# A Stability-Indicating RP-HPLC Method for Erlotinib: Gamma Irradiation-Induced and ICH-Guided Stress Degradation Studies

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(Received on 26th March 2025, accepted in revised form 13th July 2026)

**Summary:** Erlotinib (OSI-774), an FDA-approved epidermal growth factor receptor (EGFR) inhibitor, is extensively used in treating non-small cell lung cancer (NSCLC) and other malignancies. This study explores erlotinib's chemical instability under various stress conditions, including hydrolytic, oxidation, thermal, and photolytic stress, as well as its environmental impact due to drug residues in effluents. A stability-indicating reverse-phase liquid chromatography (RP-LC) method was developed to quantify erlotinib and its degradation products in pharmaceutical formulations. Gamma irradiation, an advanced oxidation process, was evaluated for its efficacy in degrading erlotinib in aqueous solutions. The study revealed a significant increase in degradation efficiency with higher absorbed doses and acidic pH conditions. These findings underscore the potential of gamma irradiation as an effective environmental remediation strategy for removing pharmaceutical contaminants and provide the first investigation of erlotinib's degradation via gamma irradiation.

**Keywords:** Erlotinib; Gamma irradiation; HPLC; Degradation products; Environmental contamination

## Introduction

Erlotinib (OSI-774), branded as Tarceva®, is a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor widely used in the treatment of non-small cell lung cancer (NSCLC), pancreatic cancer, and other malignancies. By inhibiting EGFR-mediated signaling pathways, erlotinib suppresses tumor cell proliferation, angiogenesis, and metastatic progression. Owing to its important role in targeted cancer therapy, maintaining the quality, efficacy, and stability of erlotinib throughout its shelf life is essential for ensuring therapeutic performance and patient safety. Erlotinib has the chemical formula $C_{22}H_{23}N_3O_4$ and a molecular weight of 393.43 g mol−1 (Fig 1) [1].

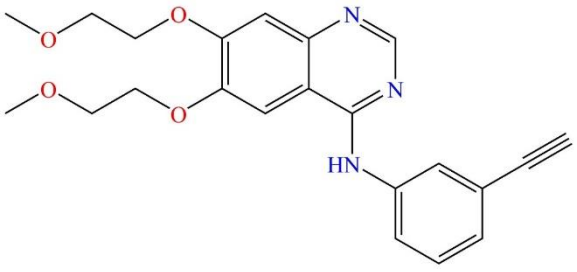


Fig 1: Chemical structure of Erlotinib.

Erlotinib is available for purchase in tablet form and is marketed under multiple brand names. However, pharmaceutical compounds may undergo chemical degradation when exposed to various environmental and processing conditions. Erlotinib is particularly susceptible to hydrolytic and oxidative degradation, especially after dissolution, where changes in the chemical environment may accelerate degradation processes [2]. Previous studies have demonstrated that erlotinib can undergo degradation under acidic, alkaline, and oxidative conditions, emphasizing the importance of evaluating its stability and developing reliable analytical methods capable of monitoring degradation products [3].

In addition to pharmaceutical stability concerns, increasing global cancer incidence has led to greater consumption of antineoplastic drugs, raising concerns regarding their environmental occurrence and persistence [4]. Anticancer drugs may enter aquatic environments through hospital and domestic wastewater systems. Several studies have reported the occurrence of antineoplastic agents in surface waters, municipal wastewaters, hospital effluents, and wastewater treatment plant discharges [5–8]. Consequently, understanding the environmental fate and degradation behavior of these compounds has become increasingly important.

Advanced oxidation processes (AOPs) have attracted considerable attention for the degradation of persistent pharmaceutical contaminants in water systems. Among these technologies, gamma

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irradiation has demonstrated high efficiency in the degradation of various pharmaceuticals and organic pollutants without the addition of chemical oxidants [9–19]. Previous studies have successfully applied gamma irradiation for the degradation of compounds such as cytarabine, ibuprofen, and sulfadiazine in aqueous media [14,17,19]. However, despite the growing interest in radiation-based AOPs, comprehensive investigations concerning the degradation behavior of erlotinib under gamma irradiation conditions remain limited. To the best of our knowledge, no detailed study has combined ICH-guided forced degradation assessment with gamma irradiation-induced degradation of erlotinib using a validated stability-indicating RP-HPLC method.

Several analytical methods have been reported for the determination of erlotinib in pharmaceutical formulations and biological matrices. These include chromatographic and spectroscopic approaches as well as studies focused on degradation behavior and impurity profiling [20–27]. Among these techniques, reverse-phase high-performance liquid chromatography (RP-HPLC) remains one of the most widely used approaches because of its sensitivity, selectivity, and suitability for routine quality control applications.

According to ICH guidelines, forced degradation studies are an essential component of pharmaceutical development because they provide information regarding degradation pathways, intrinsic stability, and potential degradation products. Furthermore, analytical procedures used for stability assessment should be stability-indicating and should be thoroughly validated to ensure accurate quantification of the active pharmaceutical ingredient in the presence of degradation products, impurities, and excipients [28–31]. Although several studies have reported forced degradation and analytical determination of erlotinib, the available literature mainly focuses on conventional stress conditions.

Therefore, the present study aimed to develop and validate a stability-indicating RP-HPLC method for the determination of erlotinib and to apply the validated method for the quantitative analysis of erlotinib in pharmaceutical formulations. Furthermore, the developed method was employed to investigate the degradation behavior of erlotinib under ICH-recommended stress conditions, including acidic, alkaline, oxidative, thermal, and photolytic degradation, as well as under gamma irradiation-based advanced oxidation process (AOP) conditions in aqueous solutions.

## Experimental

*Reagents and chemicals*

The chemotherapeutic agent, Erlotinib (Molecular formula $C_{22}H_{23}N_3O_4$, molecular mass 393.43 g/mol, λmax 372 nm) obtained from Sigma-Aldrich with the purity of≥99% (Steinheim, Germany). As an organic modifer, ACN (Sigma-Aldrich, Stein, Germany, suitable for HPLC, gradient grade, ≥99.9%) was utilized. The orthophosphoric acid (Riedel–de Haen Germany; minimum 85%) sodium hydroxide (≥98%, pellets (anhydrous), Merck, Darmstadt, Germany) were used for mobile phase preparation. Dead time was measured using uracil (99.0%, Sigma-Aldrich, Steinheim, Germany). The Milli-Q system (Direct Q3 UV system, Millipore, Bedford, MA, USA) was used to create ultra-filtered water.

*Equipment*

In order to carry out HPLC analysis, an Agilent 1260 series high-performance liquid chromatography (HPLC) system was utilized. This system featured a ternary solvent pump, an online degasser, an automatic injection system, a column heater, and a multi-wavelength detector. Analysis was conducted at a wavelength of 250 nm with a flow rate of 1.0 ml·min$^{-1}$. The X-Terra RP 18 (150 × 4.60 mm i.d. × 5 µm) column was chosen as the stationary phase at 25°C due to its peak shape and analysis time. A mobile phase consisting of 40% (v/v) acetonitrile-water solution containing 20 mM orthophosphoric acid was utilized. The samples were exposed to gamma radiation using a $^{60}$Co radioactive source (RSS8 source set, Spectrum Techniques, USA).

*Degradation Procedures*

At room temperature, solutions of erlotinib were subjected to the presence of a source of cobalt 60. It was necessary to position the medication solutions at a distance of five centimeters from the radiation source in order to get the desired absorbed dosage value. The following formula was used to determine the quantity of the absorbed dose in R/hour:

$$X = \pi \, x \, \Gamma \, x \, A \, x \, ln[\frac{(r^2 + h^2)}{h^2}]$$

where $\boldsymbol{\pi}$=3.14, $\boldsymbol{\Gamma}$ is the gamma constant (1.32 R.m$^2$/hr.Ci for Co-60), A is the total activity divided by the disc area, r and h are the radius of the disc and the height above the center of the disc, respectively [32]. In order to observe the degradation mechanism and products caused by different gamma radiation doses,

three different radiation doses between 0-6 Gy were applied to the drug solutions.

Forced degradation studies were performed to assess the stability-indicating efficacy of the proposed RP-HPLC technique. Erlotinib underwent acidic, alkaline, oxidative, thermal, and photolytic stress conditions. A stock solution of erlotinib (1 mg $ml^{-1}$) was prepared in methanol. Appropriate aliquots were transferred into volumetric flasks and subjected to the respective stress conditions. After completion of each degradation treatment, acidic and alkaline samples were neutralized with equivalent amounts of base or acid, respectively. The stressed samples were diluted with the mobile phase to the required concentration prior to RP-HPLC analysis.

The drug material in solution was subjected to acid hydrolysis using 1 N hydrochloric acid and heated at 100°C for 30 minutes. Alkaline hydrolysis was conducted utilizing 0.1 N sodium hydroxide under identical conditions. Oxidative degradation experiments were conducted by exposing the medication samples to 3% and 30% hydrogen peroxide solutions, there after heating them at 100°C for 30 minutes [31].

Thermal degradation investigations were conducted on the solid medicinal material by subjecting it to dry heat at 100°C for durations of 6 hours and 24 hours. The photolytic degradation was examined by subjecting the solid drug material to UV radiation at 254 nm.

Upon concluding the degrading treatments, the samples were diluted in methanol to create stock solutions at a concentration of 1 mg $ml^{-1}$. Suitable aliquots of the stock solutions were subsequently diluted with the mobile phase to achieve the necessary concentration for chromatographic analysis. All stressed samples were analysis by the established stability-indicating RP-HPLC method to assess the degree of degradation and the separation of Erlotinib from its degradation products.

*The Assessment of Pharmaceutical Dosage Forms*

The erlotinib formulation, specifically Tarceva® 100 mg tablets, was obtained from a local pharmacy. Five tablets were individually weighed, and their average weight was calculated before being ground into a fine powder. An amount of the powdered tablets equivalent to 100 mg of erlotinib was carefully measured and transferred into a 100 ml volumetric flask. Approximately 50 ml of the mobile phase was added to the flask, and the mixture was sonicated for 30 minutes at a controlled temperature to ensure complete dissolution of the powder. The solution was then diluted to the 100 ml mark with the same solvent. Following this, 1.0 ml of the prepared solution was accurately pipetted into a 10 ml volumetric flask and further diluted with the mobile phase to the mark, ensuring thorough mixing. The concentration of the substance was quantified using the corresponding regression equation.

## Results and Discussion

To determine the best conditions for analyzing Erlotinib using chromatography for drug analysis, various combinations of acetonitrile-water solutions (with 20 mM orthophosphoric acid) were evaluated as the mobile phase. The analysis was conducted using an X-Terra RP 18 stationary phase with dimensions of 150 × 4.60 mm i.d. × 5 µm. The mobile phase consisted of Acetonitrile in a 40:60 (v/v) ratio, with the pH adjusted to 5.0 using 1 M sodium hydroxide. This composition resulted in well-defined and resolved chromatographic peaks, with no tailing seen. An excellent linear correlation ($r^2 = 0.999$) was established for Erlotinib within the concentration range of 3–50 µg $ml^{-1}$, as shown in Table 1. Using the conditions described above, a satisfactory chromatographic peak resolution was obtained in a short analysis time (5 min). Also, the capacity factor is 1.24, and the theoretical plates is 8558 in this situation.

Table-1: Statistical analysis of the calibration data for Erlotinib.

| | |
|---|---|
| **Linear range (µg $ml^{-1}$)** | **3.0-50** |
| **Slope** | **71.221** |
| **Intercept** | **62.62** |
| **Correlation coefficient** | **0.9991** |
| **SE of slope** | **0.854** |
| **Detection Limit (µg $ml^{-1}$)** | **0.044** |
| **Quantification Limit (µg $ml^{-1}$)** | **0.133** |
| **Tailing factor (T)** | **1.088** |
| **Theoretical plates (N)** | **8558** |
| **RSD % (for retention time)** | **0.031** |

The method's precision and reproducibility were evaluated by analyzing standard solutions in the mobile phase, with replicates being conducted. The mean recovery and RSD, which were employed to assess the repeatability and reproducibility, are summarized in Table-2. Table-2 indicates that no statistically significant difference was observed for the assay, as concluded by within-day and between-day testing. The concentrations under investigation exhibited RSD percentage values ranging from 0.086 to 0.521. The results of this investigation suggest that the methodology demonstrates an exceptional level of precision.

Table-2: Summary of intra-day repeatability and inter-day reproducibility precision statistics for Erlotinib.

| Concentration | Intra-day | Inter-day |
|---|---|---|
| | Mean Recovery* % ± RSD % | Mean Recovery* % ± RSD % |
| 6 | 100.410 ± 0.358 | 100.573 ± 0.521 |
| 12 | 99.721 ± 0.215 | 99.759 ±0.243 |
| 25 | 99.803 ± 0.086 | 100.643±0.141 |

*Each value is obtained from five experiments (n=5)

The established RP-HPLC method was effectively utilized for the analysis of Erlotinib in a commercial tablet formulation. The findings are encapsulated in Table-3. The examined formulation indicated a claim of 100 mg Erlotinib per tablet, while the experimentally ascertained quantity was 99.485 mg (n = 5). The test value was 99.485% of the label claim, demonstrating exceptional concordance between the labeled and measured contents. The approach exhibited high precision, evidenced by a low %RSD value of 0.0751. The results validate that the suggested method is appropriate for routine quality control and quantitative analysis of Erlotinib in pharmaceutical formulations.

Table 3. The results of Erlotinib in a commercial tablet formulation

| Pharmaceutical Product Tarceva® Tablets | |
|---|---|
| Label Claim (mg/tablet) | 100.0 |
| Amount Found (mg/tablet) (n=5) | 99.485 |
| Assay (%) | 99.485 |
| Mean Recovery (%) | 99.485 |
| %RSD | 0.0751 |

Conducting stress tests on the drug material can assist in detecting potential degradation products, which in turn aids in determining the degradation pathways and inherent stability of the molecule. Additionally, it helps validate the effectiveness of the analytical processes used to determine stability. The stress testing investigations, along with the monitoring of the standard drug solution in the presence of its breakdown products, demonstrated a significant level of specificity for this method. Fig 2 displays the efficiency of erlotinib elimination. It is essential to maintain in consideration that the number of H+ and OH- ions in aqueous solutions might fluctuate as the pH of the solution is changed [33–35]

chromatograms of erlotinib obtained under various degradation settings and gamma irradiation at pH 5. There was no significant degradation products detected when the sample was subjected to UV and heat conditions for 6 and 24 hours. Stressed samples that underwent base hydrolysis exhibited observable breakdown products. However, the highest amount of breakdown products was observed when oxidation was carried out using peroxide.

Table 4 presents the outcomes of the forced degradation investigations utilizing the suggested technique, demonstrating the percentage of degradation and the purity of drug peaks in the chromatograms. The quantities of degraded compounds are presented in Table 4, together with their corresponding percentages.

Table-4: Impacts of Hydrolytic, Oxidative, Thermal, and Photolytic Stress Conditions on Erlotinib.

| Applied Stress Conditions | Waiting Time | %Assay |
|---|---|---|
| 1 M HCl | 30 min (at 100 °C) | 85.74 |
| 1 M NaOH | 30 min (at 100 °C) | 96.15 |
| 3% and 30% H2O2 | 30 min (at 100 °C) | 63.85 / 51.01 |
| Thermal | 6-24 hours (at 100 °C) | 99.95 / 99.90 |
| UV @ 254 nm | 6-24 hours (at room temp.) | 99.98/ 99.93 |

The Fig 3 displays the variations in Erlotinib elimination rates at different levels of gamma irradiation dosage. The clearance percentages of Erlotinib were shown to increase as the absorbed doses rose. This suggests that gamma irradiation is a highly efficient technique for eliminating this drug from a water-based solution. The removal rate after 2, 4, and 6 Gy radiation dose was 3.34, 11.9, and 30.3, respectively.

Throughout the process of ionizing radiation degradation, a number of different pH values (pH = 2.0, pH = 3.0, pH = 4, and pH = 5.0) were investigated in order to determine the influence that pH has on the

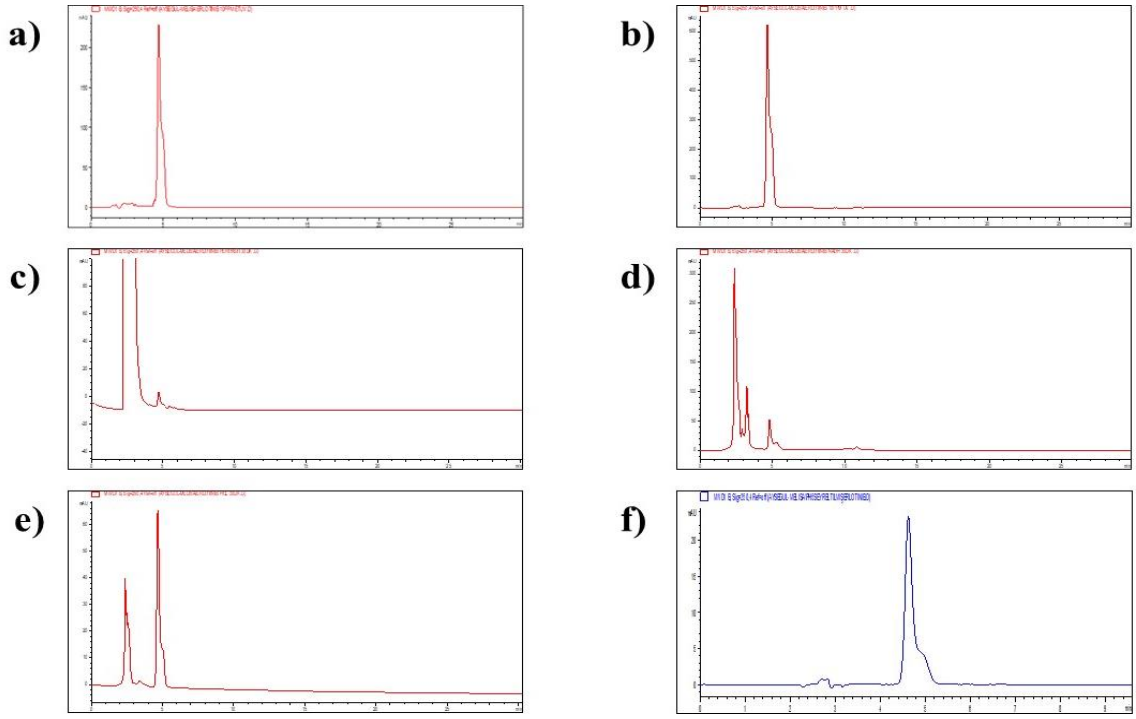


Fig. 2: Standard LC chromatograms of pharmaceuticals subjected to severe stress conditions: (a) at 100°C for 24 hours; (b) under UV light (254 nm) for 24 hours; (c) 30% H2O2 at 100°C for 30 minutes; (d) 1 M NaOH at 100°C for 30 minutes; (e) 1 N HCl at 100°C for 30 minutes; (f) gamma irradiation at pH 5.

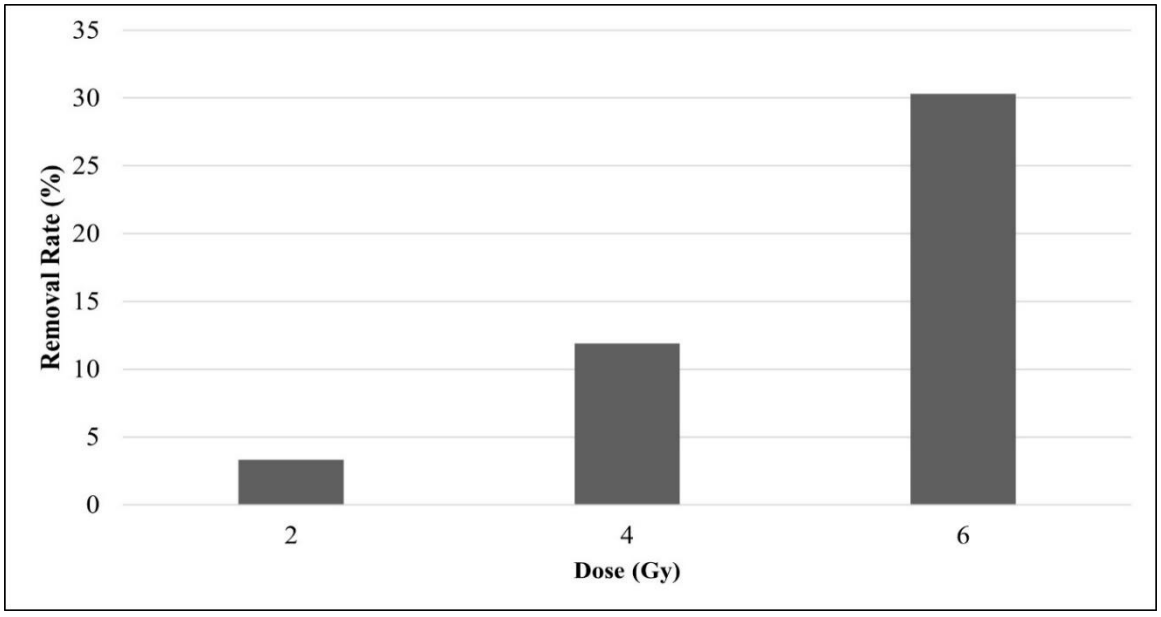


Fig 3: Effect of gamma irradiation dosage on Erlotinib degradation.

The degradation of erlotinib and the pH of the solution under gamma irradiation are strongly correlated, as illustrated in Fig 4. The removal rate for pH = 2.0, pH = 3.0, pH = 4, and pH = 5.0 was 66.76, 62.97, 50.22, and 38.59, respectively. The radical composition that is produced during gamma irradiation is altered by a change in the concentration of $H^+$ and $OH^-$ in solution. The elimination percentages of Erlotinib increased as a result of the acid solution.

## Conclusion

The present research suggests using RP-LC as a method for determining the amount of erlotinib present in pharmaceutical formulations. The simplicity, speed, high sensitivity, accuracy, and precision of this approach are some of the distinguishing characteristics that set it apart.

In addition, the findings of stress testing that was carried out in accordance with the rules established by the International Conference on Harmonization (ICH) demonstrate that the procedure is both selective and stability-indicating. As a result of the research that was conducted, it was discovered that gamma irradiation is a very efficient method for removing erlotinib from the aqueous solution. Within the acid solution, the percentage of erlotinib that was removed rose, but within the alkaline solution, it dropped. In addition to the best of our knowledge, this is the first detailed investigation of erlotinib degradation under gamma irradiation using a validated stability-indicating RP-HPLC method.

However, gamma irradiation should not be considered a universal treatment method for the removal of all organic contaminants from water. The degradation efficiency is strongly dependent on the physicochemical properties of the target compound, water matrix characteristics, and irradiation conditions. Although gamma irradiation offers advantages such as the absence of added chemical oxidants and the generation of minimal secondary waste, its environmental sustainability, energy requirements, and economic feasibility should be evaluated for each specific application before large-scale implementation.

## Acknowledgements

The authors declare that there is no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## References

1. A. A. Abdelgalil, H. M. Al-Kahtani and F. I. Al-Jenoobi, Erlotinib, *Profiles Drug Subst. Excipients Relat. Methodol.,* **45,** 93 (2020).
2. H. Lieberman and N. M. Vemuri, In *The Practice of Medicinal Chemistry*, C. G. Wermuth, D. J. Aldous, P. Raboisson and D. Rognan, Eds., 4th Ed., Academic Press, p. 767 (2015).
3. K. Kalyani, V. Anuradha, R. Sasidhar and S. Vidyadhara, Validation and Forced Degradation Studies for the Determination of Erlotinib in Bulk and Pharmaceutical Dosage Forms by RP-HPLC, *Art. Pharm. Chem. J.,* **3,** 44 (2016).
4. J. Pinillos, Adsorption of Erlotinib, 2016, Available from: https://bibliotecadigital.udea.edu.co/bitstream/10495/35697/1/PinillosJuan_2016_AdsorptionErlotinib.pdf.
5. P. Verlicchi, A. C. Garrigos and M. Al Aukidy, *Occurrence of Cytostatics in Different Water Compartments, in Fate and Effects of Anticancer Drugs in the Environment*, Springer, Cham, p. 221 (2020).
6. G. W. Aherne, A. Hardcastle and A. H. Nield, Cytotoxic Drugs and the Aquatic Environment: Estimation of Bleomycin in River and Water Samples, J. Pharm. Pharmacol., **42,** 741 (1990).
7. T. Steger-Hartmann, K. Kümmerer and J. Schecker, Trace Analysis of the Antineoplastics Ifosfamide and Cyclophosphamide in Sewage Water by Two-Step Solid-Phase Extraction and Gas Chromatography-Mass Spectrometry, *J. Chromatogr. A.,* **726,** 179 (1996).
8. J. P. Besse, J. F. Latour and J. Garric, Anticancer Drugs in Surface Waters: What Can We Say About the Occurrence and Environmental Significance of Cytotoxic, Cytostatic and Endocrine Therapy Drugs, *Environ. Int.,* **39,** 73 (2012).
9. H. Khouri, F. Collin, D. Bonnefont-Rousselot, A. Legrand, D. Jore and M. Gardes-Albert, Radical-Induced Oxidation of Metformin, *Eur. J. Biochem.,* **271,** 4745 (2004).
10. F. Collin, H. Khoury, D. Bonnefont-Rousselot, P. Thérond, A. Legrand, D. Jore and M.Gardès-Albert, Liquid Chromatographic/Electrospray Ionization Mass Spectrometric Identification of the Oxidation End-Products of Metformin in Aqueous Solutions, *J. Mass Spectrom.,* **39,** 890 (2004).
11. J. Rivera-Utrilla, M. Sánchez-Polo, M. Á. Ferro-García, G. Prados-Joya and R. Ocampo-Pérez, Pharmaceuticals as Emerging Contaminants and Their Removal from Water. A Review, *Chemosphere,* **93**, 1268 (2013).
12. R. O. Abdel Rahman and Y.T. Hung, Application of Ionizing Radiation in Wastewater Treatment: An Overview, *Water,* **12**, 19 (2019).
13. J. Wang and L. Chu, Irradiation Treatment of Pharmaceutical and Personal Care Products (PPCPs) in Water and Wastewater: An Overview, *Radiat. Phys. Chem.,* **125,** 56 (2016).

14. R. Ocampo-Pérez, J. Rivera-Utrilla, M. Sánchez-Polo, J. J. Lopez-Penalver and R. Leyva-Ramos, Degradation of Antineoplastic Cytarabine in Aqueous Solution by Gamma Radiation, *Chem. Eng. J.,* **174,** 1 (2011).
15. L. A. W. Abdou, O. A. Hakeim, M. S. Mahmoud and A. M. El-Naggar, Comparative Study Between the Efficiency of Electron Beam and Gamma Irradiation for Treatment of Dye Solutions, *Chem. Eng. J.,* **168,** 752 (2011).
16. T. H. Kim, M. Lee and C. Park, Gamma Ray Irradiation for Sludge Solubilization and Biological Nitrogen Removal, *Radiat. Phys. Chem.,* **80,** 1386 (2011).
17. B. G. Zheng, Z. Zheng and J. B. Zhang, Degradation of the Emerging Contaminant Ibuprofen in Aqueous Solution by Gamma Irradiation, *Desalination,* **276,** 379 (2011).
18. R. Melo, S. C. Verde and J. Branco, Gamma Radiation Induced Effects on Slaughterhouse Wastewater Treatment, *Radiat. Phys. Chem.,* **77,** 98 (2008).
19. Z. Guo and F. Zhou, Gamma Irradiation-Induced Sulfadiazine Degradation and Its Removal Mechanisms, *Chem. Eng. J,* **191,** 256, (2012)
20. N. Negreira, J. Regueiro, M. López de Alda and D. Barceló, Degradation of the Anticancer Drug Erlotinib During Water Chlorination: Non-Targeted Approach for the Identification of Transformation Products, *Water Res.,* **85,** 103 (2015).
21. A. A. Mahajan, P. B. Miniyar, A. S. Patil, R. U. Waghmare, J. J. Patil, K. Mohanraj et al., Separation, Identification, and Characterization of Degradation Products of Erlotinib Hydrochloride Under ICH-Recommended Stress Conditions by LC, LC-MS/TOF, *J. Liq. Chromatogr. Relat. Technol.,* **38,** 629 (2015).
22. K. Kalyani, V. Anuradha, R. Sasidhar and S. Vidyadhara, Validation and Forced Degradation Studies for the Determination of Erlotinib in Bulk and Pharmaceutical Dosage Forms by RP-HPLC, *Art. Pharm. Chem. J.*, **3,** 44 (2016).
23. S. T. Latha, S. Ananda Thangadurai, M. Jambulingam, K. Sereya, D. Kamalakannan and M. Anilkumar, Development and Validation of RP-HPLC Method for the Estimation of Erlotinib in Pharmaceutical Formulation, *Arab. J. Chem.,* **10,** 1138 (2017).
24. M. A. Mukthinuthalapati and V. R. K. C. Bukkapatnam, Analytical Techniques for the Determination of Erlotinib HCl in Pharmaceutical Dosage Forms by Spectrophotometry, *Chem. Sci. Trans.,* **3,** 2, 2014.
25. L. Faivre, C. Gomo, O. Mir, F. Taieb, A. Schoemann-Thomas, S. Ropert et al., A Simple HPLC-UV Method for the Simultaneous Quantification of Gefitinib and Erlotinib in Human Plasma, *J. Chromatogr. B,* **879,** 2345 (2011).
26. C. Karunakara, U. Aparna, V. Chandregowda and C. G. Reddy, Separation and Determination of Process-Related Impurities of Erlotinib Using Reverse-Phase HPLC with a Photo-Diode Array Detector, *Anal. Sci.,* **28,** 305 (2012).
27. B. Mandal, P. Balabathula, N. Mittal, G. C. Wood and H. Bhattacharjee, Development and Validation of a Spectrofluorimetric Method for the Determination of Erlotinib in Spiked Human Plasma, *J. Fluoresc.,* **22,** 1425 (2012).
28. M. E. Swartz and I. S. Krull, *Analytical Method Development and Validation,* Marcel Dekker: New York, 1997.
29. ICH, Topic Q2A Validation of Analytical Procedures, Methodology, PMP/ICH/281/95. 2005.
30. C. M. Riley and T. W. Rosanske, *Development and Validation of Analytical Methods,* Elsevier: Amsterdam, The Netherlands, 1996.
31. ICH, Stability Testing of New Drug Substances and Products (Q1AR), International Conference on Harmonization; IFPMA, Geneva, 2000.
32. J. J. Bevelacqua, *Contemporary Health Physics*, Wiley, 2009.
33. N. Getoff, Radiation-Induced Degradation of Water Pollutants: State of the Art, *Radiat. Phys. Chem.,* **46,** 1079 (1996).
34. G. V. Buxton, C. L. Greenstock, W. P. Helman et al., Critical Review of Rate Constants for Reactions of Hydrated Electrons, Hydrogen Atoms and Hydroxyl Radicals (.OH/O-) in Aqueous Solution, *J. Phys. Chem. Ref. Data*, **17,** 513 (1988).
35. P. Drzewicz, P. Panta, W. Gluszewski et al., Effect of Selected Scavengers on Radiolytic Degradation of 2,4-Dichlorophenol for Environmental Purposes, *J. Radioanal. Nucl. Chem.,* **242**, 601 (1999).