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Fluoroquinolone antibacterial drugs: Review of physicochemical problems, analysis techniques, and solutions

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Abstract

Fluoroquinolones are a class of second-generation quinolone antibiotics. Some fluoroquinolone drugs have problems concerning their photostability. There are also problems of physicochemical properties related to hygroscopicity, incompatibility with its excipient during formulation, and interactions with other drugs. Efforts to increase photostability and reduce hygroscopicity continue, as do efforts to solve the problem of incompatibility with certain excipients and interactions with other drugs. If these issues are not resolved, they will cause problems during their manufacture and administration to patients, which will affect the therapeutic value of the drugs. Efforts to improve the stability of fluoroquinolones have been reported, such as preparing co-crystals and complexes with polymers. This research has shown potential, but the challenge is to have a deeper understanding of the physicochemical characteristics of fluoroquinolone drugs have insight into other problem-solving approaches with respect to the composition of the formula, the manufacturing process, equipment, and even packaging used in formulating the drug. A deeper understanding the problems will lead to appropriate solutions, such as improving photostability, reducing hygroscopicity, choosing excipients during formulation, and using the correct drug.

Keywords: Fluoroquinolone, Physicochemical property, Photostability, Hygroscopicity, Incompatibility, Interaction

1. Introduction

Antibiotics are subdivided into several classes based on their molecular structures. The classes of antibiotics include beta-lactam antibiotics, macrolides, quinolones, tetracyclines, sulfonamides, glycopeptides, aminoglycosides, and oxazolidinones [1]. Currently, there are four generations of the quinolone class. The first generation was effective only against gram-negative bacteria. Then, generation II of quinolones added the F (florine) atom into its structure, thus the name fluoroquinolone. This created generation IIa and increased the activity of quinolone. The next modification added a piperazine ($C_4H_{10}N_2$) ring in the R7 position and the cyclopropyl group in the R1 position, which increased the drug's activity toward gram-negative bacteria. Adding the alkylated piperazine group to R7 and methoxy (–OCH3) to R8 provided increased activity toward gram-positive bacteria. This version is called generation IIb quinolone. The third generation of quinolone was developed by adding the Cl (chlor) atom to the R8 position, which increased its activity toward gram-positive bacteria. Generation IV of quinolone added N (nitrogen) to the R8 position, which increased the drug's activity toward anaerobic bacteria [2].

Compounds derived from the fluoroquinolone class of antibacterial drugs include ciprofloxacin (CPX), levofloxacin (LVX), ofloxacin (OFX), norfloxacin (NFX), lomefloxacin (LMX), moxifloxacin (MFX), pefloxacin, and sitafloxacin (STX). The fluoroquinolones have stronger antibacterial activity than the quinolones. Fluoroquinolones are well absorbed after oral administration and some of their derivatives are available in parenteral form [3,4]. Fluoroquinolone is sensitive to light, so it and may experience photodegradation and phototoxicity, and photodegradation can cause photoallergies. Photodegradation and phototoxicity depend on the photostability of the compound, which is related to its structure. Irradiation of

fluoroquinolone can reduce its antibacterial activity and form photoproducts with unwanted side effects. In CPX, exposure to room light for 1 hour can form several photoproducts [5].

Some fluoroquinolone-derived antibacterial drugs, such as LVX and STX, are reported to have high hygroscopicity [4,6]. There is also an interaction between the fluoroquinolone class of drugs and certain excipients, which should be considered when choosing excipients during the formulation of medications. Those interactions can cause undesirable changes to the pharmacokinetics and pharmacodynamics of the drug [7,8].

These problems deserve attention and the effort to fix them, such as making LVX in the form of co-crystals with metacetamol compound to reduce hygroscopicity and increase photostability [6]. Manufacturing drug complexes can also increase photostability as in the formation of CPX drug complexes with cyclodextrin and cucurbit (7)-uril (CB7), which can increase photostability up to three times [9,10]. Then there are various analytical techniques to identify the problem and determine the success of the solution, such as a dynamic vapor sorption analyzer, which is used for hygroscopicity-related analysis [6], High-performance liquid chromatography (HPLC) can be used to promote photostability and analyze drug interactions [11,12], and Fourier transform infrared spectroscopy (FTIR), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) can be used to analyze drug incompatibility [7].

This review concerns physicochemical problems in fluoroquinolone. Understanding a drug's physicochemical properties is essential for developing a drug that is safe to use, therapeutically effective, stable from when it is manufactured until it is taken, and acceptable to consume [13]. Fluoroquinolone antibiotics were chosen for this review because their problems are more complex than those of other antibiotic classes. Prior research, which discusses the problems of the fluoroquinolone class and efforts to address its problems can be an inspiration and a reference for research in other suitable formulations to develop fluoroquinolone products that are effective, safe, acceptable, and stable.

2. Physicochemical problems of fluoroquinolone

2.1 Hygroscopicity

One of the fluoroquinolone drug compounds is levofloxacin (LVX) which has hygroscopicity problems. LVX is in the form of anhydrate, but because of its high hygroscopicity, it easily changes into a hemihydrate (LVX.0.5 H_2O) or a monohydrate (LVX.H_2O) in normal conditions. Its crystalline structure is shown in Figure 1 [14]. Dehydration of the hemihydrate form of LVX causes changes in the crystal lattice and produces a physical mixture (alpha, beta, gamma), including amorphous LVX. Therefore, during the manufacturing process, drying LVX hemihydrate can produce an amorphous form, which is unstable chemically and physically [15].

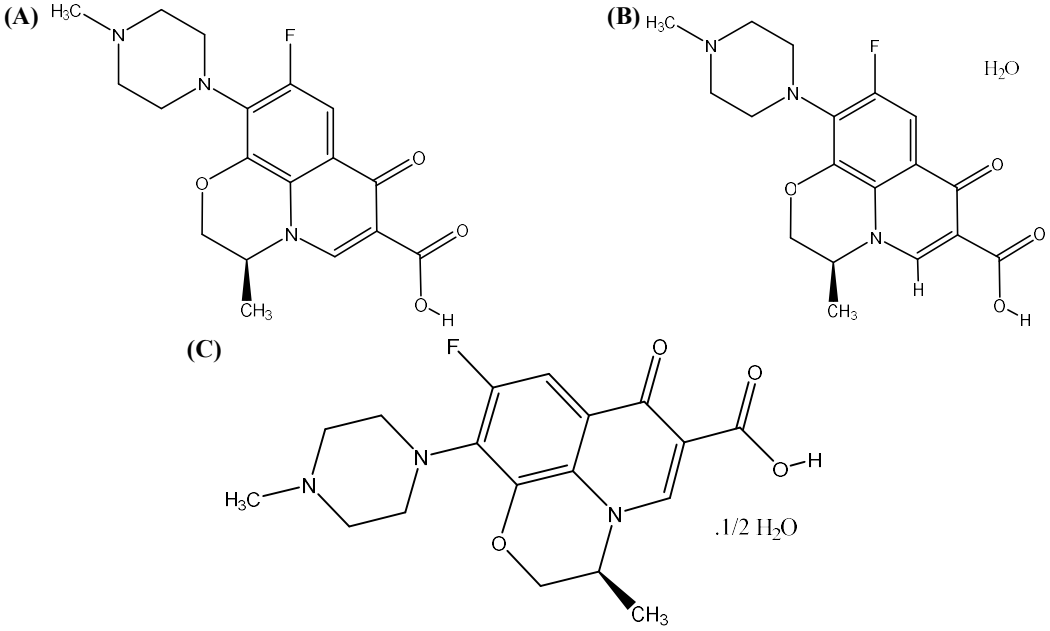

Figure 1 Chemical structure: (A) levofloxacin anhydrate (B) levofloxacin monohydrate (C) levofloxacin hemihydrate.

2.2 Photostability

2.2.1 Photodegradation

Fluoroquinolone can experience photodegradation because it is sensitive to light. Several factors can affect the photodegradation of the fluoroquinolone compound. They include organic compounds, pH, light intensity, and the structure of the compound itself [5]. The photodegradation of fluoroquinolone with a piperazine ring such as LVX occurred in 2 stages in the solution. The piperazine ring is degraded by light, forming a 7-amine derivative, which degrades further into a combination of CO_2 intermediate polar. The resulting products from the degradation, such as descarboxyl-LVX, desmethyl-LVX, diamine-LVX, desfluoro-LVX, desformyl-LVX, and LVX-N-oxide have been identified as decomposition products. The rate of LVX photodegradation within a pH range of 2-12 follows the rate of first-order kinetics [11]. The same occurs with NFX, CPX, and nalidixic acid, which follow the rate of first-order kinetics.

Several factors affect the photodegradation of LVX in a solution, including the pH of the solution and characteristics of the solvent [6]. In pH 10, the degradation of LVX is twice as fast as pH 7. LVX in a solution of pH 6.0-7.5 is formed as a zwitterion with pKa (5.59 and 7.94) close with the isoelectric point. The rate of LVX photodegradation in a solution depends on the specific ionic reactivity in a certain pH range. Other than that, the dielectric constant of the solvent and viscosity can affect the rate of photodegradation linearly because the reaction occurs more easily in a polar solution compared to an organic solution, and it is limited in a viscous solution.

Ion concentration and type affect the degradation process, which leads to the formation of photoproducts. Photodegradation of CPX produces two products: 7-[(2-aminoethyl) amino] 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and 7-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid. MFX produces three photodegradation products [16]. LMX produces two photodegradation products after it is subjected to radiation [17].

2.2.2 Phototoxicity

Not only does photostability affect the stability of drugs; it also affects the photosensitivity of the human body, including phototoxicity and photoallergy. According to Budai *et al*., the level of phototoxicity of fluoroquinolone derived from the highest was LMX > OFX > CPX [5]. Fluoroquinolone-derived drugs with halogen atoms at position 8 such as LMX, sparfloxacin, fleroxacin, and clinafloxacin provided the highest phototoxicity and caused photolability. Meanwhile, fluoroquinolone-derived drugs with a methoxy group at position 8 provided the least phototoxicity, and they were more photostable. However, LVX, which has a halogen atom at position 8 and aminodifluorophenyl group or isoxazolyl group at position 1 provides lighter and milder phototoxicity and is more photostable [18]. The substituent at position C-5 from the quinoline ring also affects the phototoxicity of fluoroquinolone. The presence of an electron-donating group, such as an amino group at position C-5, makes it easier to excite the drug at a shorter wavelength. This makes it more photostable because 95% of UV light that penetrates the earth is UV-A (315–400 nm) [19]. Other than that, the substituent at position N-1 also affects the level of phototoxicity from fluoroquinolone [20].

Several factors that may affect phototoxicity are half-life, metabolism, skin penetration, cell permeation, subcellular localization, and photoreactivity. Phototoxicity can be caused by the localization of drugs in cellular targets, such as CPX mediated by an intracellular target like DNA. The phototoxicity of fluoroquinolone is also associated with the formation of reactive oxygen. A study that radiated fluoroquinolone using UV-A, detected hydrogen peroxide (H_2O_2) and p-nitroso-dimethylaniline bleaching as a sign of the formation of radical hydroxyl, and the reduction of cytochrome c as a sign of the formation of superoxide. The presence of H_2O_2 and p-nitroso-dimethylaniline bleaching is related in parallel with the phototoxic potential of fluoroquinolone [21].

2.3 Drug-Excipient Interactions

2.3.1 Levofloxacin

Nisar *et al*. reported the interaction of LVX with the excipients sodium starch glycolate, magnesium stearate, lactose, and microcrystalline cellulose [7]. Based on the activation energy calculated using the Ozawa–Flynn–Wall equation, the interaction between LVX and the excipient of sodium starch glycolate, magnesium stearate, and microcrystalline cellulose was physical. Table 1 shows that the activation energy of pure LVX was 118.05 kJ/mol. This means there was no significant difference in activation energy between pure LVX and LVX with tested excipients other than lactose. LVX with lactose excipient experienced a drastic decrease in activation energy compared with pure LVX. This showed a strong chemical interaction between the drug and lactose. Therefore, this excipient is not compatible with LVX in a solid formulation.

Table 1 Comparison of activation energy between pure levofloxacin and excipients [7].

Sample	Activation energy (kJ/mol)
LVX	118.05
LVX – microcrystalline cellulose	95.77
LVX – sodium starch glycolate	94.14
LVX – magnesium stearate	94.11
LVX – lactose	39.93

As seen in Figure 2 and Figure 3, the peak absorption of FTIR LVX characteristics was obtained for the -OH group from the -COOH group around 3261.4 cm^{-1}, and the peak of -CO around 1725.1 cm^{-1}. The peak of aromatic C-H was observed in the range of 2900–3000 cm^{-1} [22]. The main functional band from the above mixture appeared in several regions: C-N strain at 1236 cm^{-1}, aromatic C-H strain at 1473 cm^{-1}. The absorption band of 1630 and 1600 may be associated with the carbonyl group and C=C in LVX, strain band of O-H at 1630 cm^{-1}, CH_2- strain at 2929 cm^{-1} was observed for all mixtures of the drug and excipients. Meanwhile, in LVX – lactose, the other absorption band of O-H extended at 3642 cm^{-1}. This indicated a chemical interaction between LVX and lactose. This interaction made lactose incapable of formulating solid preparation. Only physical interaction is needed, while chemical interaction may cause the pharmacokinetics of the drug [7].

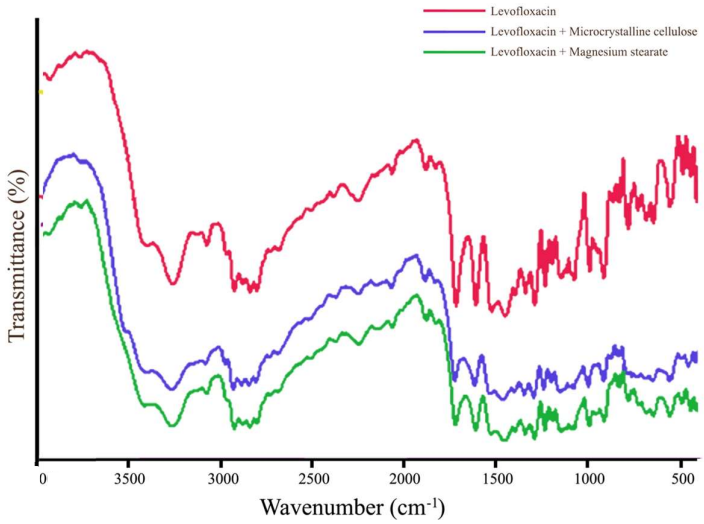

Figure 2 FTIR spectra of levofloxacin (red), levofloxacin-microcrystalline cellulose (blue), and levofloxacin-magnesium stearate (green) [7].

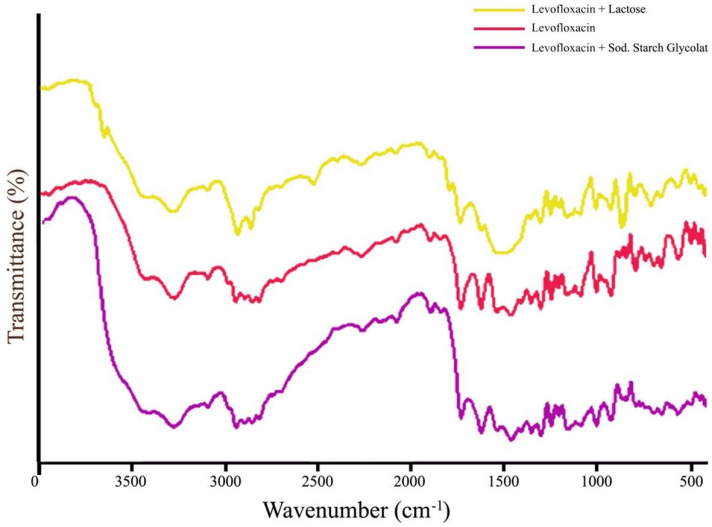

Figure 3 FTIR spectra of levofloxacin (red), levofloxacin–lactose (yellow), and levofloxacin-sodium starch glycolate (purple) [7].

2.3.2 Moxifloxacin HCl

Misra *et al*. reported that MFX HCl was incompatible with several solvents, including sorbitol, dicalcium phosphate anhydrous, and emcompress [23]. The hygroscopic nature of sorbitol reduces the physical stability of MFX HCl, which is shown by discoloration after a week in storing conditions. Compatibility tests on several excipients with MFX HCl showed differences in stability. Based on the remains of MFX HCl stored in ambient conditions, the highest stability was found when it was used with Avicel PH101. Less stability occurred when it was used with dicalcium phosphate anhydrous, followed by lactochem FP, pearlitol, Avicel PH102, lycatab, lactopress SD, dextrose anhydrous and emcompress. The lowest stability occurred with sorbitol. However, if stored at 50 °C, the order of stability changes. The highest stability occurs with lactochem FP, followed by dicalcium phosphate anhydrous, avicel PH101, lactopress SD, avicel PH102, lycatab, dextrose anhydrous, pearlitol, and neosorb, then emcompress.

In a liquid phase, the above excipients did not significantly change pH. This showed that the excipients had no buffer capacity, thus they will not affect the stability of MFX HCl in terms of pH. The most significant pH changes occurred using emcompress and dicalcium phosphate, which was from 1.4 to 3.6. This was suspected to be the factor causing discoloration. The rate of MFX HCl degradation increases along with an increase in pH.

2.3.3 Norfloxacin

Oliveira *et al*. reported that, based on the analysis with differential scanning calorimetry and thermogravimetric analysis (DSC-TG), there was no sign of incompatibility between NFX and several excipients [24]. microcrystalline cellulose, Mg stearate, colloidal silicon dioxide, lactose monohydrate, and Opadry II White.

2.4 Drug-drug interactions

2.4.1 Drugs containing cations

Fluoroquinolone group drugs interact with drugs containing cations, such as antacids and supplements containing calcium, iron, or zinc by forming a chelate complex, making them difficult to be absorbed Fluoroquinolone group drugs interact with drugs containing cations, such as antacids and supplements containing calcium, iron, or zinc by forming a chelate complex. This makes them difficult to absorb [25].

2.4.2 H2 receptor agonist and proton pump inhibitor

H2 receptor agonist and proton pump inhibitor can change the pH of the stomach, thus using them together can cause the absorption of fluoroquinolone drugs. Drugs such as cimetidine can inhibit tubular secretion in the kidneys, thus reducing the clearance of fluoroquinolone [26].

2.4.3 Probenecid

Probenecid inhibits tubular secretion in the kidneys, reducing the systemic clearance of fluoroquinolone drugs [27].

2.4.4 Theophylline

Fluoroquinolone can inhibit the clearance of theophylline. More specifically, it inhibits the affinity of cytochrome P450 (CYP) isoenzyme 1A2 [28].

2.4.5 Warfarin

There are three mechanisms of interaction between warfarin and fluoroquinolone drugs. First, fluoroquinolone inhibits warfarin elimination, especially during the metabolism stage. Second, warfarin exchange from the protein binding site by fluoroquinolone. In some patients, there is a prolonged prothrombin time after fluoroquinolone therapy. Third, the inhibition of intestinal flora produces vitamin K by fluoroquinolone. The best mechanism for interaction between fluoroquinolone and warfarin of these three was the inhibition of warfarin metabolism by fluoroquinolone [29].

2.4.6 Nonsteroidal Anti-Inflammatory Drugs (NSAID)

NSAIDs bind gamma-aminobutyric acid (GABA) neurotransmitters, while quinolone inhibits the binding of GABA to a synaptic membrane [27].

3. Analysis of fluoroquinolone problems

3.2 Analysis of Hygroscopicity

Shinozhaki *et al*. used a dynamic vapor sorption analyzer at a constant temperature of 25 °C. They showed that LVX anhydrate quickly changes into LVX.H_2O with RH increase of 0% to 10% [6]. In the same test, LVX in the co-crystal form had a non-hygroscopic nature and absorbed only 0.3% of water in RH of 95%.

3.2 Analysis of photostability

3.2.1 High-Performance Liquid Chromatography (HPLC)

The HPLC system uses a UV detector. HPLC analysis was conducted at room temperature (25 ± 2 °C) using an isocratic condition. Detection of LVX antibiotic stability was conducted at the 287 nm wavelength [11].

3.2.2 High-Performance Capillary Electrophoresis (HPCE)

The HPCE system analysis was conducted using an AD detector. Before each analysis, the capillary was conditioned by rinsing with 1.0 mol/L NaOH for 1.5 min, water for 1 min, and background electrolyte (BGE) for 1.5 min. After analysis, rinsing was also performed using 0.1 mol/L HCl, methanol, and water for 1 min. A phosphate buffer background electrolyte (pH = 2.5) with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) was used as separator chiral. This analysis was conducted to analyze the photodegradation of LVX and ofloxacin [30].

3.2.3 Dark Fenton Reaction

This reaction was used to produce ΣOH for indirect reaction in the identification study of photolysis product. The molecular ions conformed with the hydroxylation version of LVX mass (378 m/z) observed in ES (+) [31].

3.2.4 Mass Spectroscopy

Mass spectrophotometer (MS) of the LC-MSD type with electrospray ion source (ESI/MS) can perform MS measurement in a positive mode. The capillary volt used was 4000 V, and the fragmentor was 50. The quadrupole was scanned at around 50–1000 m/z. The capillary temperature was maintained at 35 °C. Nitrogen was applied with 35 psi and 13 L/min, as a nebulizer and dryer gas. This method can analyze the photostability of LVX [5].

3.2.5 Ultra-performance liquid chromatography-mass spectrometry/mass spectrometry (UPLC-MS/MS)

This method made it possible to determine the resulting products of photodegradation from fluoroquinolone. Chromatography separation was conducted using the UPLC BEH Acquity column (bridged ethyl hybrid) C18; 2.1 x 100 mm, with a particle size of 1.7 µm. The column was maintained at 40 °C. The chromatogram was recorded using a Waters PDA eλ detector. The concentration of the compound (%i) after photodegradation was calculated from the quotient of the peak area (Ai) to the total of all peak areas (ΣA) in the chromatogram according to the formulation, %i = (Ai/ΣA) 100 at λ = 294 nm. The spectrum was analyzed within the range of 200–700 nm with a resolution of 1.2 nm and a sample collection rate of 20 points/s [5].

3.3 Analysis of incompatibility

3.3.1 Fourier transform infra-red spectroscopy (FTIR)

FTIR is an easy, fast, and accurate method for determining the compatibility between drugs and their excipients [32]. Drugs with and without excipients were added with IR grade KBr ground with pestle and

mortar. Nisar *et al*. reported that the scanning of LVX and its excipient can be performed in the range of 4000-400 cm^{-1} [7].

3.3.2 Thermogravimetric analysis (TGA)

TGA can be used for pyrolysis experiments conducted in a nitrogen atmosphere (20 mL/min) in the range of 30-600 °C with a heating speed of 7.5; 10, 12.5; and 15 °C/min for pure LVX testing or with an excipient. The compatibility of drugs with their excipients can be seen from the reduction of activation energy calculated by the Ozawa–Flynn–Wall equation. The activation energy of the pure fluoroquinolone group was compared with the fluoroquinolone group plus the excipient. The difference in activation energy was not significant between pure drugs and drugs with excipients. This means that there were problems of stability and compatibility with the formulation. However, the interaction between drugs and their excipients revealed a drastic decline in activation energy compared to a pure drug [7].

3.3.3 Differential scanning calorimetry (DSC)

This method is used to analyze the drugs and their mixture thermally. In the thermal analysis of MFX HCl, the drug sample and its mixture were directly scaled on a DSC aluminum container and scanned at 30–350 °C with a heating speed of 20 °C/min under a dry nitrogen atmosphere (50 mL/min) [23]. Meanwhile, the thermal analysis of LVX incompatibility with its excipient used a range of heat of 25–500 °C with a heating speed of 10 °C /min under dry nitrogen atmosphere (20 mL/min) [7]. A closed empty container, which is a standard reference, was put inside. Using this method, the incompatibility of the drug and its excipient can be observed by looking at the changes of enthalpy compared to the standard reference without an excipient.

3.3.4 Analysis of drug interaction

The interaction of fluoroquinolone group antibiotics can be analyzed using the HPLC instrument [12]. The samples that can be used include plasma, serum, urine, sputum, feces, saliva, and bile. Fluoroquinolone testing used the isocratic mobile phase and the reverse phase. Adding tetrabutylammonium phosphate and other amine compounds helps to avoid tailing. The wavelength used for the fluoroquinolone group was 254-270 nm.

4. Solutions to fluoroquinolone problems

4.1 Reducing the hygroscopicity of fluoroquinolone

4.1.1 Formation of co-crystals

The formation of fluoroquinolone group drugs in the form of co-crystal can reduce hygroscopicity [6].

4.1.2 Formation of levofloxacin ethoxycarbonyl-1-ethyl hemiacetal ester

Otori *et al*. successfully synthesized levofloxacin ethoxycarbonyl-1-ethyl hemiacetal ester (LVX-EHE) with 99% purity [33]. LVX EHE can prevent the formation of chelate and its hygroscopicity is highly stable in normal conditions.

4.2 Enhance photostability of fluoroquinolone

4.2.1 Made into co-crystals

LVX was made into co-crystals with metacetamol (MEC). This form can reduce hygroscopicity and increase the photostability of LVX. The LVX-MEC crystal showed an increase in photostability in solid, liquid, and suspension forms. The increased photostability of LVX because of co-crystallization with MEC can be explained by the formation of a new crystal structure. In the LVX-MEC crystal, the MEC hydroxy group is linked with the N3 from N-methylpiperazine in LVX by a hydrogen bond, substituting an electron charge in the N-H bond to nitrogen. This can break the nitrogen-free electron pair in the electron orbital and avoid oxidation of N-methylpiperazine in LVX [6].

4.2.2 Made into a complex with cyclodextrin

Complexation was conducted between CPX and α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin. Forming a complex with α-cyclodextrin causes an increase in CPX photostability. However, β-cyclodextrin and γ-cyclodextrin showed no effect. Cyclodextrin is known to accelerate or slow down various types of reactions. The roles of cyclodextrin include catalyzing the formation of substrate complex, competitive inhibition, saturation, and stereospecific catalysis. The reaction rate increases when the targeted molecule is forced to stay in a reactive conformation. In this CPX-cyclodextrin complex, CPX was inserted into cyclodextrin to improve stability [9].

4.2.3 Formation of a complex with cucurbit (7)-uril (CB7)

Forming a complex between CPX and CB7 increases photostability up to three times. The cationic form of CPX (CPX-H+) and neutral form (CPX) formed strong bonds with CB7. Interaction of CPX–CB7 modulated the photophysical nature of CPX, increasing its photostability [10].

4.2.4 Made into an encapsulated liposome

LMX was made into encapsulated liposome by adding l-dipalmitoyl-phosphatidylcholine (DPPC) and dioleoyl-phosphatidylcholine (DOPC). Then, it was made into three formulas: DPPC small unilamellar vesicles (SUV), DPPC multilamellar vesicles (MLV), and DPPC/DOPC (70:30) small unilamellar vesicles (SUV). The results showed a slightly different degradation constant in the liposome medium compared to the aqueous medium. However, it did not provide a significant difference in accelerating or inhibiting photodegradation by UV-B. Meanwhile, a formula containing DOPC can inhibit LMX degradation without UV irradiation. Photoproducts can still be produced in the presence of lipid, although in a different way, and a different photoproduct results. The composition of the lipid significantly affects the degradation process. That process occurs by losing CO_2 or increasing the frequency of dehydrogenation and defluorination [5].

4.2.5 Combination of fluoroquinolone with calix (4)-arene in the form of nano supramolecular

This study used an NFX fluoroquinolone drug combined with a nitric oxide photodonor (NOPD) and made it into a nano supramolecular with the aggregate basis of micellar calix(4)-arene. The derivation of calix (4)-arene used was p-sulfonatecalixarenes because of its water solubility, the ability to bond, good biocompatibility, and easy preparation. This form can bond NFX and NOPD in one system without causing interactions. NOPD is an antibacterial agent that can overcome multi-drug resistance. This system can inhibit the complex formation responsible for the photodegradation of NFX, and it can provide an environment with low polarity according to NOPD, thus NOPD can be trapped. Therefore, this system can increase the photostability and effectiveness of fluoroquinolone antibiotics [34].

5. Prospects for future research

This literature study shows the potential success in solving the problems of several fluoroquinolone drugs. The success rates of the studies that have overcome the problems are expected to be reference points for conducting other studies to address the problems of fluoroquinolone drugs. As a result, the use of fluoroquinolone antibiotics in the future will not have any problems, especially related to the physicochemical properties of these drugs.

6. Conclusion

Fluoroquinolone is a group of antibiotics. Several physicochemical problems in the fluoroquinolone group of drugs have been reported in the literature. Some of these drugs were reported to have poor photostability, were hygroscopic, or had incompatibilities with their excipients in the formulations. Using fluoroquinolone drugs along with other drugs can cause an interaction between the drugs. Regarding these problems, there are several analysis techniques and solutions that can be recommended.

7. Conflict of Interests

The authors declare that there are no conflicts of interest.

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