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Ecologically Validated UV Method for Etodolac Estimation in Pharmaceutical Formulation Using Green Hydrotropic Solution and Forced Degradation Study for Stability Detection

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Abstract: In challenging assignments for advancing practices of quantification of Etodolac, hydrotropic solubilization succeeded in enhancing poor water solubility and precluded the use of costlier toxic organic solvents. In the present investigation, among more than a few hydrotropes screened, sodium acetate as a green and sustainable solvent (4M) confirmed the solubility enhancement of Etodolac by 160 times. A titrimetric method was performed to determine the Etodolac in bulk and marketed tablets using a 4M sustainable sodium acetate hydrotropic solution. In the titrimetry method, Etodolac was titrated with 0.1N NaOH by following both the I.P. method and the proposed method, and the quantity of the drug was quantified. Similarly, Etodolac (in bulk and tablets) was also estimated through the U.V. method. In the UV method, 4M sodium acetate showed characteristic absorption peaks and obeyed the Beer-Lambert law for 1–6 µg/mL. The RSD values were also calculated and found within acceptable limits for the accuracy and precision of the method. The U.V. spectrophotometric method of multivariate calibration has shown values at the lower limit for Etodolac estimation compared to Titrimetry. Thus, for establishing the stability of Etodolac, forced degradation against strong acid, base, oxidation, and light was also performed as it was observed that a molar sodium acetate hydrotropic solution had shown a remarkable enhancement in solubility of a drug reported by both analytical strategies. Hence, recommended to be used for routine analysis of other drugs.

Keywords: Etodolac; hydrotrope; sustainable; solubility, green chemistry; Titrimetry; UV validation, degradation study.

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1. Introduction

Lipophilicity and poor aqueous solubility are one of the most facing critical issues of newly synthesized drugs, thus have given the new scientific concept for research and innovation to establish new ways in the field of improving and enhancing better and possible ways to combat the solubility issues so that further it could be applied in the analytical field. Similarly, to exert the therapeutic action of the same drug, the body fluids must transport it by traversing the required lipoidal biological membrane barrier and hence exerted lipophilicity. It

is also proven that drugs' side effects are directly caused by poor aqueous solubility [1-4]. Hence, increasing the aqueous solubility of drugs can be a valuable aid in increasing efficacy or reducing side effects. As solubility enhancement is still a developing concept, several ways and technical approaches are rehearsed daily for achieving a milestone. Among the recent developments, "Hydrotropy" has gained much interest as it claims the enormous enhancement in the solubility of drugs in the desired solvent (water) by assisting "Hydrotropes" as a third component that meticulously improves and upgrades the solubility of poorly dissolvable drugs of BCS Class-II. Hydrotropes are organic or inorganic non-micelle-forming agents and can be used as liquids or solids, organic or inorganic. Structurally, including two essential parts, an anionic group brings about high aqueous solubility, and a hydrophobic aromatic ring or ring system helps accept solvents. Numerous hydrotropes have been listed to strengthen the aqueous solubility of various drugs, and these are Urea, Sodium benzoate, Sodium citrate, Sodium salicylate, and Sodium acetate. Due to the unique characteristics of these hydrotropes, the applicability of sodium acetate as a hydrotropic solubilizing agent was used as an introductory in solubility enhancement of one of the BCS Class-II drugs, i.e., Etodolac [5,6].

Etodolac is a class of NSAIDs drugs used to cure inflammatory and analgesic effects. Its analgesic activity is known for inhibiting and inactivating the cyclooxygenase enzyme and subsequently inhibiting prostaglandin synthesis. Its utility is observed in curing mild to moderate pain, fever, and hence inflammation. [7-14].

The prime importance of this research is to reflect the substantial enhancement in the solubility of Etodolac by sodium acetate as a hydrotrope and its further implementation in the titrimetric estimation of Etodolac bulk drug and marketed tablet formulations to exempt the use of various organic solvents as used in various standard I.P. methods. Similarly, for more reproducible results, the applied titrimetric method was further compared with the U.V. spectrophotometry method, the most widely used method for drug quantification. Consequently, based on the results, the U.V. method was validated on various parameters. Similarly, to establish the stability of Etodolac, stress degradation studies were performed.

2. Materials and Methods

2.1. Materials.

Etodolac was supplied as a gift sample by Akums Drugs and Pharmaceutical Ltd, Raipur, Haridwar. CDH supplied sodium acetate and phenolphthalein. Merck, India, supplied ethanol. S.D supplied with sodium hydroxide. Fine Chem limited. All other chemicals and solvents were used of analytical grade. Etogesic label claims 600 mg commercial tablets manufactured by Zydus Healthcare Ltd, Ahmedabad, were purchased from the local market.

2.2. Preliminary drug identification study.

For the identification of the selected drugs, the infrared spectrum of pure Etodolac was recorded using Fourier transform infrared spectroscopy (FTIR) as a neat analysis method. Here, the sample of drugs was spread on a KBr plate and pressed under hydraulic pressure in this method. Thus, infrared radiation is exposed to the sample, and the signals are collected by the detectors, which sequentially liberate spectra that provide the detailed functional groups the molecule. Hence, the drug was detected by FTIR in which the spectra are recorded under the wavenumber of 4000 cm^{-1} to 650 cm^{-1}.

2.3. Preliminary solubility studies.

The equilibrium solubility studies were implemented in a variety of hydrotropic agents. The aqueous solution of hydrotropic agents, i.e., sodium acetate, was prepared individually at a molar concentration. A solution of a selected hydrotropic agent was accurately measured in their corresponding vial, and thus, an accurate amount of drug was added and kept in a water bath shaker until a saturated solution was obtained. Then, the vial of the respective agent was shaken on a water bath shaker for 12 hours, and allowed to equilibrate for 24 hours to attain equilibrium solubility. The solubility enhancement ratio was then determined.

2.4. Quantitative estimation of Etodolac.

Quantitative determination of Etodolac was performed by Titrimetry method and UV spectrophotometric method using selected sodium acetate (4M) as a hydrotropic solution.

2.5. Titrimetric analysis procedure for the bulk drug and tablet formulation.

Quantification of bulk drug Etodolac was carried out by sodium acetate in the following manner. Firstly, 25 ml of 4M sodium acetate hydrotropic solution was prepared and transferred to a 250 ml conical flask, followed by the addition of accurately weighed Etodolac, and the entire solution was shaken for 10 min for complete dissolution. Consequently, titrimetric estimation was performed with 0.1 M sodium hydroxide using phenolphthalein as an indicator, and blank titration was also performed to explicit errors. Each ml of 0.1 M sodium hydroxide is equivalent to 0.02543 g of $C_{16}H_{14}O_3$ (Standardized data). Drug content was determined (n=3).

Similarly, for the marketed tablet Etodolac estimation, the weight of 20 marketed tablets was taken and converted into the fine powdered form using a simple trituration method. Drug- hydrotrope solution was prepared by taking an acceptable powder equivalent to 100 mg of Etodolac and then dissolved in 25 ml of 4M sodium acetate solution. Subsequent filtration through a Whatman filter paper no. 41 was done, and latterly the obtained filtrate was titrated with 0.1 M sodium hydroxide solution using phenolphthalein as an indicator. Drug contents were determined (n=3).

The Official Indian Pharmacopoeia method was used as a standard method for analyzing the bulk drug Etodolac [9-11]. For estimation, pre-weighed 100 mg of Etodolac was dissolved in 25 ml of 95% of ethanol solution, which was previously neutralized with phenolphthalein solution, followed by 25 ml of water to make up the required volume. 0.1 M sodium hydroxide solution was further used for titrimetric estimation. Reportedly, each ml of 0.1 M sodium hydroxide is equivalent to 0.02543 g of $C_{16}H_{14}O_3$. Drug content was determined (n=3) accordingly. The same procedure was repeated for the estimation of marketed etodolac tablets.

2.6. UV Spectrophotometric method.

2.6.1. Preparation of Calibration curve and standard stock solution in 4M Sodium acetate solution.

The prerequisite of the U.V. method as a preparation of a standard stock solution of Etodolac was prepared by taking 100 mg of drug in 100 mL of 4 M sodium acetate solution

followed by subsequent shaking and strength of 100µg/ml drug-hydrotrope solution was obtained, and sonicated for 1hour. To find the required λ max of Etodolac, the entire prepared solution was scanned in the U.V. range of 400–200 nm. The λ max of Etodolac was observed at 281 nm and used for further analysis. Preparation of the standard calibration curve for defining the linearity and the regression equations, appropriate aliquots of 1-6 µg/ml from the prepared stock solution were prepared. The absorbances were measured at 281 nm [15-20].

2.6.2. Etodolac tablet formulations estimation.

For Etodolac in tablet estimation, 4M hydrotropic sodium acetate solution was used. A simple procedure of making 100 ml solution drug hydrotrope was processed. Previously weighed equivalent 100 mg tablet powder was taken and dissolved into 20 ml of 4M sodium acetate solution followed by vigorous shaking and subsequent filtration through filter paper no. 4. The obtained drug filtrate was diluted appropriately with distilled water, and the analysis was carried out using a U.V. spectrophotometer at 281 nm against a reagent blank. The drug content of the tablet formulation was calculated. Similarly, for recovery, different spiking concentrations, i.e., 15 and 20 mg of the standard drug to pre-estimated samples, were used, and the contents were reanalyzed by the developed U.V. method [20-26].

2.7. UV method validation.

The ICH guideline has mentioned that any analytical method developed must be validated with different analytical parameters for the selected analytical method to establish the accuracy and precision of results. Thus, it was further validated based on the results obtained for Etodolac analysis, specifically by the U.V. method. Perquisites for routine drug analysis, the selected analytical method must be precise, accurate, specific, and robust. [26-29].

2.7.1. Accuracy.

The accuracy of the validated U.V. method has been measured in terms of the percent recovery of Etodolac in marketed form. Any slight change in the drug concentration in the hydrotropic solution was determined.

2.7.2. Linearity.

The linearity of Etodolac in the range of 1-6 µg/ml was evaluated to check the sample solutions, which were analyzed by U.V. spectrophotometer by following the required standard calibration curve method, which has linearity at a selected wavelength or not. The relatable regression equation, Beer's law limits, slopes, and intercept were calculated.

2.7.3. Limits of detection (LOD) and quantification (LOQ).

The minimum amount of analyte which is detectable and quantified by the analytical method for analyzing the drug sample is generally reflected by LOD and LOQ values. A simple mathematical formula can be used for LOD and LOQ calculations by using the obtained values for 'Slope' of the calibration curve of the analyzed drug:

LOD = Standard Deviation X 3.3/Slope of a calibration curve

LOQ = Standard Deviation X 10/Slope of the calibration curve

2.7.4. Precision.

Precision is considered an essential parameter for avoiding any errors. Thus, Etodolac sample solutions were analyzed by UV method to find the closeness of agreement between the exact and known values of the Etodolac. All measurements were performed on the same day (Intraday) and subsequent days (Interday).

2.7.5. Robustness.

To ensure the suitability of the analytical instrument for its intended use, the robustness parameter was studied.

2.8. Stability indicating-stress degradation study.

The prime requirement of stability testing of new drug substances and products is to reveal the inherent stability characteristics of the active therapeutic substance, which is an essential criterion per the ICH. Hence, stress degradation studies on Etodolac were performed against the effect of strong acid and bases, light and hydrogen peroxide degradation to detect the stability, and the following given below procedure has opted for every study [30-33].

2.8.1. Etodolac acid degradation.

2.8.1.1. Standard Etodolac solution.

10 mg bulk Etodolac drug in methanol was transferred to a volumetric flask to achieve a 1mg/ml concentration. After 30 mins, an aliquot solution was diluted with 0.1N hydrochloric acid to get a final 100 mcg/ml concentration. The solution was scanned in UV region, and maximum absorbance was recorded at 281mn. A similar method was performed for 60 min and 90 min intervals.

2.8.1.2. Sample preparation.

Etodolac tablets were powdered and dissolved in methanol in the volumetric flask to achieve a 1mg/ml concentration. Then, after 30 mins of duration, 100 mcg/ml final concentration were established by diluting an aliquot solution with 0.1N hydrochloric acid. The solution was scanned in UV region, and maximum absorbance was recorded at 281mn. The same procedure was reported for 60 min and 90 min intervals.

2.8.1.3. Blank preparation.

A Blank solution of 1N HCl was prepared similarly. After the stipulated time, the absorption of the resulting solution showed maxima of 281nm against reagent blank treated in the same way. Three such determinations were made, the assay value was estimated, and the obtained were concurrent.

2.8.2. Etodolac alkali degradation.

2.8.2.1. Standard Etodolac solution.

10 mg bulk Etodolac drug in methanol was transferred to a volumetric flask to achieve a 1mg/ml concentration. After 30 mins, an aliquot solution was diluted with 0.1M NaOH to get a final concentration of 100 mcg/ml. The solution was scanned in UV region, and maximum absorbance was recorded at 281nm. A similar method was performed for 60 min and 90 min intervals.

2.8.2.2. Sample preparation.

Etodolac tablets were powdered and dissolved in methanol in a volumetric flask to achieve a concentration of 1mg/ml. Then, after 30 mins of duration 100 mcg/ml final concentration were established by diluting an aliquot solution with 0.1M NaOH. The solution was scanned in UV region, and maximum absorbance was recorded at 281nm. The same procedure was applied for 60 min and 90 min intervals.

2.8.2.3. Blank preparation.

A Blank solution of 0.1M NaOH was prepared similarly. After the stipulated time, the absorption of the resulting solution showed maxima of 281nm against the reagent blank treated in the same way. Three such determinations were made, the assay value was estimated, and concurrent values were recorded.

2.8.3. Etodolac oxidative degradation.

10 mg bulk Etodolac drug in methanol was transferred to a volumetric flask to achieve a 1mg/ml concentration. After 30 mins, an aliquot solution was diluted with 10% H_2O_2 to get a final concentration of 100 mcg/ml. The solution was scanned in UV region, and maximum absorbance was recorded at 281nm. A similar method was performed for 60 min and 90 min intervals.

2.8.3.1. Sample preparation.

Etodolac tablets were powdered and dissolved in methanol in a volumetric flask to achieve a 1mg/ml concentration. Then, after 30 mins of duration, 100 mcg/ml final concentration was established by diluting an aliquot solution with 10% H_2O_2. The solution was scanned in UV region, and maximum absorbance was recorded at 281nm. The same procedure was applied for 60 min and 90 min intervals.

2.8.3.2. Blank preparation.

A Blank solution of 10% H_2O_2 was prepared similarly. After the stipulated time, the absorption of the resulting solution showed maxima of 281nm against reagent blank treated in the same way. The following procedure was repeated thrice. Three such determinations were made, the assay value was estimated, and concurrent values were recorded.

2.8.4. Sunlight degradation study.

2.8.4.1. Standard Etodolac solution.

10 mg Etodolac was transferred to a volumetric flask and dissolved in distilled water to achieve a 1mg/ml concentration. After 30 mins, an aliquot solution was diluted with distilled to get a final concentration of 100 mcg/ml. The solution was scanned in UV region, and maximum absorbance was recorded at 281nm.

2.8.4.2. Blank preparation.

A Blank preparation of Etodolac solution was prepared similarly. The procedure was repeated thrice. After the stipulated time, the absorption of the resulting solution showed maxima of 281 nm against the reagent blank treated in the same way. Three such determinations were made, and the assay value was estimated concurrently.

2.8.4.3. Sample preparation.

Etodolac tablets were powdered and dissolved in distilled water in a volumetric flask to achieve a 1mg/ml concentration. Then, after 30 mins of duration, 100 mcg/ml final concentration was established by diluting an aliquot solution with methanol. The solution was exposed to sunlight, and maximum absorbance was taken at 281nm by UV spectroscopy. The same procedure was applied for 48h and 72 hrs.

3. Results and Discussion

3.1. Drug identification.

FTIR spectral studies of Etodolac were performed under a wavenumber of 4000 cm^{-1} to 650 cm^{-1} to identify the drug, and the Etodolac confirmed the observed frequencies 3338.41 cm^{-1} (Hydrogen bonded alcohol and phenol), 1739.48 Cm $^{-}$1 (Aldehydes and Ketones), 1407.81cm $^{-1}$ (Nitro compounds), 1031.68 cm $^{-1}$ (Alcohol, Ethers) and 748.34 cm $^{-1}$ (Alkanes) and shown in Figure 1:

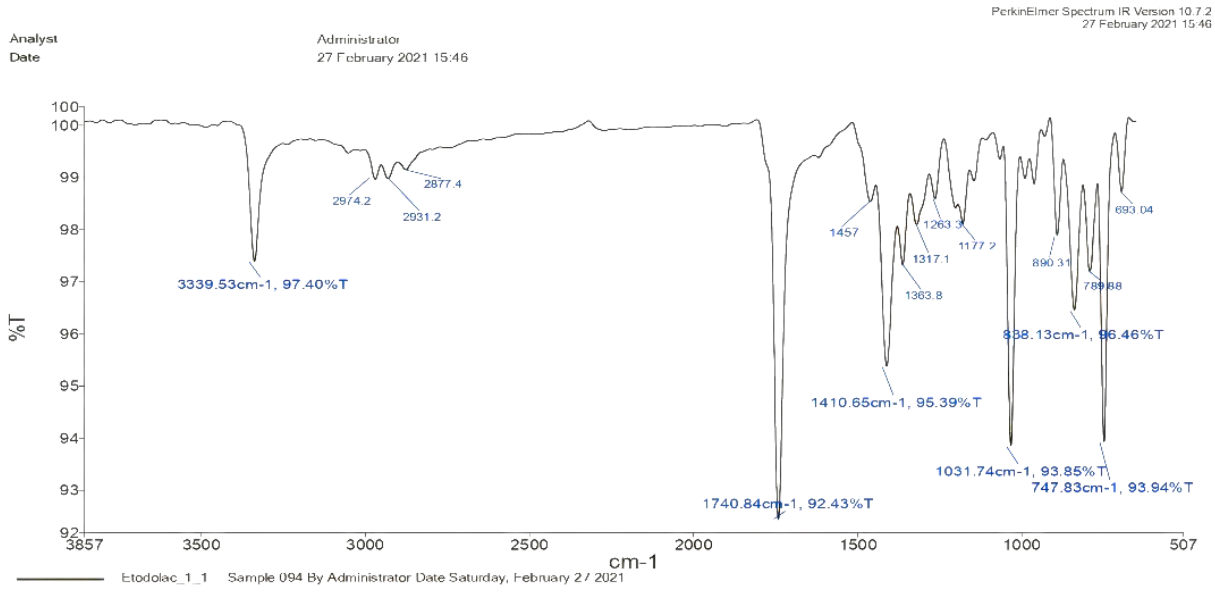

Figure 1. IR spectra of Etodolac.

3.2. Solubility studies of Etodolac.

In equilibrium solubility studies, a substantial enhancement in the solubility of Etodolac was observed in 4M sodium acetate hydrotropic solution compared to solubility in distilled water, as mentioned in Table 1 given below:

Table 1. Preliminary Solubility Studies of Bulk Etodolac.

Drug (mg)	Solvent system	Solubility (%w/v)	Temperature (^{0}C)	Solubility enhancement ratio
Etodolac	Distilled water	0.08%	25 ^{0} C	-
	4M sodium acetate	12.8%	25 ^{0} C	160.0

3.3. Etodolac bulk drug and tablet formulation estimation by Titrimetry.

All values of the mean percent drug estimated in bulk drug and commercial tablet formulation using 4M sodium acetate solution were close to 100 with lower values of standard deviation percent coefficient of variation and standard error, indicating the accuracy of the investigated method in Table 2 and Table 3.

Table 2. Etodolac bulk drug estimation with statistical evaluation (n=3).

Amount of bulk Drug taken (mg)	Method of analysis	% Drug estimated (Mean ± S.D.)	Standard error
100	IPM	97.176±0.870	0.6152
100	SAM	98.276±0.166	0.117

IPM = Indian Pharmacopoeia method, **SAM**= Sodium acetate method

Table 3. Etodolac marketed tablet formulation with statistical evaluation (n=3).

Amount of tablet formulation taken (mg)	Method of analysis	Label claim per tablet(mg)	% Drug estimated (Mean ± S.D.)	Standard Error
100	IPM	400	97.75±0.260	0.303
100	SAM	400	98.47±0.400	0.231

3.4. Preparation of calibration curve and linearity range.

Aliquots of 1-6 µg/ml concentration were prepared accordingly to observe the required drug absorbance at 281 nm. Based on the observed absorbances, a standard curve was plotted, and data is presented in Table 4, Figure 2. Linearity data are shown in Table 5.

Table 4. Represent the calibration data of Etodolac bulk drug.

S.no.	Concentration(µg/ml)	Absorbance (281nm)
1	1 µg/ml	0.19
2	2µg/ml	0.34
3	3 µg/ml	0.49
4	4 µg/ml	0.62
5	5 µg/ml	0.78
6	6 µg/ml	0.96

3.5. Analysis of tablet formulation.

Previously weighed equivalent 100 mg tablet powder was taken and dissolved into 20 ml of 4M sodium acetate solution followed by vigorous shaking and subsequent filtration through filter paper no. 4. The obtained drug filtrate was diluted appropriately with distilled water, and the analysis was carried out using a U.V. spectrophotometer at 281 nm against a reagent blank. The drug content of the tablet formulation was calculated, and data are shown in Table 6.

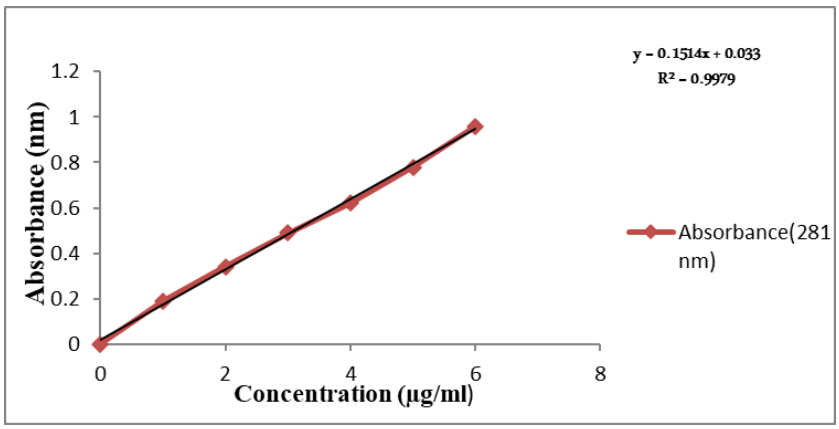

Figure 2. The calibration curve of Etodolac bulk drug.

Table 5. Linearity data of Etodolac.

S.No	Parameters	Etodolac
1	Working Λmax	281 nm
2	Linearity range	1-6µg/ml
3	Regression equation	Y= 0.1514x +0.033
4	Slope*	0.155
5	Intercept*	0.017
6	Correlation coefficient, r^{2*}	0.997
7	Intraday precision	1.119
8	Interday precision	1.120
9	LOD, µg/mL LOQ, µg/mL	0.7772 2.335

*Average of three determinations.

Table 6. Analysis of marketed tablets with statistical evaluation (n=3).

Amount of Etodolac in Tablet formulation	Label Claim (mg)	Percent recovery estimated (mean ± SD)	Standard* Error
100	400	97.92±1.1610	0.759
100	400	98.19±1.217	0.573

*Average of three determinations

3.6. UV method validation.

The developed method for estimating Etodolac was validated as per ICH guidelines.

3.6.1. Accuracy.

The proposed UV method was validated for accuracy parameters by assessing the recovery studies using different spiking concentrations, i.e., 15 and 20 mg of the standard drug to pre-estimated samples. The resulting solutions were then reanalyzed by the proposed methods. Drug content and percentage recovery were calculated and are shown in Table 7.

Table 7. Results of recovery studies of tablet formulations.

Amount of drug taken	Spiked amount of standard drug	Percent recovery* estimated (mean ± SD)	Standard Error
50	15 mg	61.92±1.1610	0.759
50	20 mg	72.19±1.217	0.573

***** Average of three determinations

3.6.2. Limit of detection (LOD) and limit of quantification (LOQ).

The value of LOD and LOQ for Etodolac was found to be 0.7772 µg/ml and 2.335 µg/ml, respectively, indicating the high sensitivity of the proposed UV method.

3.6.3. Precision.

The precision of the methods was studied on the same and different days at 281 nm wavelength, and data are shown in Table 8 and Table 9.

Table 8. Statistical analysis of intraday precision.

S.No	Concentration (µg/mL)	Average Absorbances			Average* % RSD
		Morning	Afternoon	Evening	
1.	1	0.185	0.186	0.186	
2.	3	0.187	0.188	0.187	1.119
3.	6	0.190	0.190	0.192	
%RSD		1.096	0.868	1.393	

Table 9. Statistical analysis of Interday assay precision

S.No	Concentration (µg/mL)	Average Absorbances			Average* % RSD
		Day 1	Day 2	Day 3	
1.	1	0.190	0.190	0.192	
2.	3	0.187	0.186	0.187	1.120
3.	6	0.185	0.188	0.186	
%RSD		1.098	0.868	1.393	

* Average of three determinations.

3.6.4. Robustness.

The robustness of UV method was evaluated at different instrumental parameters, i.e., changed wavelength in the range of ±2 of λ max, to confirm the closeness of agreement between the known and expected values. The drug sample solutions were examined at three different wavelengths in a UV-visible spectrophotometer, and the results are shown in Table 10.

Table 10. Robustness of UV method.

S.No	Concentration µg/mL	282 nm	283 nm	285 nm
1.	1	0.186	0.185	0.187
2.	3	0.187	0.184	0.190
3.	6	0.190	0.187	0.191
	Mean*	0.18766	0.18533	0.18933
	SSD*	0.0017	0.0012	0.0017
	%RSD	0.9056	0.672	0.8977

* Average of three determinations.

3.7. Stress degradation studies.

It was performed per ICH guidelines for establishing the stability conditions for Etodolac. Good recoveries were reported that indicated no effect of stress conditions on the stability of Etodolac, data shown in Table 11.

Table 11. Stress degradation study.

Applied Stress condition	Process time	Standard Assay values	Samples Estimated values	Degraded Percentage	Result
Hydrochloric acid (0.1N) acid hydrolysis	30	63.08%	54.10%	8.98%	Degradation Observed
	60	61.31%	52.05%	7.21%	
	90	58.46%	51.14%	7.32%	
Sodium hydroxide (0.1M) Alkali hydrolysis	30	76.12%	68.21%	7.91	Degradation Observed
	60	74.86%	63.10%	11.76	
	90	73.85%	60.08%	13.77	
Hydrogen peroxide 10%	30	64.86%	58.20%	6.66	Degradation Observed
	60	62.34%	56.01%	6.33	
	90	58.42%	52.74%	5.68	

Applied Stress condition	Process time	Standard Assay values	Samples Estimated values	Degraded Percentage	Result
oxidative hydrolysis					
Sunlight	24	65.26%	59.01%	6.25	Degradation Observed
	48	61.45%	54.67%	6.78	
	72	60.34%	52.23%	8.11	

4. Conclusions

It is concluded that the proposed methods using sodium acetate are unique, inexpensive, accurate, rapid, eco-friendly, sustainable, and green approaches. None of the analytical methods have involved any costlier, toxic organic solvents. Hence, no hazardous effects were reported during the experiments. Both of the methods have their precision and accuracy. Titrimetry methods have avoided using organic solvents, whereas spectrophotometric methods stand suitable for avoiding any critical experimental variables. Thus, both analytical approaches are suggested for routine analysis of other drugs.

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Conflicts of Interest

The authors declare no conflict of interest.

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