

## Research Article

# Determination of Ketorolac in the Effluent from a Hospital Treating Plant and Kinetics Study of Its Photolytic Degradation

**Hector Hugo Ortega Soto, Jorge Javier Ramírez García, Paula Gamboa Suárez, and Angie Michelle Dávila Estrada**

*Laboratorio de Análisis Instrumental, Facultad de Química, Universidad Autónoma del Estado de México, Paseo Colón Esq. Paseo Toluca, 50120 Toluca, MEX, Mexico*

Correspondence should be addressed to Jorge Javier Ramírez García; [jjramirezg@uaemex.mx](mailto:jjramirezg@uaemex.mx)

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In this work, two specific, sensitive, and rapid analytical methods were developed. One of them was for the determination of ketorolac in a hospital wastewater treatment plant where there is no interference with other organic substances; the other one was for the determination of the degradation kinetics in aqueous medium. Ketorolac was extracted from wastewater samples through solid-phase extraction (SPE) cartridges, then it was identified and quantified by high-performance liquid chromatography (HPLC). Ketorolac was detected in concentrations between 0.1376 and 0.2667  $\mu\text{g/L}$ . Photolytic degradation was performed on aqueous solutions of ketorolac tromethamine reference substance, at a concentration of 50  $\mu\text{g/mL}$ . Samples were in direct contact with ultraviolet light in a dark chamber, equipped with two mercury lamps (254 nm) at a radiation source of 15 W. The results of the photolytic degradation were adjusted to a first-order model, obtaining a half-life of 4.8 hrs.

## 1. Introduction

Ketorolac is a drug that has analgesic, anti-inflammatory, and antipyretic properties and is indicated in the short-term treatment of mild to moderate pain postoperatively and in musculoskeletal trauma, in addition to pain caused by nephritic colic. This drug is contraindicated when the patient has active gastroduodenal ulcer, gastrointestinal bleeding, in patients with moderate or severe renal impairment [1].

The analgesic activity of ketorolac is due to the elimination of formation of prostaglandins, through the inhibition of the enzyme prostaglandin system [1]. The chemical structure of ketorolac is shown in Figure 1.

Ketorolac is metabolized by hydroxylation and conjugation with glucuronic acid. The renal route is the primary route of excretion of both the drug and its metabolites, which is approximately 92% of the dose, about 40% as metabolites

and 60% as ketorolac. Approximately 6% of the dose is excreted in feces [2].

Data obtained in a study to determine the toxic effects of ketorolac on *Cyprinus carpio*, Galar-Martínez and collaborators in 2014, concluded that ketorolac in a concentration range of 1 to 60 mg/L caused oxidative stress and cytotoxicity, specifically in the liver, brain, and blood.

Different authors indicate that the wastewater treatment plants do not remove the drugs in their entirety, because they do not have unitary operations that devote their process to the removal or elimination of drugs, since they depend on the physicochemical properties of each substance for which, in some cases, a decrease in the quantity of drugs after treatment barely persists [3–5].

Several studies have determined the presence of ketorolac in different matrices. For example, Gómez et al. in 2006 determined that the amount of ketorolac in the effluent of a hospital treatment plant ranged between 0.2  $\mu\text{g/L}$  and

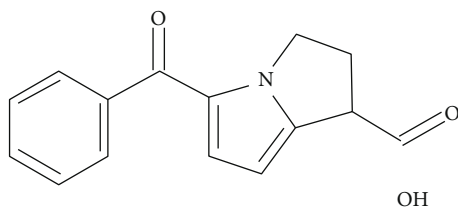


FIGURE 1: Chemical structure of ketorolac.

59.5  $\mu\text{g/L}$ . Oliveira et al. in 2015 determined ketorolac in influent and effluent from wastewater treatment plants of different hospitals, finding it in concentration ranges from 0.03  $\mu\text{g/L}$  to 1.15  $\mu\text{g/L}$  [5, 6].

Because drug concentrations in wastewater are in the order of  $\mu\text{g/L}$  and in some cases  $\text{ng/L}$ , the use of high-performance liquid chromatography coupled to a mass spectrometry detector is very common, which is significantly more sensitive than spectrophotometry detectors, but has the disadvantage that it is more expensive. However, the methodology presented in this research uses UV spectrophotometry detection, and a suitable sensitivity has been demonstrated by validation that can allow the quantification of ketorolac in wastewater in a less expensive way and can be replicated in other laboratories that do not have a mass spectrometry detector.

The objective of this work is to develop and validate analytical methodologies by high-resolution liquid chromatography for the quantification of ketorolac in wastewater of a hospital treatment plant and a second methodology that is capable of separating and quantifying ketorolac in solution and that can be used for the determination of the kinetics of photolytic degradation, and thus determine the persistence of ketorolac in the effluent of a hospital treatment plant.

## 2. Methodology

**2.1. Materials and Instruments.** Sigma-Aldrich® ketorolac tromethamine reference substance was used, formic acid of the brand Fermont® 88% analytical reagent grade. The Fermont brand chromatographic grade methanol and the water used were HPLC grade from the Millipore® Milli-Q brand purification equipment, and the cartridges used for solid-phase extraction (SPE) were Sep-Pak®, vac 6 cc (1 g) C18, corresponding to the Waters® brand.

The high-performance liquid chromatography equipment used for the development and validation of analytical methods was Waters brand and consisted of a model 1525 pump, a model 717 automatic injector system, and a model 2487 dual wave spectrophotometric detector. The software controller of the chromatographic system was Waters Breeze®.

### 2.2. Analytical Methodology

**2.2.1. Quantification of Ketorolac in Wastewater.** The reference solutions and samples used are of a concentration of 10  $\mu\text{g/mL}$  of ketorolac, using ketorolac tromethamine

reference substance, which is dissolved in chromatographic grade methanol.

The mobile phase is a mixture of methanol with acidified water in a ratio of 60% : 40% *v/v*. The acidified water is prepared by the dilution of 5.6 mL of 88% formic acid brought to 1000 mL capacity with Milli-Q water.

Validation of the methodology and analysis of the samples were carried out under the following chromatographic conditions: the column used is an Agilent® Zorbax SB C8 brand of 250  $\times$  4.6 mm with a particle size of 5  $\mu\text{m}$ , flow velocity of 1.0 mL/min, and injection volume of 20  $\mu\text{L}$  at a wavelength for detection of 318 nm.

The samples from the hospital treatment plant were extracted by SPE; the cartridges were previously conditioned with 5 mL of methanol chromatographic grade and later with 5 mL of Milli-Q water. The extraction was carried out to 250 mL of residual water, at the end, washing was performed with 10 mL of Milli-Q water. The elution of the sample was performed with 5 mL of methanol chromatographic grade. This solution was injected into the liquid chromatograph under the above-described conditions and quantified by comparing the external standard of 10  $\mu\text{g/mL}$  of ketorolac.

**2.2.2. Ketorolac Determination in Aqueous Solution.** The reference solutions and samples used are of a concentration of 50  $\mu\text{g/mL}$  of ketorolac, using ketorolac tromethamine reference substance, which is dissolved in Milli-Q water.

The mobile phase is a mixture of methanol with acidified water in a 50% : 50% *v/v* ratio. The acidified water is prepared by the dilution of 5.6 mL of 88% formic acid and brought to 1000 mL capacity with Milli-Q water.

Validation of the methodology and analysis of the samples were carried out under the following chromatographic conditions: the column used is an Agilent Zorbax SB C8 brand of 250  $\times$  4.6 mm with a particle size of 5  $\mu\text{m}$ ; flow rate of 1.5 mL/min; the injection volume of 20  $\mu\text{L}$  at a wavelength for detection of 323 nm.

**2.2.3. Validation of the Analytical Method.** The analytical methodologies were validated based on the guide for the validation of analytical methods of the International Conference on Harmonization (ICH) determining the parameters of specificity, suitability, system accuracy, system linearity, method linearity, repeatability, detection, and quantification limits [7].

The evaluation of the specificity was carried out by means of the injection, under the previously described conditions, from different samples that could interfere with the ketorolac analytical signal. These injected samples belong to a target, reference solution, and forced degradations by stress conditions of the reference solutions (acid, basic, and photolytic degradation).

A sixfold injection of a ketorolac reference solution determined the suitability of the system. The calculation of the chromatographic parameters was performed using the Breeze liquid chromatograph software.

The determination of linearity of the system was performed by analyzing 8 levels of ketorolac reference concentration (by triplicate), corresponding to 10% to 400%

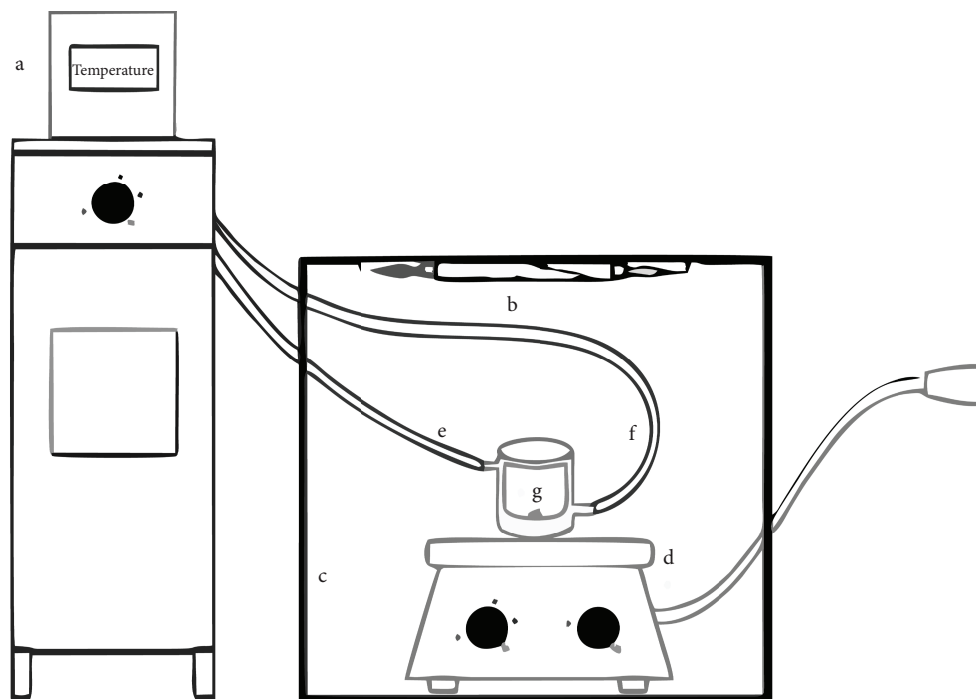


FIGURE 2: Photolytic degradation: (a) water, (b) radiation source, (c) container, (d) agitation plate, (e) and (f) in and off recirculation water, and (g) reaction cell.

of the working concentration ( $10 \mu\text{g/mL}$  for the residual water quantification and  $50 \mu\text{g/mL}$  for determination of photolytic degradation). The slope, ordered to the origin, and coefficient of determination by linear regression were calculated, in addition to the calculation of confidence interval for the slope ( $IC_{\beta 1}$ ).

The precision parameter was performed at three levels: system, repeatability, and intermediate accuracy. The evaluation of the precision of the system was carried out by the injection of 6 reference solutions of ketorolac at work concentration, coming from the same stock, calculating the average, standard deviation, and coefficient of variation.

The determination of the repeatability was performed by independently preparing a sixfold solution of ketorolac at the working concentration, for its subsequent quantification with the comparison with an external standard, determining the percentage of recovery, the average recovery rate of the six solutions, the standard deviation, and the coefficient of variation.

Intermediate precision was evaluated by quantifying 3 samples containing the working concentration; the analysis was carried out by 2 analysts on two different days ( $n = 12$ ). The average of recovery, standard deviation, and coefficient of variation was obtained.

Accuracy was determined by calculating the recovery of three levels of ketorolac in triplicate ( $n = 9$ ), quantification using an external standard, and obtaining the recovery of each of the samples, the mean recovery, the standard deviation, coefficient of variation, and confidence interval for the mean ( $IC_{\mu}$ ).

The limits of detection and quantification were determined by performing a calibration curve at three levels of

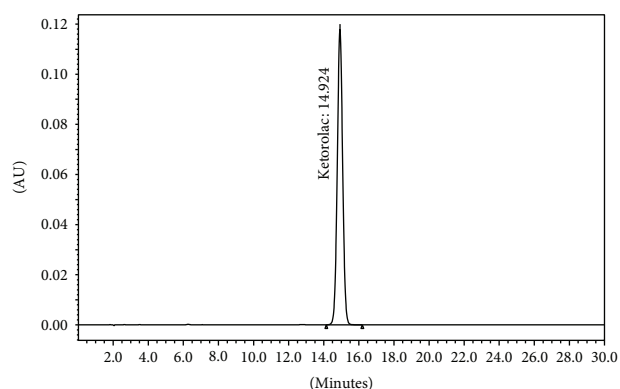


FIGURE 3: Chromatogram for the reference solution of ketorolac.

concentration. Subsequently, the slope, ordered to the origin, standard deviation of the regression, and coefficient of determination were calculated, all by linear regression.

**2.2.4. Quantification of Wastewater Samples from the Treatment Plant.** The samples were taken in a timely manner from a wastewater treatment plant of a hospital located in the city of Toluca, in the state of Mexico, Mexico. The samples were refrigerated immediately after being taken for further processing by SPE using the methodology indicated above.

**2.3. Photolytic Degradation Kinetics.** The system for the determination of degradation kinetics consists mainly of the following components: a quartz cell placed on a stirring grid that contains the sample and allows the flow

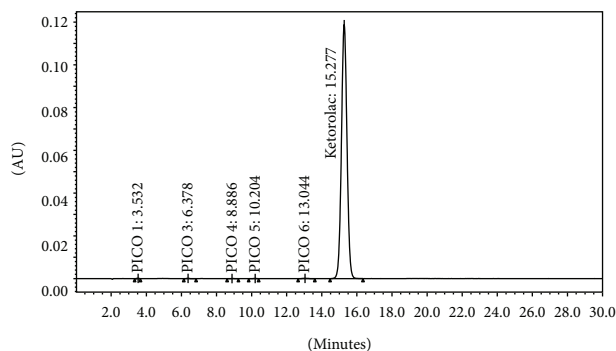


FIGURE 4: Chromatogram for the photolytic degradation of ketorolac and its degradation products.

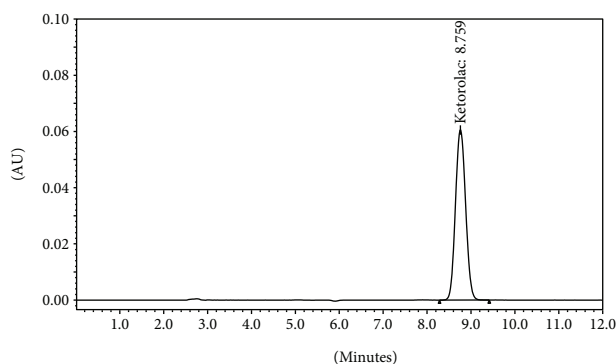


FIGURE 5: Chromatogram for the reference solution of ketorolac in wastewater determination.

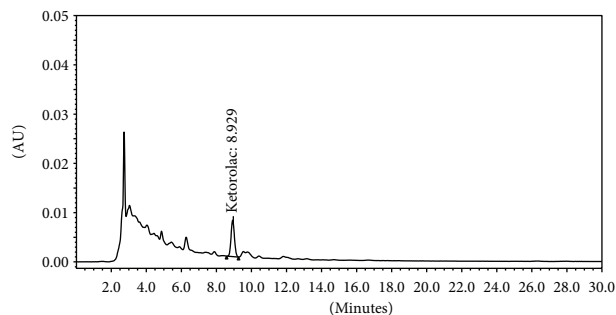


FIGURE 6: Chromatogram for the sample wastewater hospital treatment plant.

of radiation, a recirculating water bath keeping the cell at a constant temperature, and a source of UV radiation from a mercury lamp at 254 nm. These components were inside a glass tank lined with black polyethylene that prevents reflection of the radiation. Figure 2 shows the scheme for the photolytic degradation.

For the experimentation, 100 mL of a solution of ketorolac in water with a concentration of 50  $\mu\text{g/mL}$  ( $2.0 \times 10^{-4}$  mol/L approx.) was placed inside the reaction cell and initiated the radiation, keeping the temperature of the cell at 18°C. Samples of 2 mL of the ketorolac solution were taken at different times. Subsequently, each sample was placed inside vials for analysis

TABLE 1: Suitability results for the system.

Parameter	Ketorolac in wastewater	Ketorolac and degradation products
Retention time (Rt)	8.7 min	14.1 min
Peak area	973919.0	2888463.2
Theoretical plates ( $N$ )	6830.1	11096.6
Capacity factor ( $K'$ )	3.9	6.8
Tailing ( $T$ )	1.1	1.0

TABLE 2: Precision results for ketorolac in wastewater.

	Precision of the system ( $n = 6$ )	Precision Repeatability ( $n = 6$ )	Interday precision ( $n = 12$ )
Average	956364.8	99.8	99.8
Standard deviation	7733.2	0.7	1.8
RSD (%)	0.8	0.7	1.8
Statistic $T_{0.95}$	—	2.571	—
$IC_{(\mu)}$	—	100.6	—
	—	99.1	—

TABLE 3: Precision results for ketorolac and its degradation products.

	Precision of the system ( $n = 6$ )	Precision Repeatability ( $n = 6$ )	Interday precision ( $n = 12$ )
Average	2911596.8	101.1	100.1
Standard deviation	41727.1	1.0	0.9
RSD (%)	1.4	1.0	0.9
Statistic $T_{0.95}$	—	2.571	—
$IC_{(\mu)}$	—	102.17	—
	—	100.01	—

TABLE 4: Linearity results for the system.

Parameter	Ketorolac in wastewater	Ketorolac and degradation products
Slope	96078.6	61337.7
Origin	-21767.2	-29360.2
Range	2.07-41.5	5.05-107.8
$R^2$	0.9970	0.9986
$IC_{(\beta_0)}$	93773.5-98383.7	60356.8-62318.6

by HPLC under the conditions described above. This methodology was carried out in triplicate for each of the radiations.

### 3. Results and Discussion

3.1. Analytical Method Validation for the Quantification of Ketorolac and Its Degradation Products. The specificity of the analytical methodologies was demonstrated by the chromatograms obtained from the individual injection of

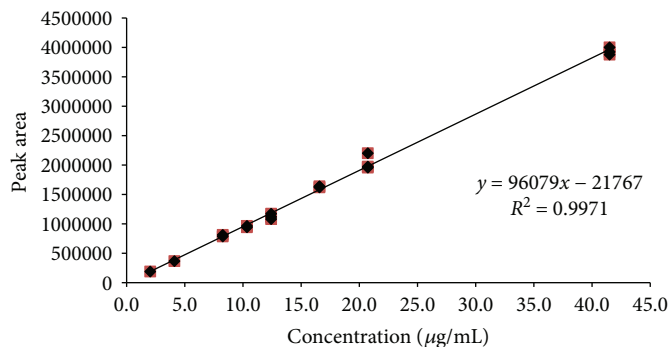


FIGURE 7: Linearity determination of ketorolac in wastewater.

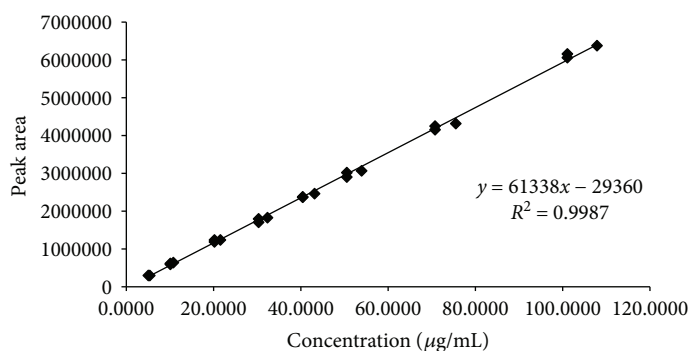


FIGURE 8: Linearity of ketorolac degradation products.

TABLE 5: Accuracy results for ketorolac in wastewater.

Level	% recovery	Average	SD	RSD (%)	Global average (n = 9)	SD (n = 9)	Global RSD (%) (n = 9)
40%	100.7	101.8	0.9	0.9	100.0	1.8	1.8
	102.1						
	102.5						
100%	98.4	98.9	1.2	1.2	100.0	1.8	1.8
	100.2						
	98.0						
400%	101.4	99.4	1.7	1.8	100.0	1.0	1.0
	98.3						
	98.5						

different and possible components of the real sample; due to the fact that degradation products were not available in pure way, forced degradations were carried out on a solution of reference substance of ketorolac. In Figures 3 and 4, the chromatograms obtained for the determination of degradation products can be observed. In the case of the methodology for the quantification of ketorolac in wastewater, the chromatograms are shown in Figures 5 and 6.

During the determination of the suitability of the system, a sixfold reference solution was injected under the described conditions, checking the retention time, area under the curve, theoretical plates, capacity factor, and collection

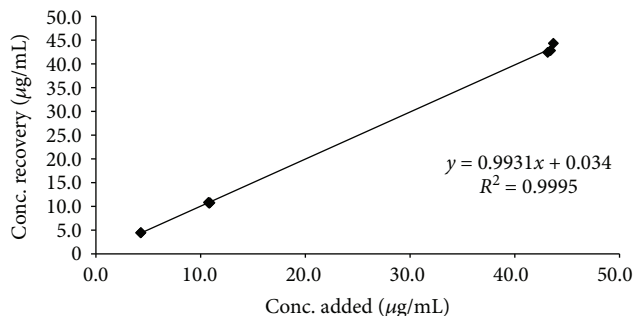


FIGURE 9: Accuracy for ketorolac in wastewater.

TABLE 6: Accuracy results for ketorolac in the degradation products.

Level	% recovery	Average	SD	RSD (%)	Global average (n = 9)	SD (n = 9)	Global RSD (%) (n = 9)
40%	101.0	100.4	0.8	0.8	100.0	1.0	1.0
	99.5						
	100.7						
100%	98.5	99.1	1.5	1.5	99.8	1.1	1.1
	100.8						
	98.0						
400%	99.3	100.0	1.0	1.0	100.0	1.0	1.0
	99.6						
	101.2						

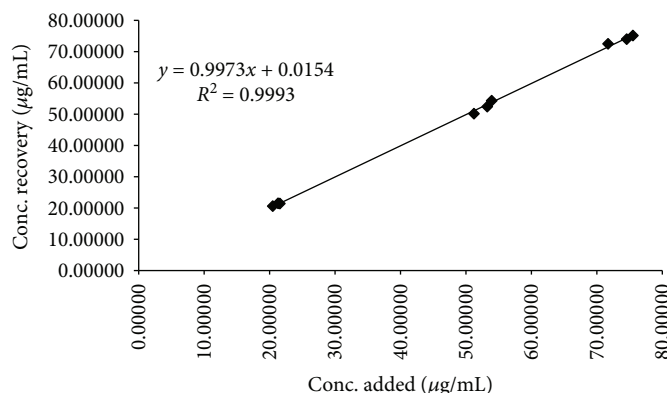


FIGURE 10: Accuracy for ketorolac in the degradation products.

factor. Table 1 shows the results obtained in the test for the two methodologies.

The results obtained in the precision parameter for quantification of ketorolac in residual water are shown in Table 2.

The results obtained in the precision parameter for quantification of ketorolac and degradation products are shown in Table 3.

The linearity was evaluated at 8 levels of concentration and in the two methodologies with a coefficient of determination  $> 0.98$ . Table 4 shows the results obtained for the linearity of the system.

Figures 7 and 8 show graphs with concentration versus area under the curve for the linearity of the system.

The accuracy of the method was determined by quantifying added water with an exact amount of ketorolac at three concentration levels, by triplicate each.

In the case of the determination of ketorolac in residual water, the levels of 40%, 100%, and 400% were evaluated. The results are shown in Table 5, and in all samples analyzed, a recovery between 98.0% and 102.5% is obtained, obtaining a global average ( $n=9$ ) of 100.0%, with a coefficient of variation of 1.8%.

Graphing the data added quantity versus quantity recovered gives a coefficient of determination of 0.999 and slope of 0.9931, and the ordinate to the origin passes through zero (Figure 9).

The accuracy results obtained for ketorolac and degradation products are shown in Table 6; all recovery results are between 98.0% and 101.2%, with a global mean ( $n=9$ ) of 99.8% and a coefficient of variation of 1.1%. By plotting the added concentration versus concentration recovered (Figure 10), a coefficient of determination ( $R^2$ ) of 0.9993 was obtained as well as a slope of 0.9973, and an ordinate to the origin is near zero.

The limit of detection and quantification for both methodologies was determined by analyzing a standard curve at low concentration levels.

For the quantification of ketorolac in residual water, the limit of detection and quantification were 0.00934  $\mu\text{g/mL}$  and 0.02832  $\mu\text{g/mL}$ , respectively, and  $R^2$  was 0.998. The calibration curve obtained during the determination is shown in Figure 11.

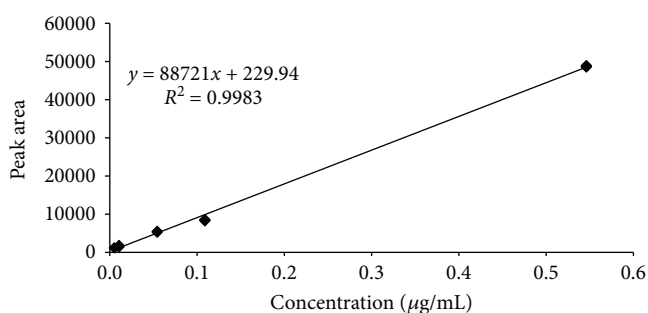


FIGURE 11: LOD and LOQ for ketorolac in wastewater.

Figure 12 shows the curve obtained for the limit of detection and quantification in the methodology for the determination of ketorolac in the presence of its degradation products, which obtained a coefficient of determination of 0.99998. The calculated limit of detection was 0.00283  $\mu\text{g/mL}$ , while the quantification limit was 0.00859  $\mu\text{g/mL}$ .

3.2. *Quantification of Ketorolac in Wastewater from a Hospital Treatment Plant.* The results obtained by high-resolution liquid chromatography on samples obtained from the effluent from a hospital wastewater treatment plant located in the city of Toluca, State of Mexico, Mexico, are shown in Table 7; each sample was analyzed by triplicate.

3.3. *Photolytic Degradation Kinetics.* The results obtained by the high-resolution liquid chromatography analysis on the samples generated in photolytic degradation with UV radiation are shown in Table 8.

These results, concentration (mol/L) with respect to time (h), can be observed in Figure 13.

With the data obtained in Table 8, calculations were made for the determination of the order of reaction according to the equations indicated by Fogler. Slope, ordered to the origin, and coefficient of determination ( $R^2$ ) were determined in each of the reaction orders. The results are shown in Table 9.

As seen in Table 9, the order of reaction 1 or first order has the highest determination coefficient with respect to the others; doing a study of residuals, it is observed that there is no marked tendency.

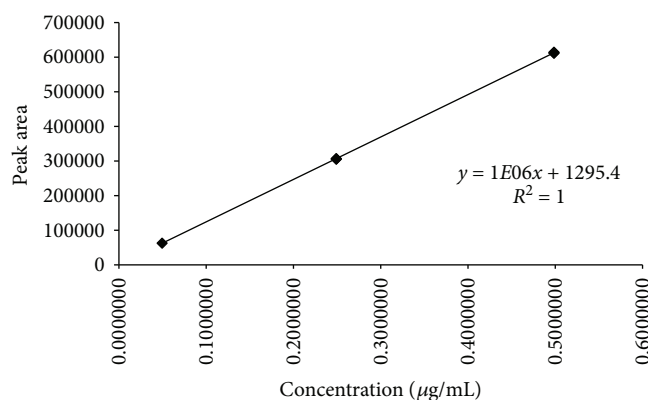


FIGURE 12: LOD and LOQ for ketorolac the degradation products.

TABLE 7: Quantification results for ketorolac samples in wastewater.

Sample	Conc. (µg/L)	Average	SD	RSD (%)	Global average (n = 9)	Global RSD
M1_1	0.2109					
M1_2	0.2424	0.2258	0.016	7.0		
M1_3	0.2242					
M2_1	0.2590					
M2_2	0.2667	0.2559	0.013	5.0	0.2117	22.3
M2_3	0.2419					
M3_1	0.1658					
M3_2	0.1376	0.1534	0.014	9.4		
M3_3	0.1568					

Figure 14 shows the first-order kinetics, as mentioned above. This is the model that best fits the data obtained by both coefficient of determination and study of residuals. The plot of residuals for the first-order kinetics for UV photolytic degradation of ketorolac is shown in Figure 15.

The results obtained during the validation process show that there are two methodologies, one for the quantification of ketorolac in residual water and another for the quantification of ketorolac and the presence of its photolytic degradation products, which are accurate and precise, with a limit of detection and quantification low enough to be able to identify and quantify the samples from hospital wastewater that was analyzed.

As observed in the chromatograms obtained in the specificity tests, there is no interference by the matrix or degradation products in the quantification of ketorolac; this can be due to two causes: the first is that there is a good separation between the ketorolac peak and the other components of the sample due to a good selection of the chromatographic conditions and the second is the working wavelength in the detector, since while most organic compounds have their maximum absorption in the region of the spectrum of 200 nm to about 260 nm, the ketorolac under these working conditions had its maximum at 323 nm and 318 nm, respectively.

TABLE 8: Degradation results for ketorolac with ultraviolet radiation.

Time (h)	Sample 1 Ketorolac (mol/L)	Sample 2 Ketorolac (mol/L)	Sample 3 Ketorolac (mol/L)
0	0.0001997875	0.0001997875	0.0001932206
0.5	0.0002023158	0.0002009421	0.0001949987
1	0.0002029341	0.0002005465	0.0001943721
3	0.0002083404	0.0001981625	0.0001913357
4	0.0002037832	0.0001924920	0.0001882330
5	0.0002009338	0.0001825738	0.0001775599
6	0.0002066012	0.0001646013	0.0001573098
7	0.0001835656	0.0001230821	0.0001170299
8	0.0001611106	0.0001001495	0.0000955237
9	0.0001383091	0.0000897662	0.0000864861
22	0.0000135506	0.0000051354	0.0000045894
25	0.0000097583	0.0000024875	0.0000023666
47	0.0000007281	0.0000004353	0.0000004399

The quantification of samples obtained from the effluent from the wastewater treatment plant from a hospital, after being treated by SPE, is as follows: an average concentration of 0.2117 µg/L was obtained, with a CV of 22.3%, which can be considered high and may be due to the type of point sampling and the treatment that was performed, which causes a wide variation.

The results of quantification of ketorolac in wastewater shows that it can be used for this purpose; it is true that liquid chromatography coupled to mass spectrometry detector systems are the most used for this type of application because of their greater sensitivity and more specialized handling; nevertheless, it represents higher costs. That is why, the methodology proposed in this research uses a spectrophotometry detector which is cheaper and widely used; with the results obtained, the samples can be considered as an option in the quantification of traces of ketorolac in residual water.

When the data were obtained during photolytic degradation with UV radiation, it was determined that this kinetics is of the first order, so that the data conform to 1 [8], since the

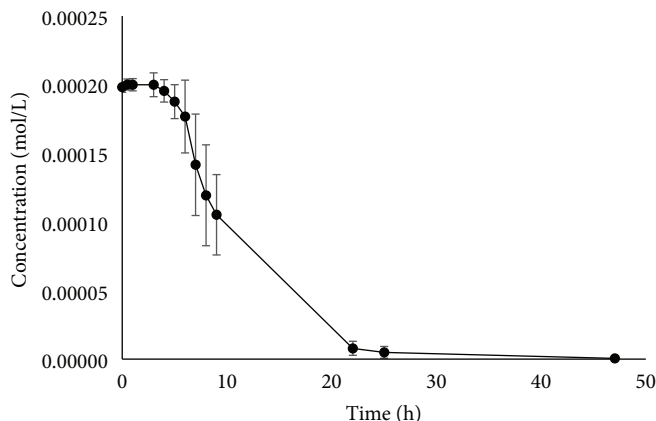


FIGURE 13: Kinetics degradation of ketorolac with ultraviolet radiation.

TABLE 9: Determination of the degradation reaction order of ketorolac with ultraviolet radiation.

	Order zero	First order	Second order	Third order
$R^2$	0.79859	0.96387	0.79912	0.69190
Slope	$-5.3194E-06$	0.145164843	36424.29224	70745005450
Origin	0.00018896	-0.41326464	-191771.8568	$-4.20727E+11$

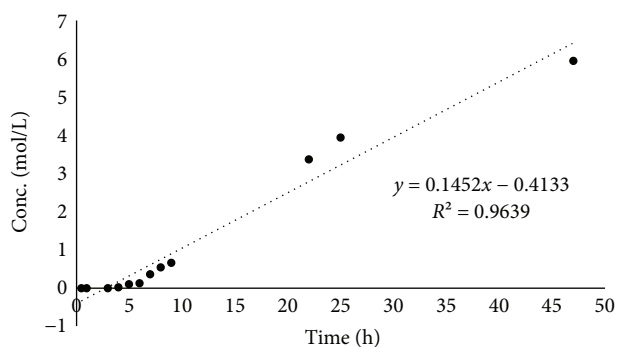


FIGURE 14: First-order kinetics degradation of ketorolac using UV radiation.

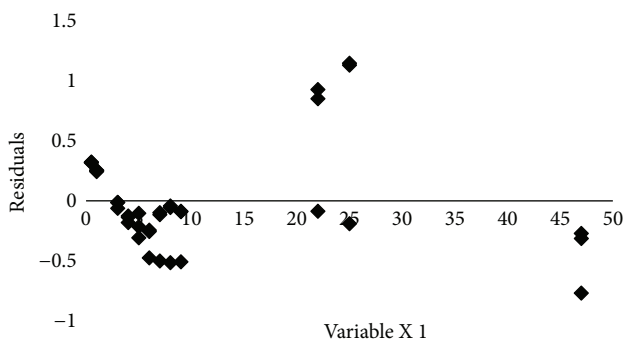


FIGURE 15: First-order residuals analysis.

correlation coefficient was greater than 0.98, in addition to the fact that the study of residuals does not indicate that there is a trend in error:

$$\ln \frac{C_0}{C_A} = k t. \quad (1)$$

By deducing from the above equation, we can obtain the average half-life for UV radiation which is 4.8 hours.

$$t_{1/2} = \frac{\ln(C_0/C_{1/2})}{k}. \quad (2)$$

#### 4. Conclusions

Two analytical methodologies were obtained for the quantification of ketorolac, the first for its quantification in residual water and the second for the determination of its photolytic degradation products. In both cases, it is guaranteed that the results obtained by these methodologies are reliable because they comply completely with the validation parameters studied.

The quantification of ketorolac in residual water of a wastewater treatment plant of a hospital located in the city of Toluca, Mexico, was carried out, resulting in an average concentration of  $0.2117 \mu\text{g/L}$ .

Photolytic degradation kinetics studies for ketorolac show that it is of the first order with a half-life of 4.8 hours for degradation with UV radiation.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

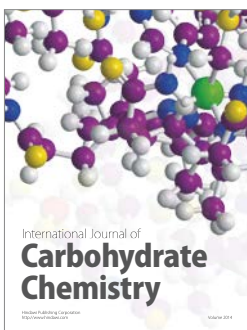
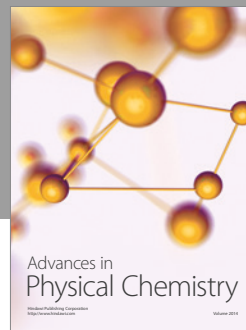
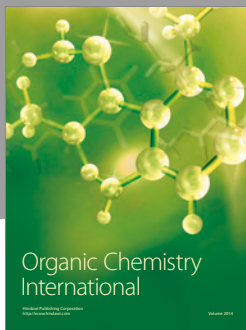


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## References

- [1] A. L. Olives, V. González-Ruiz, and M. A. Martín, “Insolation and quantitative methods for analysis of non-steroidal anti-inflammatory drugs,” *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, vol. 11, no. 1, pp. 65–95, 2012.
- [2] “U.S. Food And Drug Administration,” July 2015 [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022382Orig1s000Approv.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022382Orig1s000Approv.pdf).
- [3] R. Amdany, L. Chimuka, and E. Cukrowska, “Determination of naproxen, ibuprofen and triclosan in wastewater using the polar organic chemical integrative sampler (POCIS): a laboratory calibration and field application,” *Water SA*, vol. 40, no. 3, pp. 407–414, 2014.
- [4] M. J. Martínez Bueno, S. Herrera, D. Munaron et al., “POCIS passive samplers as a monitoring tool for pharmaceutical residues and their transformation products in marine environment,” *Environmental Science and Pollution Research*, vol. 23, no. 6, pp. 5019–5029, 2016.
- [5] T. S. Oliveira, M. Murphy, N. Mendola, V. Wong, D. Carlson, and L. Waring, “Characterization of pharmaceuticals and personal care products in hospital effluent and waste water influent/effluent by direct-injection LC-MS-MS,” *Science of the Total Environment*, vol. 518-519, pp. 459–478, 2015.
- [6] M. J. Gómez, M. Petrovic, A. R. Fernández-Alba, and D. Barceló, “Determination of pharmaceuticals of various therapeutic classes by solid-phase extraction and liquid chromatography-tandem mass spectrometry analysis in hospital effluent wastewaters,” *Journal of Chromatography A*, vol. 1114, no. 2, pp. 224–233, 2006.
- [7] International Conference on Harmonisation, *ICH Harmonised Tripartite Guideline. Validation of Analytical Procedures: Text and Methodology Q2(R1)*, 2005.
- [8] S. Fogler, *Elements of Chemical Reaction Engineering*, New Delhi, Prentice-Hall of India Private Limited, 3th edition, 2004.



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