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Optimization of High Energy Radiation-Induced Degradation of Sulfamethoxazole Using Response Surface Methodology

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ABSTRACT: Ionizing irradiation is an emerging technology for the removal of toxic pollutants, such as antibiotics, in water and wastewater. In this study, gamma radiation-induced degradation of sulfamethoxazole (SMX) was optimized using response surface methodology (RSM) based on a Box-Behnken design. LC-MS analysis identified nine intermediate products (M1–M9), elucidating a dual oxidative-reductive degradation mechanism driven by hydroxyl radicals (•OH) and hydrated electrons (e_{aq}^-). These intermediates, characterized by hydroxylation, sulfonamide bond cleavage, and aromatic ring fragmentation, aligned with pathways distinct from conventional chlorination systems, underscoring the absence of toxic halogenated byproducts. According to experimental data, The study revealed that absorbed dose (0.2–2.0 kGy) and initial SMX concentration (5–40 mg/L) critically governed SMX degradation efficiency, achieving >99% removal under optimized conditions (≥1.2 kGy for 5–10 mg/L SMX). The robust RSM model (R^2 = 0.9931) and experimental validation (±2% error) demonstrated the method's reliability in reconciling nonlinear dose-concentration interactions as well as providing an effective approach to parameter optimization, offering practical insights for enhancing the treatment efficiency of antibiotic-containing wastewater.

Keywords: Ionizing irradiation; Sulfamethoxazole; Response surface methodology; Antibiotics degradation; Optimization

1. Introduction

Sulfamethoxazole (SMX), a widely prescribed sulfonamide antibiotic, poses significant environmental risks due to its persistence in aquatic ecosystems and potential to promote antibiotic resistance [1,2]. Its high water solubility and environmental persistence (half-life of 10–30 days) lead to its frequent detection in various environmental matrices, including wastewater, surface water, and groundwater [3,4]. Studies also have demonstrated that environmental SMX residues pose acute toxicity to aquatic organisms (LC_{50} or EC_{50} values range from 0.0268 mg/L to >1000 mg/L) [5] and may facilitate the transmission of resistance genes (ARGs) via horizontal gene transfer [6,7], thereby threatening human health and ecological security.

Various technologies have been investigated for the removal of antibiotics from wastewater [8,9]. Physical adsorption technology entails the transfer of antibiotics from the aqueous phase to another phase via sequestration and concentration. Yet, it still confronts challenges related to adsorbent regeneration and the risk of secondary pollution. On the other hand, advanced oxidation processes, such as persulfate oxidation and ozonation [10], face limitations, such as toxic intermediate products and stringent reaction conditions [11,12]. For example, conventional Fenton reaction conditions require low pH. Conventional wastewater treatment processes exhibit low SMX removal efficiency (20–58%) [13,14] (Adeleye et al., 2022; Wang and Wang, 2018a). Hence, it is crucial to develop novel, high-efficiency technologies for more effective SMX removal from wastewater.

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Ionizing irradiation technology has significant potential for environmental protection due to its broad-spectrum degradability and lack of chemical agents [15–19]. Recent studies have demonstrated its versatility, including the synthesis of functional hydrogels for selective metal ion adsorption via gamma radiation [20]. Ionizing radiation technology can directly degrade target pollutants or produce highly oxidizing hydroxyl radicals (•OH) and reductive hydrated electrons (e_{aq}^-) through the radiolysis of water molecules, as shown in Equation (1), which are powerful for the removal of pollutants via oxidation or reduction pathways.

$$H_2O \rightarrow \bullet OH\ (2.7) + e_{aq}^-\ (2.6) + H\bullet\ (0.55) + H_2\ (0.45) + H_2O_2\ (0.71) + H_3O^+\ (2.6) \quad (1)$$

Previous research showed that ionizing irradiation is highly effective in the degradation of drugs and antibiotics in aqueous solution [21–28], such as sulfonamides, achieving complete degradation of 20 mg/L SMX at a dose of 1.5 kGy [29]. Furthermore, compared with UV/persulfate systems, radiation technology has shown greater adaptability to complex water matrices (e.g., containing humic acid or inorganic anions) [14]. The combination of ionizing radiation and ozone pretreatment markedly enhances the mineralization rate of SMX [30].

Response Surface Methodology (RSM) has gained traction in environmental engineering for its ability to model complex interactions between variables while minimizing experimental runs, emerging as a statistically robust framework for optimizing advanced oxidation processes (AOPs) [31,32]. By integrating mathematical modeling with experimental design, RSM systematically explores parameter interactions and identifies optimal conditions while minimizing experimental trials—a critical advantage for scaling water treatment technologies [33,34]. Recent advancements highlight its efficacy in antibiotic removal, particularly for recalcitrant pharmaceuticals like sulfamethoxazole (SMX), where nonlinear relationships between process variables govern degradation efficiency [35,36].

Since in ionizing irradiation technology, reactive species generation (e.g., •OH, e_{aq}^-) is inherently governed by nonlinear relationships between absorbed dose, pollutant concentration, and competing water constituents. Traditional single-factor approaches often fail to capture these interdependencies, necessitating multivariate optimization frameworks. Traditional single-factor approaches often fail to capture these dynamics, necessitating multivariate frameworks like RSM to unravel synergistic or antagonistic effects [37].

This study integrated response surface methodology (RSM) with gamma radiation to optimize SMX degradation. Building on previous kinetics data [29], we developed a predictive model to elucidate the interplay between absorbed dose (0.2–2.0 kGy) and initial SMX concentration (5–40 mg/L). The model not only identifies optimal conditions for near-complete degradation but also provides a framework for scaling up irradiation-based treatments, advancing the implementation of radiation technology for antibiotic-laden wastewater remediation incomplete matrices.

2. Materials and Methods

2.1. Chemicals

SMX (SMX, $C_{10}H_{11}N_3O_3S$, purity >98%) is supplied by Aladdin Industries (Shanghai, China). A 200 mg/L SMX stock solution was prepared with deionized water prior to use. Raw materials, including $NaNO_3$, Na_2CO_3, $NaHCO_3$, Na_2SO_4, NaCl, Na_2HPO_4, peptone, and glucose, were purchased from Xilong Chemical Co., Ltd. H_2SO_4, NaOH, and humic acid were obtained from Beijing Chemical Reagent (Beijing, China).

2.2. Irradiation Experiment

The irradiation experiment was performed using ^{60}Co-γ irradiation source from the Institute of Nuclear and New Energy Technology of Tsinghua University, with a dose rate of 339 Gy/min. The irradiation time is determined by the absorbed dose rate at this point and the required absorbed dose (0.2–2.0 kGy). The SMX solution sample was kept in a plastic centrifuge tube and irradiated near the irradiator at ambient temperature.

2.3. Analytical Methods

Aqueous SMX solution samples at different initial concentrations were prepared by diluting the 200 mg/L SMX stock solution with deionized water. SMX concentrations were measured by high-performance liquid chromatography (HPLC, 1200 Series, Agilent, Santa Clara, CA, USA) [14]. The column was a C18 reversed-phase column (5 mm, 4.6 × 150 mm) with a column temperature set at 30 °C, a mixed solution of 55% acetonitrile and 45% formic acid (0.1%) with a flow rate of 1 mL/min, a diode array detector (DAD) detector at 275 ± 10 nm, a 6-min run time, a retention time of approximately 2.0 min for SMX, and a 20 μL injection volume [29].

2.4. RSM Modeling

The Box-Behnken design was employed to construct the response surface model. According to the previous research on the degradation of SMX aqueous solution by low-energy X-ray irradiation, the absorbed dose directly impacts the number of active particles generated by gamma radiation and significantly influences the SMX degradation rate [28]. Moreover, generally, SMX degradation efficiency slightly decreases as its initial concentration increases [36–38]. Hence, in this study, absorbed dose (A, kGy) and initial SMX concentration (B, mg/L) were chosen as independent variables. The absorbed dose ranged from 0.2 to 2.0 kGy, and the concentration of SMX ranged from 5 to 40 mg/L. These ranges were determined based on previous experimental results [39] and actual sewage treatment requirements. The experimental data were input into the Design Expert software, and a quadratic response regression model was formulated in the following form Equation (2):

$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_{12} AB + \beta_{11} A^2 + \beta_{22} B^2 \quad (2)$$

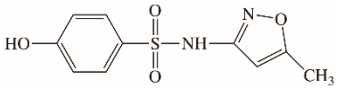
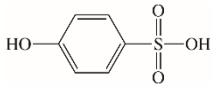
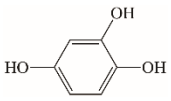
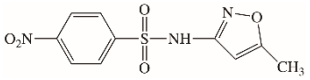
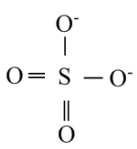
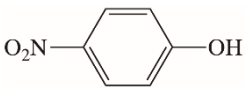
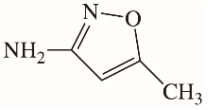
where Y represents the SMX removal rate (%), A denotes the absorbed dose (kGy), and B represents the SMX concentration (mg/L). β_0 is a constant, β_1 and β_2 are linear coefficients, β_{12} is the interaction coefficient, and β_{11} and β_{22} are quadratic coefficients. The significance and goodness of fit of the model were assessed via analysis of variance (ANOVA), and the residual analysis was performed to confirm the alignment between the model's predicted values and the experimental data.

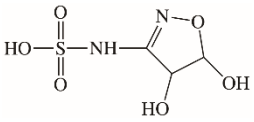
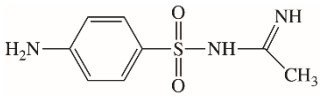
3. Results and Discussion

3.1. SMX Degradation

The gamma radiation-induced degradation of sulfamethoxazole (SMX) has been studied by our group under varying absorbed doses (0.2–2.0 kGy) and initial concentrations (5–40 mg/L) [40], with degradation efficiencies exceeding 99% at optimal conditions (≥1.2 kGy for 5–10 mg/L SMX). This investigation also built upon foundational kinetics data from Zhuan & Wang (2019) [29]. Liquid chromatography-mass spectrometry (LC-MS) analysis of irradiated samples (10 mg/L SMX, 0.8 kGy dose) identified nine intermediate degradation products (M1–M9; Table 1), elucidating a multi-pathway degradation mechanism dominated by hydroxyl radical (·OH) and hydrated electron (e_{aq}^-) reactions (Figure 1).

Table 1. Intermediates of Sulfamethoxazole Degradation by Ionizing Irradiation.

Number	M/Z	Chemical Structure	Chemical Formula
M1	254		$C_{10}H_{10}N_2O_4S$
M2	174		$C_6H_6O_3S$
M3	126		$C_6H_6O_3$
M4	283		$C_{10}H_9N_3O_5S$
M5	96		SO_4^{2-}
M6	139		$C_6H_5NO_3$
M7	99		$C_4H_6N_2O$

M8	196		$C_4H_8N_2O_5S$
M9	213		$C_8H_{11}N_3O_2S$

The first step is initial •OH attack occurs at the electron-rich aniline group of SMX, forming hydroxylated derivatives (M1), demonstrating that oxidative substitutions at aromatic amines are primary pathways in advanced oxidation processes (AOPs) for sulfonamides. Then, the S–N bond in SMX undergoes hydrolysis or radical-mediated scission, yielding M2 and subsequent desulfonation to M3 (M/Z 126), sulfonamide bond (SN) breaking has been reported in other degradation processes of sulfamethoxazole [41]. This pathway was also corroborated [42], who demonstrated that reductive species preferentially destabilize sulfonamide bonds in SMX derivatives M4 arising from nitro-group addition to the hydroxylated aromatic ring, a pathway enhanced at higher irradiation doses. This mirrors observations in chlorination systems, where halogenated byproducts form via similar electrophilic substitution [43]. Subsequent breakage of the arylsulfone (CS) and sulfonamide (SN) bonds under hydroxyl radical oxidation yielded the products M5 (M/Z 96), M6 (M/Z 139), and M7 (M/Z 99). Fragmentation of the benzene ring via •OH attack produces M6, consistent with aromatic ring-opening mechanisms reported in irradiated phenolic compounds [44]. These intermediates are also aligned with chlorination byproducts identified [44], though irradiation avoids toxic chlorinated analogues. Further •OH attack on the heterocyclic ring leads to ring-opening products. M8 and M9 are characterized by fragmented isoxazole moieties, consistent with pathways reported in electron beam irradiation (EBI) studies [45].

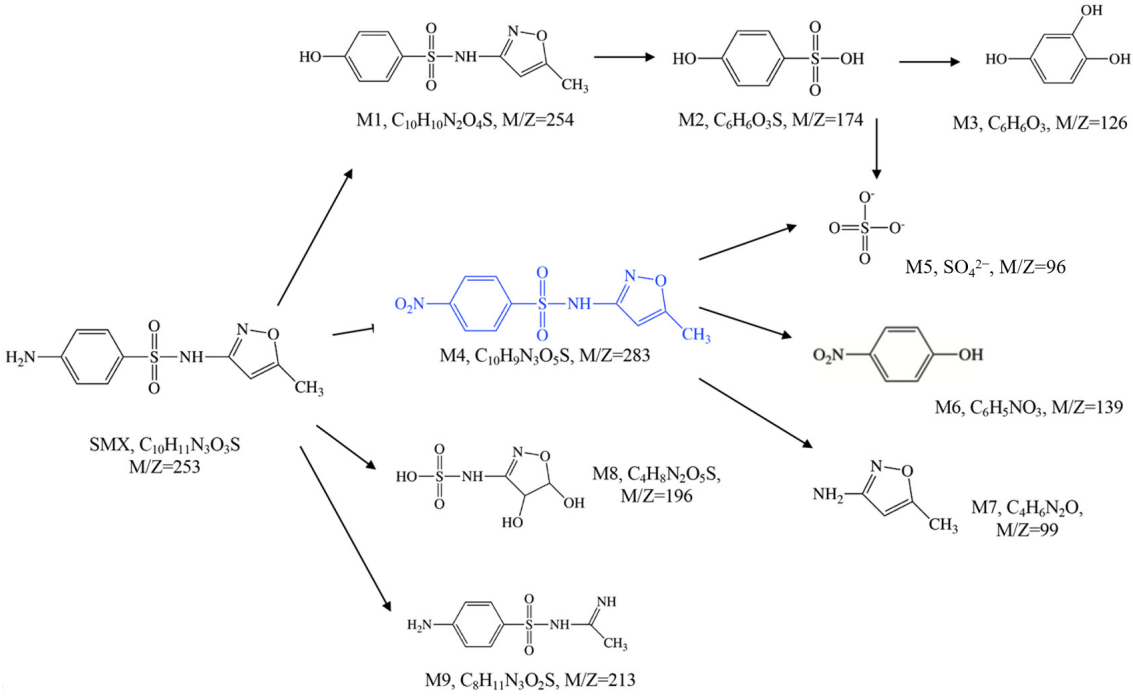


Figure 1. Possible pathways for degradation of sulfamethoxazole by ionizing irradiation.

3.2. Model Construction and Regression Analysis

The Box-Behnken design was employed to construct a quadratic regression model (Equation (2)) based on experimental data from Zhuan (2020) [40] with Design Expert. The model links the irradiation dose (A) and SMX concentration (B) to the removal efficiency (Y). Analysis of variance (ANOVA) was conducted to evaluate the significance of the model terms (Table 2). The regression equation derived from the experimental data is expressed as Equation (3):

$$Y = 94.87 + 18.06A - 9.45B + 18.29AB - 15.22A^2 - 2.19B^2 - 5.45A^2B - 8.72AB^2 + 14.17A^3 - 0.43B^3 + 13.56A^2B^2 - 5.45A^3B + 1.02AB^3 - 13.02A^4 - 2.69B^4 \quad (3)$$

Among them, A represents the absorbed dose (kGy), B represents the SMX concentration (mg/L), and Y represents SMX removal efficiency (%).

The model exhibited high predictive accuracy ($R^2 = 0.9931$, $R_{adj}^2 = 0.9883$) and statistical significance (F-value = 206.32, $p < 0.0001$). The ANOVA results (Table 2) indicated that absorbed dose (A), SMX concentration (B), and their interactions (AB, A^2B, AB^2) were the dominant factors influencing SMX degradation.

Table 2. ANOVA results for the regression model for SMX degradation.

Source of Variance	Sum of Squares	Degree of Freedom	Mean Square	*F*-Value	*p*-Value
Model	17,507.68	14	1250.55	206.32	<0.0001
A-Absorbed dose	454.09	1	454.09	74.92	<0.0001
B-SMX concentration	118.11	1	118.11	19.49	0.0003
AB	149.41	1	149.41	24.65	<0.0001
A^2	44.50	1	44.50	7.34	0.0135
B^2	1.01	1	1.01	0.1673	0.6869
A^2B	79.57	1	79.57	13.13	0.0017
AB^2	184.55	1	184.55	30.45	<0.0001
A^3	260.65	1	260.65	43.00	<0.0001
B^3	0.2303	1	0.2303	0.0380	0.8474
A^2B^2	153.55	1	153.55	25.33	<0.0001
A^3B	21.72	1	21.72	3.58	0.0729
AB^3	0.6124	1	0.6124	0.1010	0.7539
A^4	41.91	1	41.91	6.92	0.0161
B^4	1.99	1	1.99	0.3291	0.5726
Residual	121.22	20	6.06		
Sum	17,628.90	34			
$R^2 = 0.9931$, $R^2_{adj} = 0.9883$					

As shown in the table above, the model has an F-value of 206.32 and a p-value less than 0.0001, with a correlation coefficient (R^2) of 0.9931 and an adjusted R^2_{adj} of 0.9883, indicating a high degree of fit and providing a good prediction of the actual treatment outcomes.

3.3. Interaction Effects and Parameter Optimization

To elucidate the interaction between absorbed dose (A) and SMX concentration (B), Equations (4) and (5) were derived by solving the 100% removal rate thresholds:

When the absorbed dose is between 0.5 and 1.1 kGy, and the SMX concentration is between 5 and 10 mg/L, the equation f(x,y) is satisfied in Equation (4):

$$f(x,y) = -39.137x^3 + 84.191x^2 - 49.567x + 14.242 - y = 0;\ R^2 = 0.9303 \quad (4)$$

When the absorbed dose is between 1.2 and 2 kGy and the SMX concentration is between 5 and 35 mg/L, the equation g(x,y) is satisfied in Equation (5):

$$g(x,y) = -672.61x^4 + 4076.1x^3 - 9263.4x^2 + 9406x - 3592.9 - y = 0;\ R^2 = 0.9561 \quad (5)$$

Here, x represents the irradiation dose (kGy), and y represents the SMX concentration (mg/L). When the absorbed dose and the SMX concentration are substituted into the above two equations and calculated to be greater than or equal to zero, the removal rate is close to 100%.

As shown in Figure 2 (3D surface plot) and Figure 3 (contour plot), SMX removal efficiency increased monotonically with the absorbed dose but decreased at higher SMX concentrations. This trend is attributed to the enhanced generation of reactive species (e.g., •OH and e_{aq}^-) at higher doses, while elevated SMX concentrations intensified competition for these species, reducing degradation efficiency [3,12].

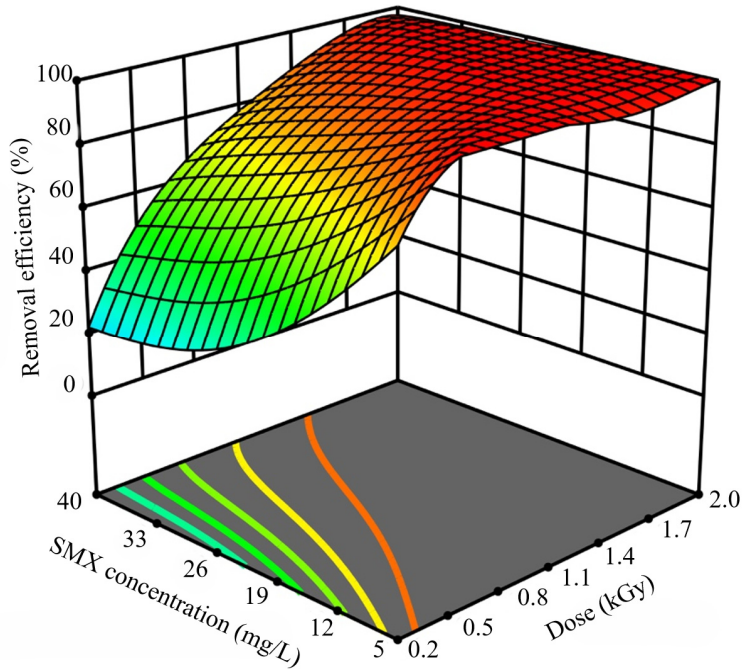


Figure 2. 3D surface plot of SMX removal efficiency under varying irradiation doses and SMX concentrations.

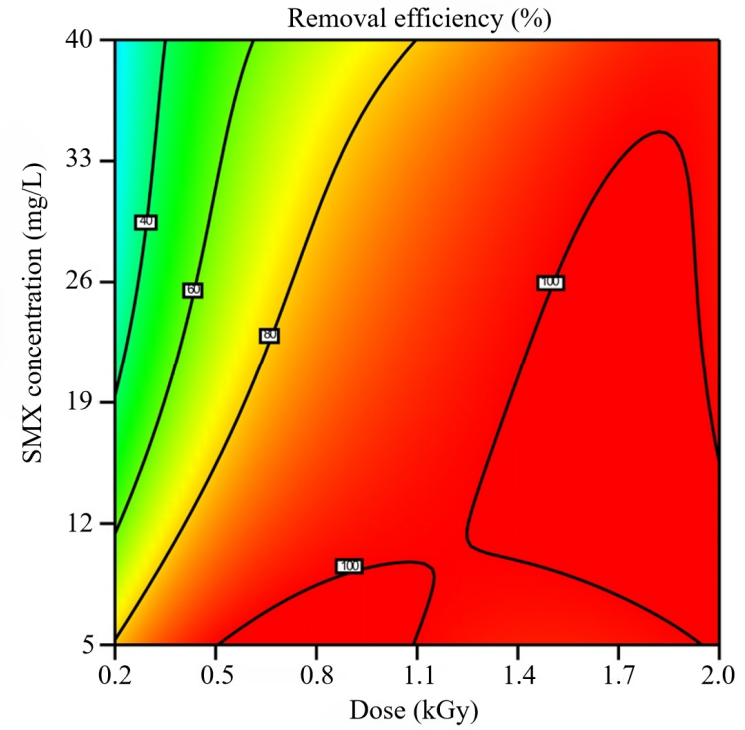


Figure 3. Contour plot of irradiation dose *vs.* SMX concentration on removal efficiency.

Optimal conditions (≥1.2 kGy) achieved near-complete removal (100%) for low SMX concentration (5−10 mg/L), validating the model's utility in parameter optimization.

3.4. Model Validation

To validate the model's predictive capability, experimental data from Zhuan (2020) [37] were compared with predicted values in Figure 4. A strong linear correlation ($R^2 = 0.997$) was observed, with errors confined to ±2%.

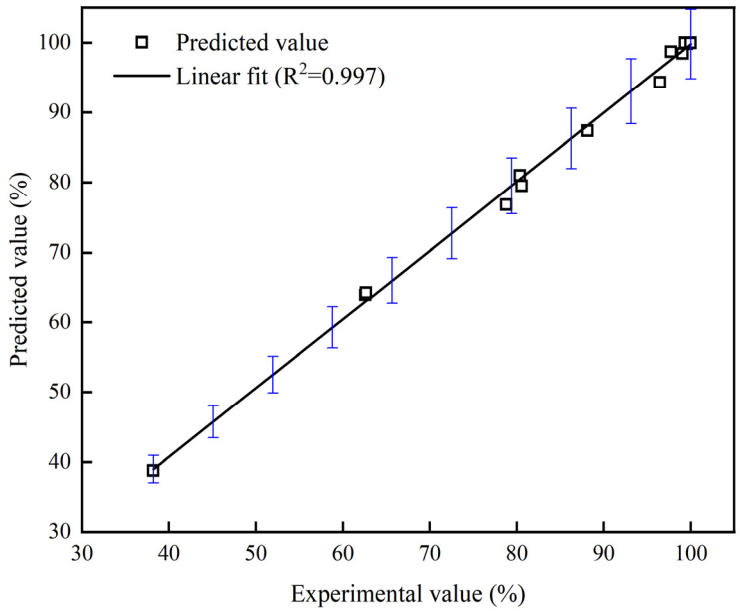


Figure 4. Correlation between experimental and predicted SMX removal efficiency.

This alignment confirms the model's reliability for optimizing irradiation parameters in complex water matrices. Hence, the comparison of experimental data and model predictions confirms that the established response surface model effectively predicts the degradation efficiency of SMX under varying irradiation doses and SMX concentrations.

4. Conclusions

This study indicated the degradation pathways of SMX using gamma radiation and developed a prediction model for optimizing the degradation efficiency using response surface methodology (RSM). The accuracy and reliability of the model were validated by comparing it with experimental data. The main conclusions are as follows: (1) The RSM model demonstrated fine predictive accuracy (R^2 = 0.9931) and a high degree of fitness, validating its utility in resolving the nonlinear interplay between absorbed dose and SMX concentration. (2) Degradation pathways, inferred from nine identified intermediates, highlighted the dominance of •OH-mediated hydroxylation and e_{aq}^--driven sulfonamide bond cleavage. (3) Optimal conditions (≥1.2 kGy, 5–10 mg/L SMX) achieved near-complete degradation, with intermediate toxicity analyses suggesting minimal ecological risks. These insights not only validate the principles of radiation-driven degradation but also bridge the gap between empirical optimization and mechanistic validation, a perspective underexplored in prior studies. Future research could focus on factors such as water quality and radiation types to optimize and expand the application scope of ionizing irradiation technology, thereby meeting the increasing requirements for the safe and efficient treatment of antibiotic wastewater.

Author Contributions

Y.S.: Data curation, Formal analysis, Investigation, Writing—original draft; Y.W.: Data curation, Investigation; J.W.: Funding acquisition, Supervision, Writing—review & editing.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data will be available upon request.

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Declaration of Competing Interest

No potential conflict of interest was reported by the authors.

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