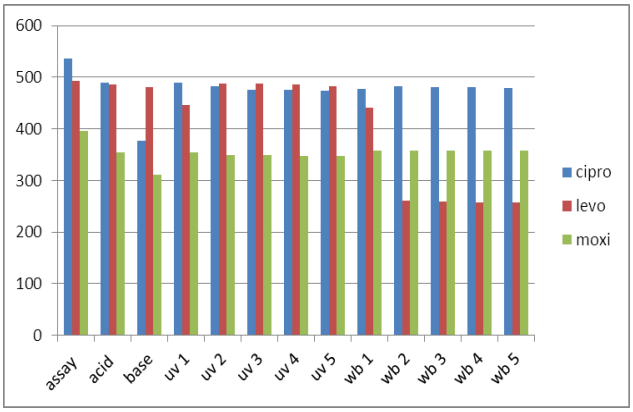


Figure 3: graphical representation of degradation vs mg/tab of Ciprofloxacin, Levofloxacin and Moxifloxacin.

DISCUSSION

Ciprofloxacin and moxifloxacin are not affected much by any of the applied parameters except the basic pH. Levofloxacin was found to be degraded by heat and the extent to which it was destroyed is much higher than the other parameters and even more than to which the other two fluoroquilones have been degraded. Moxifloxacin has been degraded by heat and UV light but to less**er** extent as compared to the other two drugs. The study has revealed that moxifloxacin is more prone to degradation than the other two drugs.

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