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Research Article

Photodegradation of Fleroxacin Injection: II. Kinetics and Toxicological Evaluation

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Abstract. Photodegradation kinetics of fleroxacin were investigated in different injections. Five commercial formulations were analyzed before and after irradiation by determining residual volumes of fleroxacin with high-pressure liquid chromatography (HPLC), and different decomposition functions and models were obtained. Concentration levels of fleroxacin in injections caused the differences in photodegradation kinetics instead of ingredients. Influences of different pH values and presence of NaCl on photodegradation of fleroxacin were observed. Low pH value decreased the efficacy of photolysis and enhanced photostability of fleroxacin injections. Tentative structure of a new degradation product afforded was proposed. An acute toxicity assay using the bioluminescent bacterium Q67 was performed for fleroxacin injections after exposure to light. The research proved that fleroxacin was more photolabile in dilute injection, and acute toxicity of dilute injection increased more rapidly than that of concentrated injection during irradiation.

KEY WORDS: fleroxacin injection; kinetics; photodegradation; toxicity.

INTRODUCTION

Fleroxacin, a synthetic fluoroquinolone antibacterial, is unstable in injections when exposed to light (1,2), as are many other fluoroquinolone formulations (3,4). The fluorine atom at C-8 in the structure of fleroxacin makes it even more photolabile (5). So, researches on photostability of fleroxacin preparations are particularly important. But there are few detailed studies on degradation of different fleroxacin injections. In our previous work, different photodegradation products of fleroxacin (shown in Fig. 1) were isolated and characterized (6), whereas photodegradation kinetics, photostability, and toxicity of different fleroxacin injections were not systematically performed.

In this paper, different fleroxacin injections were analyzed with high-pressure liquid chromatography (HPLC) before and after irradiation, and the linear regression method was used to determine kinetic parameters. Since there are various fleroxacin injections in the market, the most common specifications of which range from 2 to 100 mL, commercial formulations with five typical specifications (100 mL:200 mg, 100 mL:400 mg, 10 mL:100 mg, 10 mL:400 mg, and 2 mL:200 mg) were purchased and studied. The experimental results indicated that photodegradation kinetics of fleroxacin varied in different injections and that concentration levels of fleroxacin caused the differences in degradation rates instead of ingredients. The effect of different pH values and presence of NaCl on photodegradation of fleroxacin was investigated, because stability of injections is usually related to acidity and normal saline is often used to dilute small-volume injections for intravenous infusion.

To monitor the toxicity change of fleroxacin injection on exposure to light, a luminescent bacteria test was adopted. Recent literatures have shown that luminescent bacteria methods were widely used in toxicity analysis of antibiotics (7,8). Of the methods, a number of studies using the bacterium *Vibrio qinghaiensis* sp.-Q67 (Q67) (9) were reported with advantages of simplicity, sensitivity, and reproducibility (10–12). In this article, the acute toxicological assessment based on inhibition of the bioluminescence emitted by Q67 after 15-min periods of sample contact, was performed on fleroxacin samples for the first time. The results showed that toxicity of dilute injection increased more rapidly than that of concentrated injection during irradiation. The order of toxicity for fleroxacin and the three major photodegradation products were proposed.

MATERIALS AND METHODS

Materials

Five fleroxacin injections (pH values measured, all about 4.0) were all commercial formulations, kept in a cool and dark place before use. Fleroxacin injection A (specification, 100 mL:200 mg of fleroxacin; contains 99.7% of the labeled amount, with mannitol as additive) manufactured by Runbang Pharmaceutical Co., Ltd. (Jiangsu, China), fleroxacin injection

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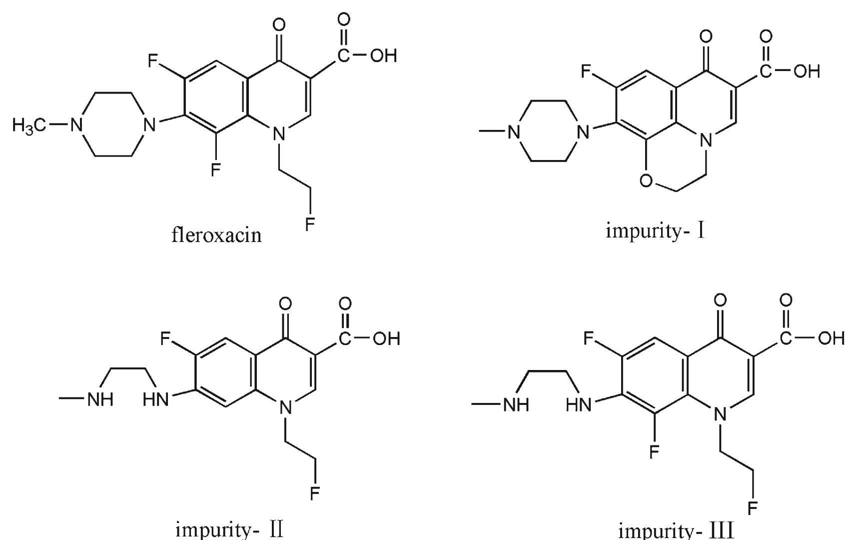

Fig. 1. Structures of fleroxacin and its photodegradation products

B (specification, 100 mL:400 mg of fleroxacin; contains 99.0% of the labeled amount, with glucose as additive) manufactured by Kelun Pharmaceutical Co., Ltd. (Sichuan, China), fleroxacin injection C (specification, 10 mL:100 mg of fleroxacin; contains 99.5% of the labeled amount, with propylene glycol and disodium edetate as additives) manufactured by Sanjing Pharmaceutical Co., Ltd. (Heilongjiang, China), fleroxacin injection D (specification, 10 mL:400 mg of fleroxacin; contains 100.2% of the labeled amount, with propylene glycol and disodium edetate as additives) manufactured by North China Pharmaceutical Co., Ltd. (Hebei, China), and fleroxacin injection E (specification, 2 mL:200 mg of fleroxacin; contains 99.9% of the labeled amount with propylene glycol and sodium calcium edetate as additives) manufactured by Changzheng-Cinkate Pharmaceutical Co., Ltd. (Jiangsu, China) were purchased from the market. Fleroxacin was supplied from Jinan Limin Pharmaceutical Co., Ltd. (Shandong, China). The freeze-dried powder of luminescent bacterium *Vibrio qinghaiensis* sp.-Q67 (Q67) and reconstitution solution were purchased from Beijing Hammatsu Photon Techniques Inc. and stored in a freezer at −20°C before use.

Sample Preparation

A series of fleroxacin solutions were prepared. A primary stock solution of 200 mg/mL was prepared by dissolving fleroxacin with 1% lactic acid and then diluted with water to produce solutions containing 2, 4, 10, 40, and 100 mg/mL of fleroxacin. Finally, pH values of all the solutions without other additives were adjusted to 4.0 with lactic acid before degradation test.

According to the amount in the commercial formulations, each kind of additive was added into the stock solutions mentioned above and diluted to produce different fleroxacin solutions containing 10% propylene glycol, 0.01% disodium edentate, 0.01% sodium calcium edentate, 5% mannitol, or 5% glucose, individually.

For investigation of the relationship between pH values and photostability of injections, pH values of injection A and injection E were adjusted to 2.0, 3.0, 4.0, 5.0, 6.0, and 7.0, and the injections were exposed to the light. All the solutions were kept in a cool and dark place before the photodegradation test.

Photodegradation Procedure

Forced photodegradation of fleroxacin solutions was conducted in Pyrex glass cells (50×50×80 mm). One hundred milliliters of sample inside the cell was kept at 30°C and irradiated from a 10-cm distance with artificial daylight while it was stirred with a magnetic stirrer during the experiment. The light source was eight cool white fluorescent lamps (Polylux XL, Hungary) which have light in a region of artificial daylight (λ range between 320 and 700 nm) according to the ID65 standard of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use rules (13) and provided an illumination of 11000 lx. After irradiation, all samples were subjected to HPLC analysis. The concentrations of the residual fleroxacin in the injections and solutions were determined at intervals of 24 h during a 7-day irradiation. Each experiment was repeated thrice.

HPLC Analytical and Semipreparative Procedure

Analytical HPLC used for determination of fleroxacin and analysis of the impurities was performed on a Shimadzu LC-20A system equipped with a photodiode array detector. The column was an Agilent XDB-C18 (250×4.6 mm i.d. packed with 5-μm particle size). The mobile phase as ref (6) consisted of acetonitrile −0.1 mol/L ammonium formate (adjusted to pH 4.2 with formic acid) (18:82, *v*/*v*). The flow rate was kept at 1.0 mL/min, and UV detection was performed at 286 nm. Semipreparative HPLC was performed on an Agilent 1200 LC system for isolation of photodegradation products. The column was Kromasil ODS (5-μm particle size, 250×10 mm i.d., 100 A; Shanghai Anpel Instrument Co., Ltd.). Samples after irradiation were injected onto the semipreparative HPLC column. The main impurities were collected, refined, and then dissolved for toxicity test.

MS Analytical Procedure

Mass spectrum (MS) data were obtained with a Xevo quadrupole–time-of-flight mass spectrometer equipped with

electrospray ionization (ESI) source coupled to a Waters HPLC system. The source temperature and desolvation temperature were 150 and 350°C, respectively. The cone voltage was 20 V, and the collision energy was 20 eV. The scanned *m/z* range was 110–1,000 Da. Data were processed through MassLynx qualitative analysis.

Kinetic Study Procedure

Relative residual concentrations (C_{red}) of samples were calculated by using the following equation:

$$C_{red} = C_t/C_0$$

where C_0 was the initial concentration of fleroxacin in injection, and C_t was the residual concentration after irradiation.

The regression tool in Excel software based on method of the least squares was used for calculation of the linear fitting equation. Relations of (a) values of concentration and time, (b) ln of concentration and time, and (c) reciprocal of concentration and time were acquired by regressing. High regression coefficients obtained from (a), (b), or (c) indicate zero-order, first-order, or second-order reaction rate law, respectively (14).

Toxicity Test Procedure

In this work, all samples were diluted to about 4 μg/mL for the luminescent bacteria tests. After 15 min of exposure of the bacteria to the sample solutions, the relative light unit of Q67 was measured using a SHG-D surveying biochemistry light instrument (Shanghai Shangli Instrument Co., Ltd.), equipped with a 12-well temperature-controlled incubator chamber. The tests was performed according to the instructions of the Q67 kit's procedure (Hammatsu Photon Techniques, Beijing, China) and the International Organization for Standardization guidelines (15). Inhibition of the bioluminescence emitted by the bioluminescent bacterium Q67 after 15-min periods of sample contact in the incubator wells at 15±0.5°C was determined three times. Water (as control sample) was used for the control test. The inhibition effect (*H*, in percent) after the contact time of 15 min was calculated by using the following relationship:

$$H(\%) = 100 \times \frac{\mathrm{Ic}_{15} - \mathrm{It}_{15}}{\mathrm{Ic}_{15}}$$

where

It_{15} was the luminescence intensity of the test sample after the contact time of 15 min;

$$\mathrm{Ic}_{15} = \mathrm{f_k} \times \mathrm{I_0}$$

where I_0 was the luminescence intensity of the Q67 suspension for the control test, f_k was calculated as the average from I_k/I_0 values measured on the control tests six times, and I_k was the luminescence intensity of the Q67 suspension with the control sample after the contact time of 15 min. Toxicity variations of injections on Q67 were expressed as *H* values obtained by the tests.

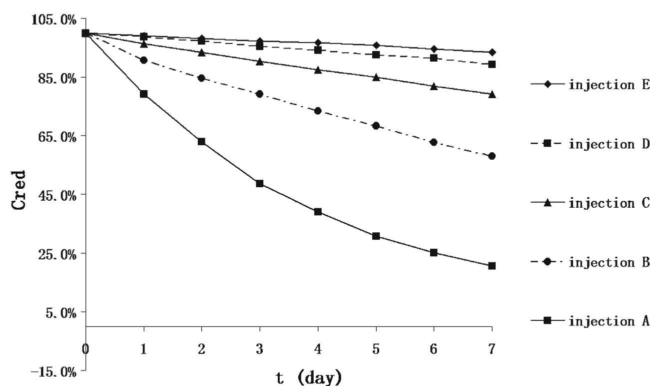

Fig. 2. The relationship between C_{red} and irradiation time

In order to compare toxicity of each photodegradation product, evaluation of concentration–effect relationships was made. Four concentration levels of sample solutions were prepared and adjusted to make *H* values range from 10% to 90% in each test, and standard linear regression analysis was adopted to obtain the following equation:

$$\lg C = b \lg \Gamma + a$$

where

C was the concentration of the sample solution, and *a* was the value of the intercept of the described line.

$$\Gamma = \frac{H}{100 - H}$$

The concentration of fleroxacin or each impurity corresponding to the inhibition value (*H*) of 50%, namely effective concentration (EC50), was calculated. The EC_{50} values (C=EC_{50}, atΓ=1) were used for toxicological ranking. By definition, the higher the EC50 value, the lower the toxic effect.

RESULTS

The Kinetic Studies of Degradation

The relative residual concentrations (C_{red}) of samples after photodegradation were shown in Fig. 2. Data in each curve were regressed with the three models mentioned in "Kinetic Study Procedure." The highest linearity coefficient (means the best fit) was observed, and the most probable decomposition function for each sample was determined. The optimum regression equations were shown

Table I. The Most Probable Photo-Decomposition Functions of Fleroxacin in Injections

Concentration of injection ($\mathrm{mgmL^{-1}}$)	Order of reaction	Regression equation	Correlation coefficient
2	First	$\mathrm{Ln}C_{red}$=−0.2279t−0.0141	0.998
4	First	$\mathrm{Ln}C_{red}$=−0.0761t−0.0068	0.999
10	Zero	C_{red}=−0.0320t+1.0036	0.996
40	Zero	C_{red}=−0.0152t+1.0015	0.997
100	Zero	C_{red}=−0.0090t+0.9999	0.996

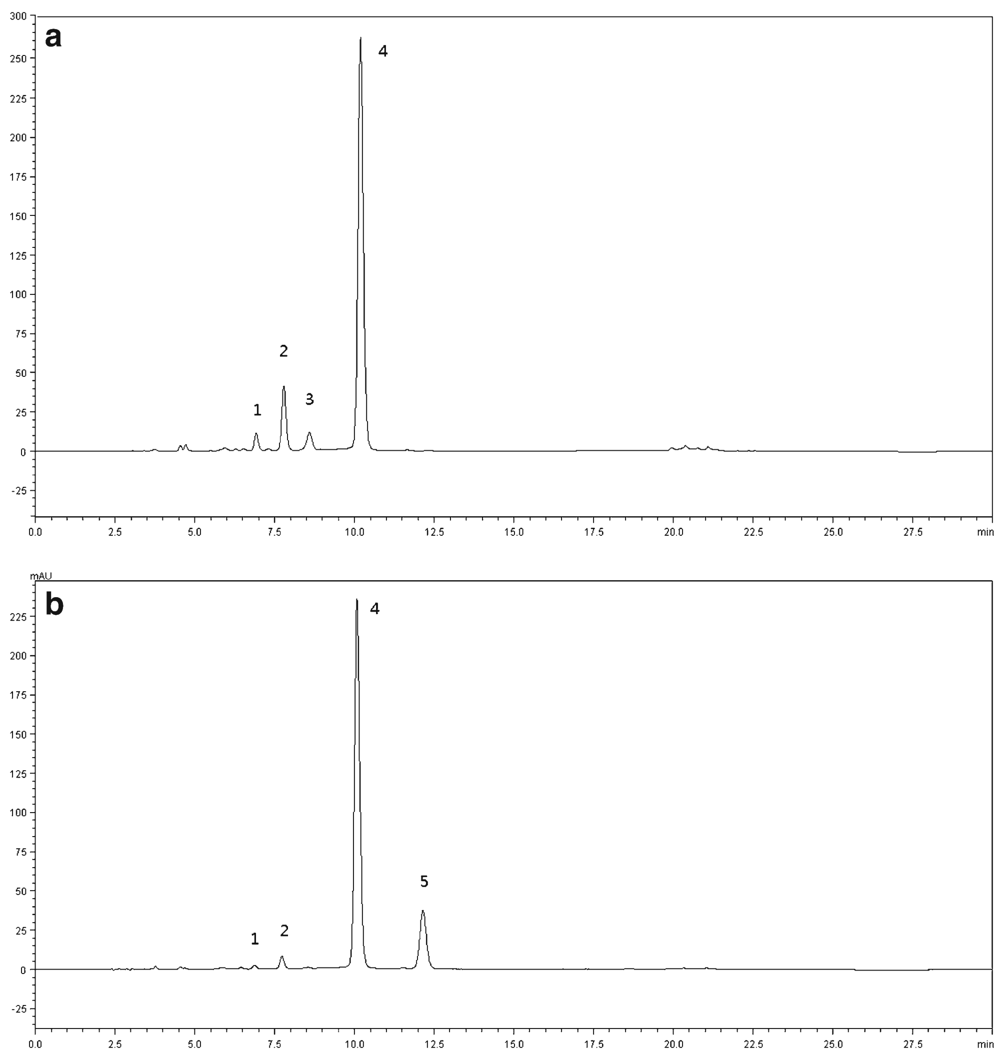

Fig. 3. Chromatograms of fleroxacin injection after irradiation. **a** Fleroxacin injection C (10 $mgmL^{-1}$). **b** Fleroxacin injection A (2 $mgmL^{-1}$) in the presence of NaCl. *Peak 1* impurity I, *peak 2* impurity II, *peak 3* impurity III, *peak 4* fleroxacin, *peak 5* impurity IV

in Table I. The results indicated that the decomposition of fleroxacin in different injections fits different kinetics models. Irradiation of fleroxacin solutions at the same concentration levels as injections, with or without each of the additives (10% propylene glycol, 0.01% disodium edentate, 0.01% sodium calcium edentate, 5% mannitol, or 5% glucose), produced the same results. Similar concentration-dependent rates of photodegradation were observed.

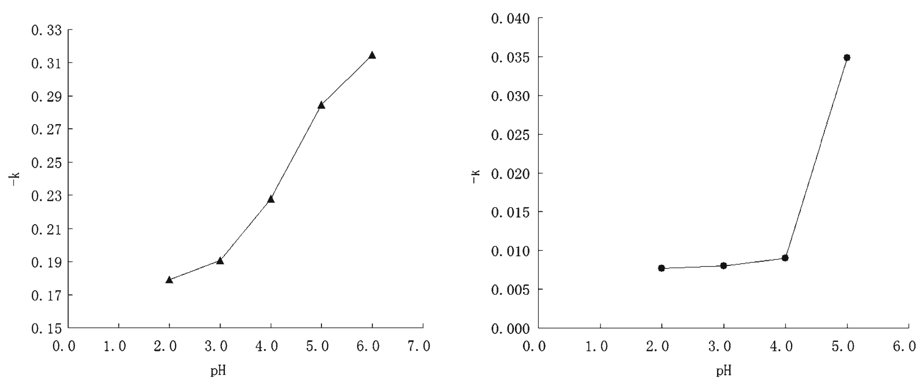

Fig. 4. Dependence of k on pH values. *Line with triangles* pH–k profile for the photodegradation of injection A (the first-order reaction), *line with circles* pH–k profile for the photodegradation of injection E (the zero-order reaction)

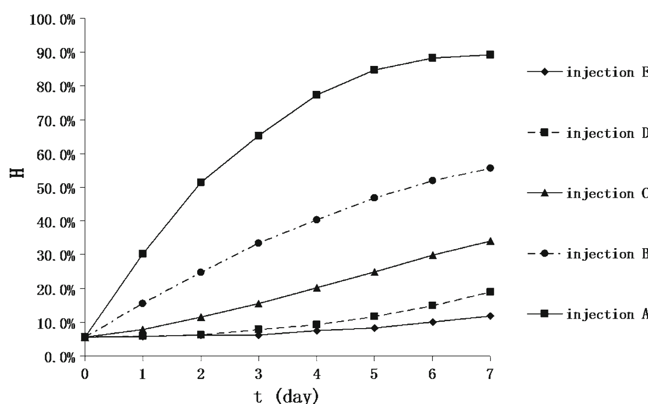

Fig. 5. The relationship between the inhibition effect of injection and irradiation time

Degradation of fleroxacin tended to follow first-order reaction relationship in injection A (concentration, 2 mg/mL) and injection B (concentration, 4 mg/mL), whereas zero-order degradation kinetics were observed in injections with concentrations above 10 mg/mL. Concentration levels of fleroxacin caused the differences in photodegradation kinetics, after excluding the interference of supplementary materials in injections by tests of solutions without additives.

HPLC analysis showed that fleroxacin injections at low concentration levels exposed to light mainly produced impurity I and impurity II. Impurity I, impurity II, and impurity III were all apparent when the concentration of the injection was 10 mg/mL (Fig. 3). When the concentration of the injection reached 40 mg/mL or above, impurity III was the main photodegradation product.

The influence of pH on reaction rate constant (k) in injection A and injection E was analyzed. Injection A at pH 7.0 and injection E at pH 6.0~7.0 produced precipitate, so the data were not used. The pH–k profile for the photodegradation of the injections was shown in Fig. 4.

Toxicity Evaluation

After photolysis under light, the injections were tested, and the relationship between H (express toxicity) calculated and irradiation time (day) was shown in Fig. 5. These observations demonstrate that toxic products in injections were formed during irradiation, and toxicity increased more rapidly for injections at low concentration levels. Results obtained from solutions without additives were in congruence with those from injections. The highest toxicity was observed in injection A and the fleroxacin solution at the lowest concentration (2 mg/mL).

Four series of solutions containing different concentrations of fleroxacin and the three isolated impurities each were tested, and standard linear regression analysis was used in data analysis. The linear regression equations obtained were:

$$\begin{aligned}
&\text{Fleroxacin}(4.49 \sim 7.53\ \mu g/mL): \ \lg C = 0.1419 \lg \Gamma - 2.2383,\ r = 0.9962\\
&\text{Impurity I}(5.13 \sim 7.80\ \mu g/mL): \ \lg C = 0.1252 \lg \Gamma - 2.1971,\ r = 0.9980\\
&\text{Impurity II}(1.87 \sim 3.23\ \mu g/mL): \ \lg C = 0.1511 \lg \Gamma - 2.6182,\ r = 0.9977\\
&\text{Impurity III}(1.46 \sim 2.51\ \mu g/mL): \ \lg C = 0.1607 \lg \Gamma - 2.7256,\ r = 0.9958
\end{aligned}$$

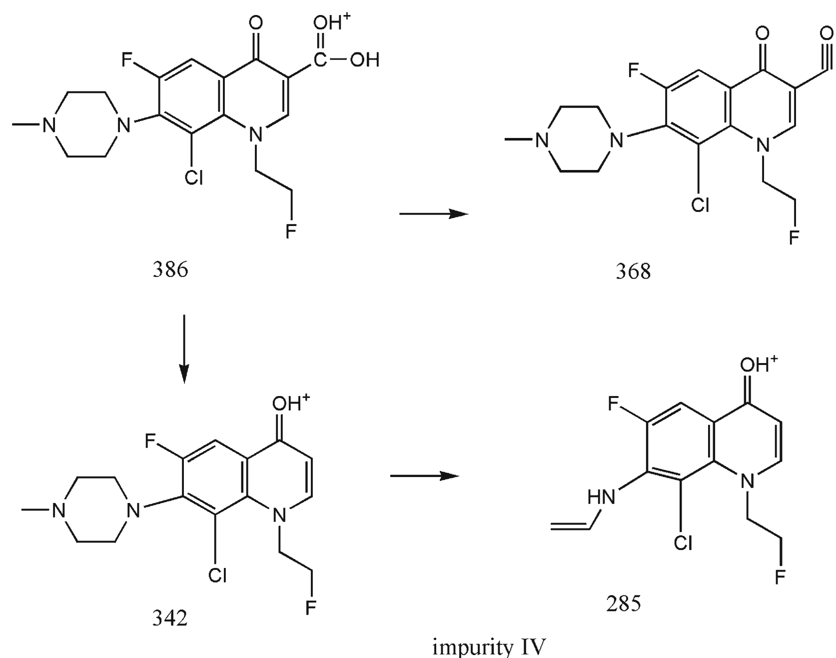

Fig. 6. MS/MS fragmentation pattern of impurity IV

The EC_{50} values of fleroxacin, impurity I, impurity II, and impurity III were calculated to be 5.78, 6.35, 2.41, and 1.88 μg/mL respectively.

DISCUSSION

In most researches on photo-decomposition of drugs, samples were always confined to diluted solutions (16,17). Most of the degradation processes followed first-order reaction relationship (18), while few (as abeprazole methanolic solutions, 0.8 mg/mL) showed zero-order kinetics (14). The influence of some reagents was reported, *e.g.*, hydroxypropyl-β-cyclodextrin had a synergistic effect on the photodegradation of ascorbic acid (19), and addition of disodium edentate did not change the degradation rate or kinetics of azithromycin (20) in solutions (concentration of 2.0 mg/mL). However, kinetic studies on the final preparations are of more practical significance for manufacturing, storage, and application, since the same drugs in different preparations or formulations tend to present different characteristics sometimes (21,22).

Generally, photolysis in injection may have a relation with concentration, temperature, pH, and additives. Manufacturing procedures for fleroxacin injections were similar, which are to dissolve fleroxacin, add additives (mannitol or glucose regulating osmotic pressure in dilute injections, propylene glycol, disodium edentate or sodium calcium edentate as stabilizer in small-volume injections), dilute, and adjust the pH value. The pH values of the five injections were all about 4.0. Samples inside the cell were kept at 30°C during degradation, and test of solutions excluded influence of ingredients. So, it was proved that photodegradation kinetics of fleroxacin in injections were dependent on concentration levels. Comparison of reaction rate constant (k) in each function implied that injections at high concentrations are more photostable, and protection of infusion injections from light should be noticed during storage and application, especially in the case of long-term infusion therapy.

A few publications described the effect of drug concentration on photodegradation, *e.g.*, the degradation rate being inversely proportional to the initial concentration of ciprofloxacin (23), but different kinetics models were not involved. In ref (24), the results obtained from the photodegradation of 4-chlorophenol within a range of concentrations from 50 to 500 mg/L showed that a first-order reaction constant is independent from the reactant initial concentration, and degradation products were all the same. In our present studies on fleroxacin injections, various kinetics, products, and toxicities were observed. After comparing the different degradation products (6) in the injections at different concentrations, the probable reasons were deduced. The photoreaction of fluoroquinolones involves heterolytic C–F bond fragmentation (25), and the fluorine atom at C-8 in the structure of fleroxacin is more photolabile in dilute injections, so photodegradation is prone to take place, following the first-order reaction kinetic relationship. However, in injections containing a high concentration of fleroxacin, large amounts of solute molecules exist, and outer molecules block transmission of light. Most of the light will be absorbed close to the sample surface if a solution contains the drug substance in a high concentration (21). And, on the other hand, gathered fleroxacin molecules caused steric hindrance to protect the C–F bond, so light can only cause part of outer molecules to degrade, which is manifested in zero-order reactions—reaction rate is independent of residual concentration of fleroxacin.

Influence of pH

The rate of decomposition of fleroxacin increased with the rising pH value, especially near its isoelectric pH value (6.45) while in the state of zwitterion. The results implied that fleroxacin injections should be designed at low pH values for better photostability as long as they do not exceed human endurance.

Influence of NaCl

Injection A with 0.1% of NaCl (added) was exposed to light and analyzed. After irradiation, the solution produced a large amount of precipitate and was filtered before being injected into HPLC. A new impurity (impurity IV) afforded was observed from the chromatogram in Fig. 3. Time-of-flight mass spectroscopy data showed that the molecular weight of impurity IV was 385.1007 Da; the matching molecular formula was $C_{17}H_{18}ClF_2N_3O_3$. Based on the ESI–mass spectroscopy spectrum, a tentative structure of impurity IV was proposed. The structure and the fragments of the impurity are given in Fig. 6.

CONCLUSION

The photodegradation of fleroxacin tends to conform to the first-order kinetics equation in large-volume injection and follows zero-order kinetics in small-volume injection, accompanied with an increase in acute toxicity. The increase is inversely proportional to the concentration level of injection under the same lighting conditions, indicative of a higher adversity risk of dilute injection upon photolysis. High concentration level and low pH value enhanced photostability of fleroxacin injections. The toxicity order of fleroxacin and the impurities in terms of EC50 was: impurity I < fleroxacin < impurity II < impurity III. The results were not described in literature before, and the conclusions were important for further studies on adverse effects, impurity profile control, and design and manufacturing of fleroxacin injections.

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