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**Review Article**

# Forced Degradation and Stability-Indicating Analysis of Ciprofloxacin, Levofloxacin and Ornidazole: A Comparative Review and Requirements for a Combined Method

Kunwar Pratap Singh[1]*, Jitendra Kumar Malik[1]

[1]Faculty of Pharmacy, P.K. University, Shivpuri, M.P. India

***Corresponding Author:** Kunwar Pratap Singh
Faculty of Pharmacy, P.K. University, Shivpuri, M.P. India

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**Abstract:** Ciprofloxacin (CIP) and levofloxacin (LEV) are antibiotics from the fluoroquinolone group, while ornidazole (ORN) belongs to the 5-nitroimidazole family. Thus, they can be co-administered or combined in one formulation, but they have different paths of degradation. In the review, degradation processes of the three drugs are compared in the event of stress in accordance with ICH Q1A(R2) and Q1B guidelines, insights are drawn regarding what results should be achieved when making a stability-indicating method (SIM) for three drugs at once. According to different publications, CIP is known to lose 19.2% under acid conditions, 23.6% under alkaline conditions, 39.7% under peroxides, 8.2% under heat treatment, and 28.1% under UV light and its main photodegradation product has already been identified. In LEV, the best understood process is that of oxidation of piperazine nitrogen to the inactive N-oxide upon the exposure to sunlight in infusion. In the case of ORN, nitroimidazole and chlorohydrin moieties render the drug particularly sensitive to light and alkali; however, the data we could collect from different resources appear to be limited. Evidence is collected into tables, reliability is graded and peak purity, mass balance, LC–MS identification and stressing in mixtures are described.

**Keywords:** Forced Degradation, Stability-Indicating Method, Ciprofloxacin, Levofloxacin, Ornidazole, Photodegradation, N-Oxide, ICH Q1A(R2), RP-HPLC.

## INTRODUCTION

The drug product must maintain its identity, strength, and purity for its entire shelf life. In order to prove that this is true, an analytical method that observes the drug in its original form while differentiating it from any degradation products that could be produced is needed. Forced degradation, in which the drug is tested in much harsher conditions than would usually be done in accelerated storage, is the experiment that shows that such a method is indeed stability-indicating. It will also document any degradation pathways and help in formulation and packaging.

Fluoroquinolones Ciprofloxacin and Levofloxacin function by targeting bacterial topoisomerase 4 and DNA gyrase [2]. On the other hand, Ornidazole, a 5-nitroimidazole, is rendered toxic towards nucleic acids by its reduced form, which is produced during anaerobic metabolism process [3]. Since both types of antibiotics are used in the treatment of mixed infections, the facility needs means and ways of testing the drugs together as well as performing stability tests of the consequently produced formulations of these combinations.

In this review, the three drugs were selected because they differ chemically with regards to degradation. The core of fluoroquinolone CIP and LEV is photoreactive, as is the piperazine ring but ORN contains a nitro-substituted imidazole and chlorohydrin chain that undergo reactions with light and alkaline substances. Therefore, it is necessary for each type of stress to be applied to a SIM in the combination. The aims of the research are as follows: (i) to present the regulatory

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framework, (ii) to collect information about the behavior of drugs under stress, (iii) with the help of this information to evaluate its reliability, and (iv) to formulate requirements for a SIM in relation to all studied drugs and stress testing protocol. The paper does not present any new laboratory data. If the data about percentage degradation has been obtained from a primary source, this source is referenced. If the data has been collected from a secondary publication, a dagger (†) is placed next to the statement.

## 2. Framework and Principles of Regulation Concerning Forced Degradation

According to ICH Q1A(R2), stress testing of the drug product occurs to determine likely degradation products, degradation routes as well as to confirm how effective the analytical method is in monitoring the above issues. Hydrolysis at various pH levels, as well as oxidation, photodegradation, and heat are considered being types of stresses applied [4]. The ICH Q1B provides the regulations regarding photostability testing (type of light and duration of exposure considered) [5], while ICH Q2(R2) defines the validation parameters of the method (specificity is the main parameter for SIM) [6]. Also, ICH Q14 provides information concerning development of analytical methods (previous knowledge and experiment design) [7].

- Degrade to a practical extent. A standard of around 5%–20% reduction of the parent compound has been reported in the literature, while the values of 10%–30% have also been used in practice. The goal is to form the main degradation products and not to induce further degradation.
- Employ different conditions of the same type of stress and carry out sampling at several time points to allow distinguishing between primary and secondary products.
- Implement controls: unstressed sample, blank, and for products, a placebo undergoing the same stress.
- Prove specificity using peak purity (diode-array detection) and, if possible, using another orthogonal method such as LC-MS.
- Consider masses: concerning the mass, an amount of the parent compound and degradation products must be similar to the original mass with a permitted deviation of 90%-110%.

**Table 1: Typical stress conditions used as starting points in forced-degradation studies**

| Stress | Typical starting conditions | Notes |
|---|---|---|
| Acid hydrolysis | 0.1–1 N HCl, room temperature to 80 °C, hours | Neutralise before injection; adjust to reach target loss |
| Alkaline hydrolysis | 0.01–1 N NaOH, room temperature to 80 °C, minutes to hours | Very labile drugs need milder conditions |
| Oxidation | 3–30% H2O2, room temperature, hours | Higher temperature accelerates but may change pathway |
| Thermal | Solid and solution, 60–105 °C, hours to days | Dry heat for solids; consider humidity |
| Photolysis | ICH Q1B exposure of solid and solution | Use dark controls; solution and solid can differ markedly |

*Starting points synthesised from the regulatory and review literature [1,4,5]; the conditions actually used must be tuned for each drug.*

## 3. Profiles of the Drugs and of Reactive Sites

Structures indicate where degradation is possible (see Table 2). The structure of the fluoroquinolone core includes the ability to absorb UV and light (see CIP and LEV useful for photo-degradation). The N-4′ nitrogen of the piperazine ring is a potential site of N-oxidation- a condition met by the presence of a secondary amine for both CIP (which has a possibility of photolytic rupture of the ring). The 5-nitroimidazole of ORN functions as a chromophore with a high near-UV absorption. The side chain chlorohydrin is also photoreactive and can undergo hydrolysis to epoxide in the presence of basic condition with the loss of $Cl^-$ [11].

**Table 2: Reactive sites and expected liabilities**

| Drug | Reactive sites | Expected main liabilities |
|---|---|---|
| Ciprofloxacin | Quinolone chromophore; C-7 piperazine; C-6 fluorine; cyclopropyl at N-1 | Photolysis (defluorination, piperazine loss); oxidation; acid and alkali to a moderate degree |
| Levofloxacin | Quinolone chromophore; methylpiperazine (tertiary N); fused benzoxazine | N-Oxidation of piperazine; acid; light in solution over long exposure |
| Ornidazole | Nitroimidazole; chlorohydrin side chain | Photolysis; alkali (epoxide formation, dechlorination); nitro-group reduction |

## 4. Ciprofloxacin

### 4.1 Behaviour under Stress

The most comprehensive quantitative data about CIP hydrochloride were obtained from a study of CIP in a C18 column with phosphate buffer (pH 3) and acetonitrile (80:20) under UV detection at 278 nm (12). CIP sensitivity order was as follows: first place was taken by oxidation, second place by ultraviolet rays, and third place by bases, in terms of relative sensitivity to acids, it was medium and with regard to heating, it did not undergo a significant change (Table 3, Figure 1). Therefore, one must attack SOP with peroxide and light rather than only acids and bases.

**Table 3: Forced degradation of ciprofloxacin hydrochloride (Bushra *et al*., [12])**

| Stress | Conditions | Degradation (%) |
|---|---|---|
| Acid | 0.1 N HCl, 70 °C, 4 h | 19.24 |
| Alkali | 0.1 N NaOH, 70 °C, 4 h | 23.63 |
| Oxidation | 3% H2O2, 70 °C, 4 h | 39.66 |
| Thermal | 60 °C, 24 h (dry, thin layer) | 8.21 |
| Photolysis | UV 254 nm, 5 days | 28.12 |

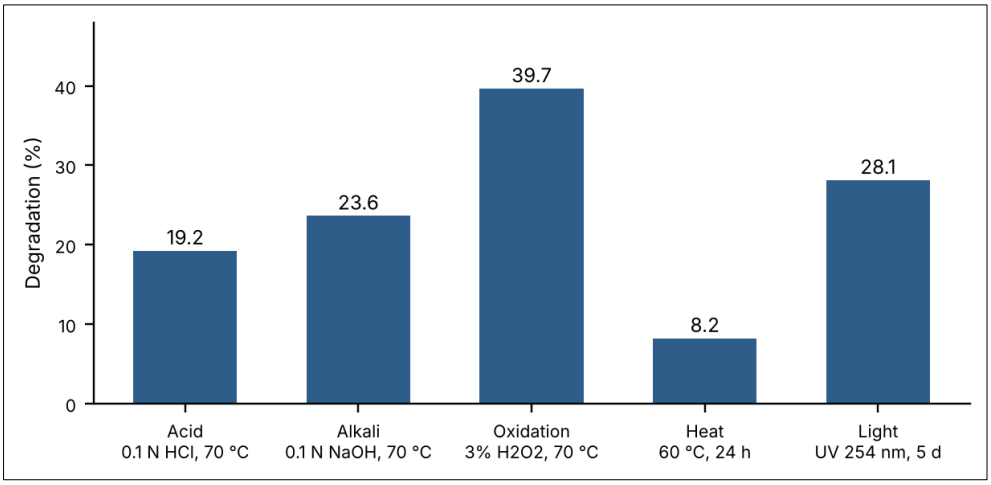


**Figure 1: Forced degradation of ciprofloxacin hydrochloride under five stress conditions (data from Bushra *et al*., [12])**

The chief product of photodegradation for CIP is known as 7-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolone-carboxylic acid, which is a result of the degradation of the piperazine ring to yield a primary amine [13]. Alabbas and Abdel-Gawad have performed quantitative analysis of CIP together with the aforementioned main product through capillary zone electrophoresis (borate buffer at pH 8.5, using 280 nm) and ultra-performance liquid chromatography (C-18; tablet size 100 × 2.1 mm; particle size 1.7 µm; phosphate buffer at pH 3.0-acetonitrile 7:3) with the findings showing a linear response from 0.5 to 50 µg/mL, with a resolution of 4.10 (CZE) and a resolution of 2.28 (UPLC) for CIP and MDP which occurred at 4.20 mins and 3.40 mins, respectively [13]. The intravenous form underwent more degradation than the tablet form, which was attributed to the fact that the intravenous solution is aqueous and acidic in nature [13].

At elevated pH levels, photolysis mechanisms change. For instance, when CIP is subjected to radiation at pH 9, it can result in the formation of five kinds of possible photodegradative products resulting from processes such as defluorination, decarboxylation, and loss of piperazine moiety, and formation of these products requires the formulation that has low monitoring capacity due to other factors also being involved [14].

## 5. Levofloxacin

### 5.1 Behavior in Terms of Photolysis and Photocatalysis

Levofloxacin is the one with the most detailed information about degradation. In infusions exposed to direct sunlight for 84 days, about 85% of the original amount of substance was preserved in Ringer's solution and about 96% in 5% dextrose and in 0.9% sodium chloride; the protected samples, however, did not deteriorate [15]. In a solar simulator (250 W/m²), the percentage of preserved material was 88% in Ringer's solution [15].

The molecule that got formed as a result of degradation was levofloxacin-N-oxide, with an ion [M+H]+ at m/z 378 and ion m/z 362 for the original molecule; it was reported that this ion is not active [15].

The HPLC method used in this study can be considered useful for the fluoroquinolone part of the combined method; the 250 x 4 mm column (5 µm) with acetonitrile–0.4% triethylamine (24:76, pH 2.5) was used at flow rate of 1 mL/min and detection wavelength of 295 nm, with levofloxacin appearing at about 3.1 min and N-oxide at 4.05 min, with a resolution of 2.9 minutes between them [15].

The previously mentioned research describes the first-order rate constants and the 10% loss duration, which allows to assess LEV's susceptibility to light exposure in practical terms (Table 4). In the case of the first-order reaction, the duration until the 10% loss is equal to ln(1/0.9)/k or roughly 0.105/k; the observed values of 53, 141, and 206 days conform to this rule. The selection of the infusion solution affects the rate approximately four times and demonstrates that the medium as well as the drug plays a role in drug photostability [15].

**Table 4: Photodegradation kinetics of levofloxacin in infusion fluids exposed to daylight**

| Infusion fluid | Rate constant k ($day^{-1}$) | Time for 10% loss (days) | Remaining after 84 days (%) |
|---|---|---|---|
| Ringer's solution | $1.99 \times 10^{-3}$ | ≈ 53 | ≈ 85 |
| 0.9% sodium chloride | $7.48 \times 10^{-4}$ | ≈ 141 | ≈ 96 |
| 5% dextrose | $5.11 \times 10^{-4}$ | ≈ 206 | ≈ 96 |

*Room temperature 23.7 ± 0.7 °C; samples protected from light were stable.*

### 5.2 Hydrolysis and Thermal Behavior

According to a reported validated stability-indicating RP-HPLC technique for levofloxacin in the presence of analytes and the degradation products, their possible presence was indicated by the work of Lalitha Devi and Chandrasekhar [16]. It is noticed that the work gives information about the depletion of around 34% in strong acid medium (5 N HCl, 60 °C, 6 h†), slight loss in the alkaline environment, and under a thermal environment (105 °C, below 0.3%†), and a loss of nearly 9% when treated with 30% of hydrogen peroxide at RT†. For our work, we are taking these reports as indicators of relative instability rather than as actual results. Overall, it can be said that LEV has shown some stability under base and heat treatment while being highly susceptible to acid, oxidation, and prolonged light exposure in the solution.

## 6. Ornidazole

There is little available quantitative information about stress tests of ornidazole in the used literature. Some works presenting the stress tests have reported the use of a validated assay method for the determination of stability of ornidazole [17]. The mechanistic studies performed for ornidazole in aqueous solutions have demonstrated various concurrent reactions taking place, including nitro-group reduction, dechlorination, N-de-nitration and cracking of the molecule in addition to the conversion of the chlorohydrin to epoxide at pH above 6, which becomes faster in alkaline conditions along with the release of nitrate, nitrite, and chloride ions [11]. There are several secondary deposition papers where it is indicated that ORN shows degradation of approximately 27% in 0.1 M HCl at the temperature of 80 °C after 4 h†, approximately 22% in 0.1 M NaOH after 4 h† and total loss in 0.5 N NaOH for 15 min†, around 5% with 30% H2O2†, around 1.5% at 80 °C for 24 h†, and around 89% after 4 h exposure to sunlight†. Although these figures only have indicative characters, their trend is determined by the chemistry: ORN is very light-sensitive and base-sensitive, and safe from oxidation and heating. There is also the stability test of ofloxacin related to ORN, which was performed in a medium consisting of acetonitrile–ammonium acetate solution with pH 5.8 (25:75) and which registered at the wavelengths of 293 and 311 nm [18].

## 7. Comparative Analysis

In Table 5, the three different drugs are presented, while the relative lability is summed up in Figure 2. Each drug has a dominant way of degradation: CIP degradation is primarily associated with oxidation and light; LEV degradation is based on n-oxidation and acid; whereas ORN degradation is related to light and alkali. The strength of evidence varies for the drugs tested, while data about CIP comes from a single study, and information about LEV and ORN comes partly from secondary studies. Thus, ranking can be regarded as qualitative.

**Table 5: Comparative stress behaviour (approximate; † = secondary source, primary study to be confirmed)**

| Stress | Ciprofloxacin | Levofloxacin | Ornidazole |
|---|---|---|---|
| Acid | 19.2% (0.1 N HCl, 70 °C, 4 h) [12] | ≈ 34%† (5 N HCl, 60 °C, 6 h) | ≈ 27%† (0.1 M HCl, 80 °C, 4 h) |
| Alkali | 23.6% (0.1 N NaOH, 70 °C, 4 h) [12] | < 1%† | ≈ 22%† (0.1 M NaOH, 4 h); ≈ 100%† (0.5 N, 80 °C, 15 min) |
| Oxidation | 39.7% (3% H2O2, 70 °C, 4 h) [12] | ≈ 9%† (30% H2O2, 25 °C, 6 h); N-oxide [15] | ≈ 5%† (30% H2O2, 25 °C, 4 h) |
| Thermal | 8.2% (60 °C, 24 h) [12] | < 0.3%† (105 °C) | ≈ 1.5%† (80 °C, 24 h) |
| Light | 28.1% (UV 254 nm, 5 d) [12]; MDP [13] | 4–15% loss in infusions over 84 d (daylight) [15] | ≈ 89%† (sunlight, 4 h) |

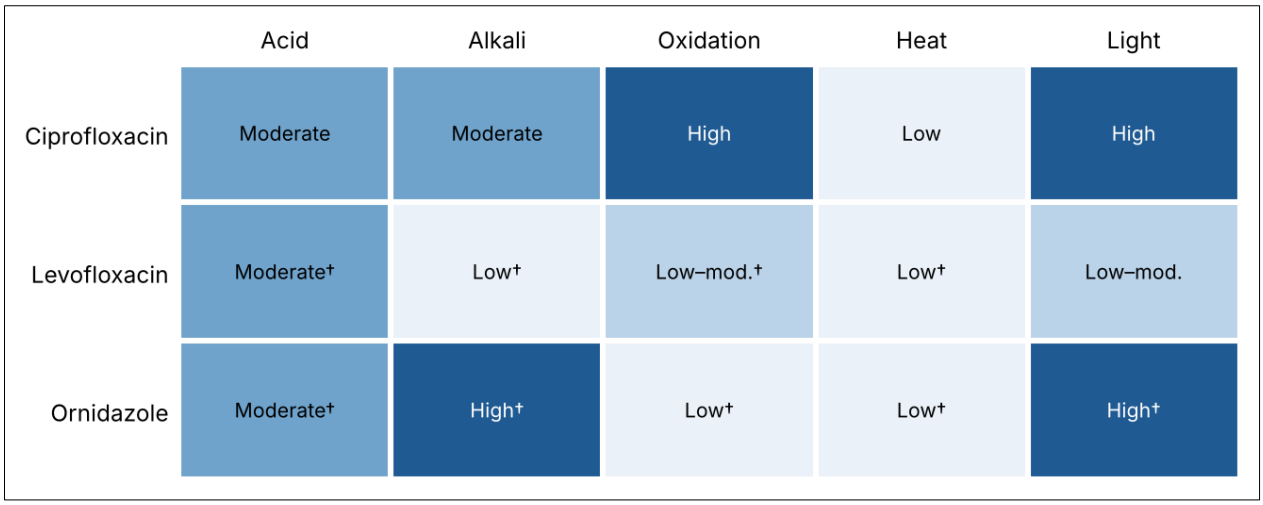


**Figure 2: Relative lability of the three drugs by stress type (qualitative grading; † = based partly on secondary sources)**

## 8. Conditions for Making a Stability-Indicating Method for the Combination

### 8.1 Separation

Separation involves the task of separating three parent components and their degradation products. Descriptions of the fluoroquinolone methods utilize C18 columns, acid mobile phases with pH 2.5–3 and detection done somewhere around 278–295 nm, as per Table 6. ORN, however, has absorption at longer wavelength and is detected at a wavelength of about 310 nm. Thus, a combined technique has to either select the best wavelength, or switch over from one wavelength to another during the run, utilizing a diode detector for monitoring wavelengths in the range of the detection.

**Table 6: Chromatographic conditions of verified stability-indicating or related methods**

| Reference | Analytes | Column | Mobile phase | Detection |
|---|---|---|---|---|
| Bushra *et al*., [12] | CIP | Phenomenex C18, 250 × 4.6 mm, 5 µm | Phosphate pH 3: acetonitrile 80: 20; 1 mL/min | 278 nm |
| Czyrski *et al*., [15] | LEV and N-oxide | LiChroCART, 250 × 4 mm, 5 µm | Acetonitrile: 0.4% TEA 24: 76, pH 2.5; 1 mL/min | 295 nm |
| Alabbas & Abdel-Gawad [13] | CIP and MDP | C18, 100 × 2.1 mm, 1.7 µm (UPLC) | Phosphate pH 3.0: acetonitrile 70: 30; 0.4 mL/min | Not stated in text |
| D'Souza *et al*., [18] | Ofloxacin, ORN | Hyperclone BDS C18, 250 × 4.6 mm, 5 µm | Acetonitrile: ammonium acetate pH 5.8, 25: 75; 1 mL/min | 293 and 311 nm |

### 8.2 Specificity, Mass Balance and Identification

Peak purity must be established for all the drugs delivered in every stressed sample using either the DAD purity angle or alternative measure. Mass balance can be defined as the combination of the drugs' assay and the area-corrected degrade products in relation to normal nondeteriorated sample where if the degradants' standard is absent then relative response factor is applied and this point needs clarifying. In situations when the mass balance is grossly under 100 % one can suggest the non-detectable and missing degrading product or even volatile profiles. Known and expected degrading agents include CIP-MDP [13], LEV N-oxide with m/z 378 [15], and other denitrified or dechlorinated ORN products [11].

Here is a worked example showing how the calculation is applied. The equation for mass balance (%) is given as: Mass balance (%) = [A(parent, stressed) + Σ A(degradant) ÷ RRF] ÷ A(parent, control) × 100. Here, A is the peak area after making the necessary dilution correction and RRF is the relative response factor for each of the degradants against the parent. Let us assume hypothetically that the stressed CIP sample gives the parent at 71.2% of the control area and two degradants contribute together 26.8% after correcting using the RRF. The mass balance in this case will be equal to 98.0% and is thus within the 90%-110% range, so all the degradants are accounted for. In case the same sample gave 82%, then the missing 18% would have to be explained somehow, probably by the presence of a degradant that is either not retained or does not absorb at the wavelength used or is volatile. Please note that these values are not derived from any experimental data but are illustrative only.

Testing should be carried out on two interactions related to the mixture. One is that a breakdown product of one drug could appear alongside another parent and therefore all the stressed solutions of the single drug need to be tested as well as the mixture. Another point relates to one component being able to awaken or protect the other due to light absorption

or oxidant consumption and therefore the results obtained from testing the mixture should be compared to the results of the single drugs rather than assuming the additive effect.

### 8.3 Handling the Sample

Photolabile samples should only be used with protection from light except for the tests involving exposing it to light, and in addition to that the solutions obtained during the stressing experiments should be neutralised before being injected.

### 8.4 Choice of Technique

RP-HPLC with DAD is usually the standard technique employed in quality-control SIM. UPLC decreases run time and reduces solvent consumption, as has been shown for CIP and its photoproduct (4.20 and 3.40 minutes using a 1.7-mm column). However, the study mentioned indicates that capillary zone electrophoresis provides better resolution (4.10 vs. 2.28) and is cheaper and more environmentally friendly, although the authors considered UPLC to be the more dependable one. To identify unknown degradation products, LC-MS or LC-MS/MS must be used (as in identifying LEV N-oxide).

### 8.5 Validation of the Method

The SIM must be validated in accordance with ICH Q2(R2) once it has been developed. The criteria proposed in Table 7 are conventional for methods of this type and are targets rather than results. Specificity is demonstrated through the forced degradation study itself.

**Table 7: Proposed validation characteristics and acceptance criteria for the stability-indicating method**

| Characteristic | Approach | Proposed criterion |
|---|---|---|
| Specificity | Stressed samples, placebo, individual and mixed standards; DAD purity | Parents pure; Rs > 1.5 to nearest degradant; no placebo interference |
| Linearity and range | At least five levels per drug, covering 80–120% of test concentration (wider for degradants) | $r^2 \geq 0.999$ |
| Accuracy | Spiked placebo at three levels, triplicate | Recovery 98–102% for assay |
| Precision | Repeatability (n = 6) and intermediate precision | RSD ≤ 2% |
| LOD / LOQ | For degradants: signal-to-noise 3 and 10 | LOQ at or below reporting threshold |
| Robustness | Small changes in pH, organic content, temperature and flow | Rs and tailing within limits |
| Solution stability | Standards and samples; light-protected | Change ≤ 2% |

## 9. Suggested Stress Protocol for Three-Drug Combination

Table 8 presents a procedure that tests each stress on individual substances and on the drug combination. Each solution helps in finding the source of each peak while the combination allows for seeing whether drugs influence each other in terms of degradation. Conditions represent the starting points that should be adjusted based on the degradation objectives.

**Table 8: Proposed forced-degradation protocol for CIP, LEV and ORN**

| Stress | Samples | Starting conditions | Acceptance / readout |
|---|---|---|---|
| Acid | Each drug; mixture; placebo | 0.1 N HCl, 60–80 °C; sample at 1, 2, 4, 8 h | 5–30% loss; Rs > 1.5 parent–degradant |
| Alkali | Each drug; mixture; placebo | 0.01–0.1 N NaOH, room temperature; sample at 5, 15, 30, 60 min | ORN may be lost quickly: use mild conditions |
| Oxidation | Each drug; mixture; placebo | 3% H2O2, room temperature; sample over 24 h | Check LEV N-oxide at m/z 378 |
| Thermal | Solid and solution | 60–80 °C, 1–7 days | Mass balance 90–110% |
| Photolysis | Solid and solution; dark controls | ICH Q1B exposure | Identify CIP–MDP and ORN products |
| All | Unstressed control, blank | — | DAD peak purity of each parent; LC–MS of major degradants |

## 10. Effects of Formulation, Shipping, and Storage

- Light protection is key, as ORN is the most photolabile, while CIP also degrades in light. Therefore products containing these compounds should be supplied in dark or opaque packaging, and special care should be taken regarding the intravenous CIP infusion as it showed even greater degradation at about amount of degradation [13].

- If LEV is stored for longer periods of time, infusions of LEV should not be exposed to daylight; research suggests that protected samples remain stable for 84 days [15].
- pH is important; that is, ORN is more active in alkaline solutions [11], and photoproducts of CIP differ at higher pH [14], that is why safer formulations will have a pH close to neutral and slightly acidic.
- When it comes to formulations containing CIP, both antioxidants and low-oxygen packaging should be assessed, because CIP has poor resistance to oxidation [12].
- Examination of compatibility with excipients and climate zone effects for the combination is also needed.

**11. Environmental and Safety Aspects**

Degradation goes beyond the effectiveness aspect; LEV N-oxide was found to be inactive, and so oxidation reduces its efficiency without introducing anything useful [15]. The main photo product of CIP has lower efficiency, and the photo products produced at pH 9 were also not biodegradable, although they did not affect Vibrio fischeri at the concentrations tested [14]. The degradation products of ORN include nitrite and nitrate ions as well as chlorinated and dechlorinated species [11]. There is no report on the toxicity of these substances towards patients as shown in the sources analyzed, resulting in the necessity of further evaluations through appropriate testing.

**11. Limitations and Knowledge Deficits**

- In the references we consulted, we did not find any forced degradation study for Cipro and of the other related compounds.
- ORN data were obtained mainly from secondary sources while Ley clenbuterol data need to be verified by primary studies.
- The structures of several CIP and ORN acids and bases are not provided in the papers we analysed.
- The conditions for inducing the stress are different in all articles reviewed, making comparisons for different drugs rather weak.
- Only a few papers discuss the impact of excipients, high humidity and storage of mixtures.
- Reports on the greenness of the stability analysis methods are almost absent.

## 13. CONCLUSION

Ciprofloxacin, levofloxacin, and ornidazole undergo degradation via diverse mechanisms: CIP primarily via oxidation and photodegradation, LEV mainly via N-oxidation and hydrolysis, and ORN mainly through photodegradation and alkaline hydrolysis. Consequently, the stress testing of the mixture should involve all five stressors where peak purity of each active substance in different stressed samples of the mixture can be proven and the quantity of degradation products accounted for. As part of that study, LC–MS should be employed to confirm that none of the degradation products is hiding under another peak. Concerning the packaging used for the mixture, it should be light-protective for ciprofloxacin-containing products while ciprofloxacin itself is required to be protected from oxidation.

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**Conflict of Interest:** None.

**Data Availability:** No new experimental data were generated for this review.

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