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Photocatalytic Degradation of Doxycycline Hyclate using Sulfur-doped Graphitic Carbon Nitride Nanoparticles

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Abstract*— Pharmaceutical contaminants in aquatic environments pose a significant risk to ecosystems and human health, necessitating the development of efficient and sustainable remediation strategies. This study evaluates the photocatalytic degradation of doxycycline hyclate using in-house synthesized sulfur-doped graphitic carbon nitride (S-g-C_3N_4) nanoparticles under UV-light irradiation activated by hydrogen peroxide. Degradation experiments were conducted in a fixed-volume reaction mixture containing 60 mg/L doxycycline solution. The reaction was found to follow pseudo-first-order kinetics with a rate constant of 0.0958 min^{-1}. Four key parameters (catalyst dosage, pH, H_2O_2 dosage, and temperature) were optimized using Response Surface Methodology (RSM) with a central composite design. The developed quadratic model exhibited strong predictive ability (R^2 = 0.922), with all linear terms, two-way interactions, and non-linear temperature squared effect found to be significant. Optimal conditions were determined to be 643.8 mg/L catalyst dosage, pH 3.56, 4.70 mM H_2O_2, and 42.68 °C, achieving an experimentally validated degradation efficiency of 94.75 %. This work demonstrates the efficiency of simple metal-free S-g-C_3N_4 nanoparticles for the removal of persistent pharmaceutical pollutants and provides a robust predictive model to support practical wastewater treatment applications, directly fulfilling the purpose of this study. Future investigations will examine performance in real wastewater matrices, scale up the experimental setup, and perform thorough economic analysis.

Keywords*— Pharmaceutical Contaminants, Wastewater, Photocatalysis, Nanoparticles, Optimization.

I. Introduction

Tetracyclines (TCs) are widely used as broad-spectrum antibiotics to treat bacterial infections. They exist in many forms including tetracycline, doxycycline, minocycline, and tigecycline. They are classified as protein synthesis inhibitors and display significant activity against Gram-positive and Gram-negative bacteria. Among this family, doxycycline hyclate is a semi-synthetic antibiotic that is extensively prescribed in human and veterinary health.

The increase of these pharmaceutical contaminants in aquatic environment, indicated by high percentages of Active Pharmaceutical Ingredients (APIs) release, pose a growing risk to ecosystems and human health [1]. Sources of which include manufacturer direct discharge streams, and municipal waste due to incorrect disposal [2,3]. Pharmaceutical water pollution is a growing concern in Bahrain where a rapid increase in drug consumption, especially during the pandemic, led to 50% rise in as the hazardous chemical discharge. An increase in population requires more medical services and treatments thus, resulting in higher medical waste [3]. This concern raised the need for sustainable remediation strategies and effective materials that degrade these pollutants in scalable and sustainable processes. Among the various materials used in this context, an arising one is graphitic Carbon Nitride (g-C_3N_4). g-C_3N_4 stands as a prominent and sustainable photocatalyst, belonging to a new class of multifunctional metal-free 2D n-type semiconductors of a polymeric structure and tunable properties. Because of its free metal, ecofriendly preparation methods with high stability, low cost and good properties to use in wide range of applications positioning it an ideal candidate for sustainable and scalable application [4]. Sulfur doping further enhances g-C_3N_4's photocatalytic activity by combating its potential drawbacks, as it narrows the bandgap, improves light absorption and prevents rapid charge recombination [5,6,7]. The S-g-C_3N_4 nanoparticles employed in this study were pre-synthesized in-house.

Several studies explored graphitic carbon nitride (g-C3N4) based photocatalysts for the removal of specifically

tetracycline-class antibiotics. Guan et al. prepared sulfur- doped g-C3N4 through a modified molten salt method which achieved photodegradation that was 20 times higher than that of pristine g-C3N4 [8]. Liu et al. synthesized g-C3N4 coupled with α-Bi_2O_3 resulting in a composite that achieved 79% degradation of doxycycline within 30 minutes under visible light irradiation owing to the addition of H2O2 and the Z-scheme charge separation [9]. Pattanayak et al. reviewed doped g-C3N4 and concluded that elemental doping narrowed bandgaps by introducing mid-gap states reducing electron-hole recombination, improving performance against tetracyclines in aquatic environments. [10]. Esfandiaribayat et al. applied Response Surface Methodology with central composite design (RSM-CCD) in a g-C_3N_4-loaded photocatalytic membrane reactor and reached 94.8 % tetracycline removal [11]. However, most reported systems rely on visible-light-driven composites or single-parameter optimization. Limited work exists on simple metal-free S-doped g-C_3N_4 for doxycycline degradation under UV/H_2O_2 activation with a four-variable RSM optimization. The present study addresses this gap.

II. Design and Implementation

A. Experimental Setup and Procedure

A standard experimental procedure was established and followed through all degradation experiments, with doxycycline hyclate, as the chosen model pharmaceutical pollutant having a complex chemical structure ($(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$) A 40 mL reaction mixture was contained in a 100 mL borosilicate glass beaker. The reaction mixture consists of a 60 mg/L aqueous doxycycline solution, to which the nanoparticles are added and stirred in the dark for 30 minutes on a magnetic stirring/heating plate. Then, a certain amount of an activator, hydrogen peroxide (H2O2), is added to initiate the reaction, and the UV-light source is switched on. The suspension is left to stir under UV irradiation at a fixed stirring speed of 240 rpm and 30 cm distance from the irradiation source. The aforementioned parameters were held constant throughout to ensure a controlled environment whilst focusing on the selected key variables to examine their impact. Aliquots / samples were drawn at predetermined time intervals using a microfilter syringe, to filter the catalyst out of the suspension. The solution is then analyzed in a UV-Visible spectrophotometer, converting the obtained absorbance data into concentration data using the calibration curve shown in Fig. 1 below.

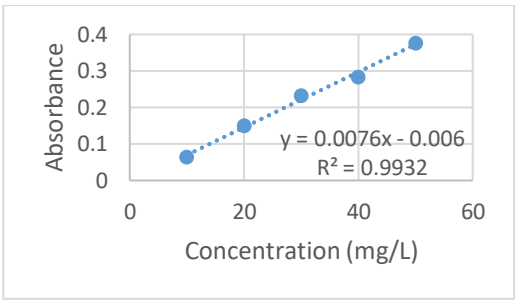

Figure 1: Doxycycline hyclate calibration curve.

B. Optimization by Design of Experiments

The photocatalytic reactions by the sulfur doped nanoparticles were subjected to a Design of Experiments framework enabling systematic investigation of multiple variables. A Central Composite Design (CCD) was selected to include center and axial points allowing the estimation of curvature and higher order effects, unlike other designs like factorial.

1) Selection of key variables and their operational ranges

The Central Composite Design examined four variables with the following ranges (coded -α to +α): catalyst dosage (150-750 mg/L), pH (1-9), activator dosage (H2O2, 4.5-10.5 mM), and temperature (10 – 70 ºC). The central levels (-1 to +1) were set at dosages/levels of 300-600 mg/L, 3-7, 6-9 mM, and 25-55 ºC for catalyst dosage, pH, H2O2 and temperature respectively. As concluded from recently published RSM-optimized studies, catalyst dosage has direct influence on the number of active sites available and affects light penetration [12], hence the selection. As for pH, it affects surface charge, pollutant adsorption, and reactive species (OH) [12]. The activator dosage initiates the reaction and is used to balance radical production [13], and temperature modulates kinetics and H2O2 stability [14].

2) Design of experiments and operational runs

The specifics of the Central Composite Design were calculated using Minitab 15, for four variables and seven center points, yielding a total of 31 runs in coded variables where α=2, as shown in Table 1 below.

III. Results and Discussion

A. Model Analysis

The results of the degradation experiments were then input into Minitab 15 to examine the effects of the four selected variables and their interactions. A second order polynomial shown in (1), was attained from Minitab's Analysis of Variance (ANOVA). Where A, B, C, and D correspond to catalyst dosage (mg/L), pH, activator dosage (mM), and temperature (ºC), respectively (uncoded units).

$$\begin{aligned} Degradation = {} & 87.39 + 1.987A - 2.694B \\ & +2.252C - 2.734D + 1.038A^2 \\ & - 0.166B^2 + 0.352C^2 - 5.221D^2 + 2.998AB \\ & -2.843AC + 4.205AD + 4.086BC \\ & -2.616BD + 2.259CD \end{aligned} \quad (1)$$

Table I. Coded and uncoded values of runs

	-α	-1	0	+1	+α
Catalyst dosage (mg/L)	150	300	450	600	750
pH	1	3	5	7	9
Activator dosage (mM)	4.5	6	7.5	9	10.5
Temperature (ºC)	10	25	40	55	70

The model yielded a R^2 value of 92.2% indicating that the model yields a well approximated prediction of actual values. The model displays a lack of fit p-value < 0.05 recommending switching to a higher order polynomial. Nonetheless, the strong predictive power exhibited by the quadratic model (R^2=0.921) led to retaining it for optimization. The model shows low pure error of 0.528, strongly suggesting reproducibility. The relationship between the selected variables is seen in the ANOVA table below shown in Fig 2.

In terms of linear variables, temperature, pH, and activator dosage displayed very strong effects with p-values < 0.01. On the other hand, catalyst dosage was found to display strong effects for 0.01< p-value < 0.1. The squared terms of all variables were found to be insignificant, apart from temperature, which exhibited strong effect suggesting a curved response for temperature. All 2-way interactions were found to be very significant except for the interaction between activator dosage and temperature, which demonstrated a moderate effect. A pareto chart was used to visualize the impact of the said variables on degradation as shown in Fig. 3.

The most significant interaction to be studied was between catalyst dosage and temperature. Temperature yields a parabolic shape where at minimum conditions, kinetics are too slow to progress, and at maximum conditions inhibit the formation of activator radicals as seen in Fig. 4 [15]. Abundance of active sites does not help if the reaction is too slow to progress or without stable activators. Conversely, less catalyst dosage can perform better under extreme conditions as sites are optimally utilized in degradation reactions in addition to allowing light pathways to reach a greater number of sites.

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	14	2453.79	175.270	13.48	0.000
Linear	4	569.24	142.311	10.95	0.000
A	1	93.85	93.852	7.22	0.016
B	1	174.20	174.205	13.40	0.002
C	1	121.77	121.770	9.37	0.007
D	1	179.42	179.416	13.80	0.002
Square	4	870.29	217.572	16.74	0.000
A*A	1	30.81	30.812	2.37	0.143
B*B	1	0.79	0.785	0.06	0.809
C*C	1	3.54	3.539	0.27	0.609
D*D	1	779.40	779.402	59.96	0.000
2-Way Interaction	6	1014.26	169.043	13.00	0.000
A*B	1	143.76	143.760	11.06	0.004
A*C	1	129.28	129.277	9.94	0.006
A*D	1	282.91	282.912	21.76	0.000
B*C	1	267.16	267.159	20.55	0.000
B*D	1	109.52	109.516	8.42	0.010
C*D	1	81.63	81.631	6.28	0.023

Figure 2: Analysis of Variance (ANOVA) table.

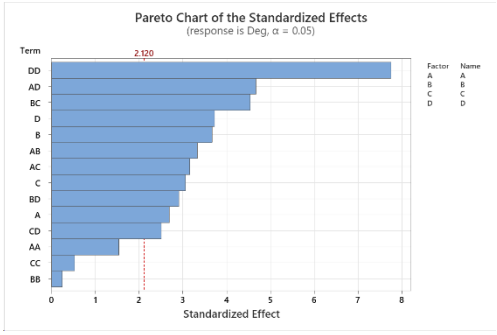

Figure 3: Pareto Chart of the standardized effects.

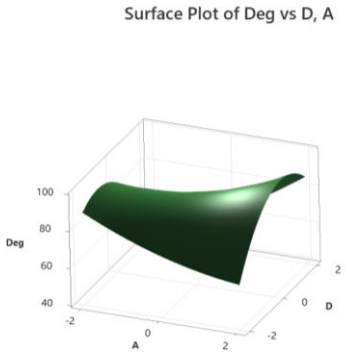

Figure 4: Surface plot of the catalyst dosage versus temperature.

B. *Response Optimizer*

Minitab 15 response optimizer was used to determine the process conditions at which degradation is maximized, at 100%. The optimum point coincided with the activator dosage being at its lowest and catalyst dosage at highest in order to facilitate catalyst retrieval. The following table provides a summary of the optimized conditions.

C. *Reaction Kinetics*

The kinetics at optimum degradation were ascertained by examining the solution at 6-minute intervals. The reaction was initially assumed to be pseudo-first order and plotting the natural logarithm of C_0/C_i against time yielded a straight line with an R^2 of 0.983, validating that the reaction does in fact follow a pseudo-first order as shown in Fig. 5 below. Whereas second order kinetics calculation yielded R^2=0.804, validating the first order assumption. The following table 3 yields the verification experiment results.

Table II. Optimal Conditions

	Coded Variable	Uncoded Variable
Catalyst dosage (mg/L)	1.292	643.8
pH	-0.719	3.56
Activator dosage (mM)	-1.865	4.80
Temperature (ºC)	0.178	42.86

Table III. Verification Experiment Summary

Rate constant (min^{-1})	0.0958
$Deg_{(Expected)}$ (%)	100
$Deg_{(Actual)}$ (%)	94.75
Model Error (%)	5.25

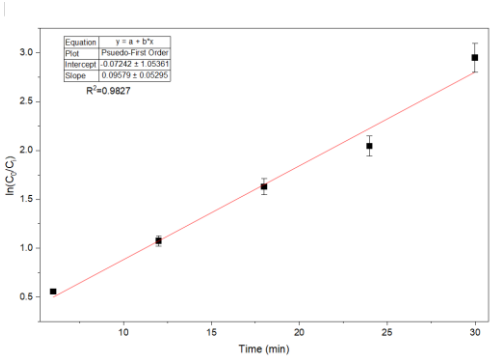

Figure 3: Pseudo-first order reaction plot.

IV. CONCLUSION

In conclusion, this work successfully presented the potential of sulfur doped graphitic carbon nitride (S-g-C3N4) as an efficient metal-free nano-photocatalyst, to tackle pharmaceutical pollution in water. The degradation experiments were optimized via a Response Surface Model (RSM), combining, for the first time, the 4 parameters: catalyst dosage, activator dosage, pH and temperature, study their effects and optimize their levels. The model yielded an R2 value of 0.921. The optimized conditions were also validated experimentally, those being 643.8mg/L catalyst dosage, 3.56 pH, 4.8 mM activator (H2O2) and 42.86 ºC temperature, yielding an experimentally validated degradation efficiency of 94.75% following pseudo-1st-order kinetics with k=0.0958 min^{-1}. The optimized degradation of doxycycline hyclate under mild conditions, exceeding 94% in 60 minutes, directly fulfills the purpose of this study, providing a practical and sustainable solution for degrading persistent pharmaceutical water pollutants. Utilizing a metal-free and low-cost photocatalyst to address the growing health and environmental threats, especially in regions experiencing rapid increase in pharmaceutical discharge.

V. CONFLICT OF INTEREST

The authors declare no competing interests.

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