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SIMULTANEOUS ESTIMATION OF ETODOLAC AND THIOCOLCHICOSIDE IN BULK AND IN TABLET FORMULATION BY UV-SPECTROPHOTOMETRY

Abstract

Two simple, rapid and reproducible simultaneous equation and Q-analysis UV--spectrophotometric methods have been developed for simultaneous estimation of etodolac (ETO) and thiocolchicoside (THC) in combined tablet dosage form. The methods involved solving simultaneous equations and Q-value analysis based on measurement of absorbance at wavelengths, 223 (λmax of ETO), 259.4 (λmax of THC) and 236 nm (iso-absorptive point). Linearity was found in the concentration range of 1-6 µg/mL and 4–24 µg/mL for ETO and THC, respectively, with correlation coefficients 0.9998 and 0.9992. The amounts of drugs estimated by the proposed methods are in excellent agreement with the label claimed. Furthermore, the methods were applied for the determination of ETO and THC in spiked human urine. The degradation behavior of ETO and THC was investigated under acid hydrolysis, alkali hydrolysis, photo- and oxidative degradation. The subsequently generated samples were used for degradation studies using the developed method. THC was found to degrade extensively under alkali hydrolysis and unaffected by other stress conditions, while ETO was found to be stable in all stress conditions. The methods were validated according to ICH guidelines. The method, suitable for routine quality control, has been successfully applied to the determination of both drugs in commercial brands of tablets.

Keywords: etodolac, thiocolchicoside, simultaneous equation method, Q-absorbance ratio method, spiked human urine, sress degradation study.

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) and used as anti-inflammatory and analgesic. It is chemically 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole-1-acetic acid [1-2]. ETO inhibits cyclo-oxygenase enzyme and subsequently inhibits prostaglandin synthesis, and is hence used as an analgesic [3]. Thiocolchicoside is also an anti-inflammatory analgesic with muscle relaxant action [4], it is chemically *N*-[(7*S*)-3-(beta-D-glucopyranosyloxy)-1,2--dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetra-hydrobenzo[*a*]heptalen-7-yl] acetamide [1-2]. THC has selective affinity for GABA receptors and activate

GABA inhibitory pathway thereby acting as a potent muscle relaxant [5].

Etodolac is official in Indian Pharmacopoeia [2], United State Pharmacopoeia [6] and British Pharmacopeia [7]. Literature survey reveals one LC-MS [8] method was found for estimation of ETO in biological fluids. Few RP-HPLC [9-10], UV-spectrophotometric [11-14] and HPTLC [15] method have been reported for estimation of ETO in combination with other drugs in bulk and in pharmaceutical dosage forms. Thiocolchicoside is official in Indian Pharmacopoeia [2]. Several RP-HPLC [16-21], UV-spectrophotometric [22-24] and HPTLC [25-26] methods have been studied for determination of THC in bulk and in pharmaceutical formulations. Literature survey revealed simultaneous estimation of ETO and THC using UV spectrophotometric [27] and RP-HPLC [28] methods.

To the best of our knowledge, UV-spectrophotometric methods have not been yet reported for

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simultaneous estimation of ETO and THC in combined dosage form. In the present work, a successful endeavor has been made to estimate both these drugs simultaneously in tablet dosage form by two simple UV-spectrophotometric methods (simultaneous equation method and Q-absorbance ratio method) [29]. However, the reported methods have poor sensitivity and are applicable only for pharmaceuticals and not for biological fluids. The methods were successfully applied to the determination ETO and THC in spiked human urine. These methods were validated according to the ICH guidelines [30-32]. The chemical structures of both drugs are as shown in Figures 1 and 2.
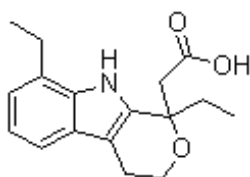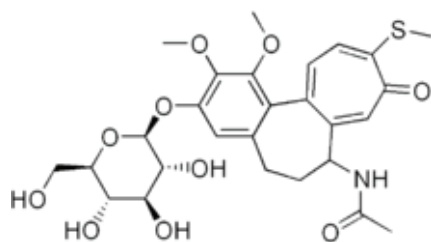

Figure 1. Chemical structure of etodolac.

Figure 2. Chemical structure of thiocolchicoside.

MATERIAL AND METHODS

Chemicals and Reagents

Thiocolchicoside and etodolac bulk drugs were obtained from Vital Lab. Pvt. ltd, Mumbai, and Inchem Lab. Pvt. Ltd, Hyderabad, India, respectively, as gift samples. Methanol (HPLC grade) was purchased from Merck (India) Ltd., Worli, and Mumbai, India. Tablet (proxym-MR) was purchased from Indian market, containing 200 mg of ETO and 4 mg of THC.

Drug free human urine was obtained from a healthy male aged about 24 years.

Instrumentation

A UV-visible spectrophotometer (Shimadzu-1700, UV Probe 2.21 software) with spectral bandwidth 1 nm was employed for all spectroscopic measurements, using a pair of 1.0 cm matched quartz cells.

Selection of common solvent

Methanol was selected as common solvent for studying spectral characteristics of drugs.

Preparation of stock standard solutions

Stock standard solutions of ETO and THC were separately prepared by dissolving 10 mg in 100 ml volumetric flask containing 50 mL methanol and the volume was made up to the mark with water to obtain final concentrations of 100 µg/mL for each sample.

Simultaneous equation method (Method-I)

From the stock solution of 100 µg/mL, working standard solutions of drugs were prepared by appropriate dilution and scanned in the UV-region, *i.e.*, 400–200 nm. Linearity was found in the concentration range of 1-6 µg/mL and 4–24 µg/mL for ETO and THC, respectively (Table 1). From the overlaid spectra (Figures 3 and 4) two wavelengths, 223 (λmax of ETO) and 259.4 nm (λmax of THC) were selected for the construction of simultaneous equation. Standard solutions were prepared at concentrations 1-6 µg/mL for ETO and 4-24 µg/mL for THC. The absorbances of these standard solutions were measured at 223 and 259.4 nm and calibration curves were plotted. Two simultaneous equations (in two variables C_1 and C_2) were formed using E(1%, 1 cm) values (Table 2).

$$A_1 = 1383.17 C_{ETO} + 509.67 C_{THC} \tag{1}$$

$$A_2 = 262.66 C_{ETO} + 433.16 C_{THC} \tag{2}$$

where C_{ETO} and C_{THC} are the concentrations in g/100 mL in sample solution; A_1 and A_2 are absorbance of

Table 1. Linearity studies; SEE - standard error of estimate; SD - standard deviation

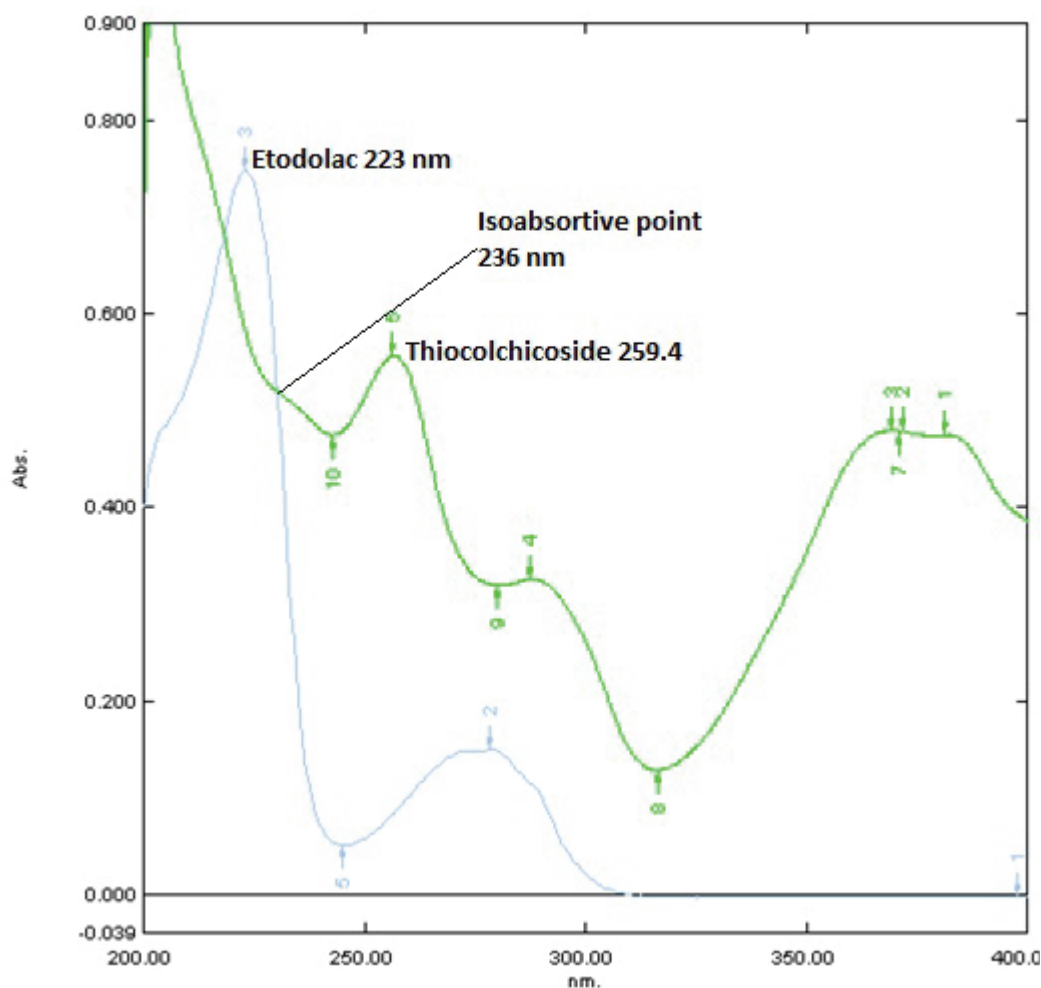| Parameter	THC	ETO
Linearity, µg mL^{-1}	4-24	1-6
Linearity equation	$Y = 0.0335X + 0.0342$	$Y = 0.1276X + 0.0393$
Slope ± SD	0.0335±0.0001	0.1276±0.0003
Intercept ± SD	0.0342±0.0005	0.0393±0.0008
Correlation Coefficient ± SD	0.9992±0.0001	0.9998±0.0003
SEE	0.00790	0.00343
Chi-square	0.00069	0.0001
Residual *SD*	0.0037	0.00307

Figure 3. Overlain spectra of ETO and THC.

mixture at selected wavelength 223 and 259.4 nm, respectively.

By applying Cramer's rule [26] to Eqs. (1) and (2), the concentrations C_{ETO} and C_{THC} can be obtained as follows:

$$C_{ETO} = (A_2 \times 433.16) - (A_1 \times 509.67) / -591451 \qquad (3)$$

$$C_{THC} = (A_1 \times 262.66) - (A_2 \times 1383.17) / -591451 \qquad (4)$$

Q-Absorbance ratio method (Method-II)

From the overlain spectrum of ETO and THC, two wavelengths were selected one at 259.4 nm, λmax of THC and other at 236 nm, which was the isoabsorptive point for both drugs. The E (1%, 1 cm) values for both the drugs at selected wavelengths are shown in Table 2.

The method employed *Q*-values, and the concentrations of drugs in sample solutions were determined using the following equations:

$$C_{THC} = \frac{Q_m - Q_y}{Q_x - Q_y} \times \frac{A_1}{ax_1} \qquad (5)$$

$$C_{ETO} = \frac{Q_m - Q_x}{Q_y - Q_x} \times \frac{A_2}{ay_1} \qquad (6)$$

where A_1 and A_2 are the absorbances of mixture at 236 and 259.4 nm, $Q_m = A_2/A_1$, $Q_y = ay_2/ay_1$ and $Q_x = ax_2/ax_1$, ax_1 (397.66), ax_2 (262.66), ay_1 (397.83) and ay_2 (433.16) are absorptivities (1%, 1 cm) of ETO and THC at 236 and 259.4 nm.

Assay of tablet formulation by Method-I and Method-II

Twenty tablets containing ETO and THC were weighed and the mean weight was calculated. These tablets were crushed and accurately weighed tablet powder equivalent to 10 mg of ETO that contains 0.2 mg THC was transferred into a 100 mL volumetric flask containing 50 mL of methanol, then 9.8 mg of THC working standard was added and the volume was made up to the mark with water, filtered through 0.45 µm Whatmann filter paper. An appropriate
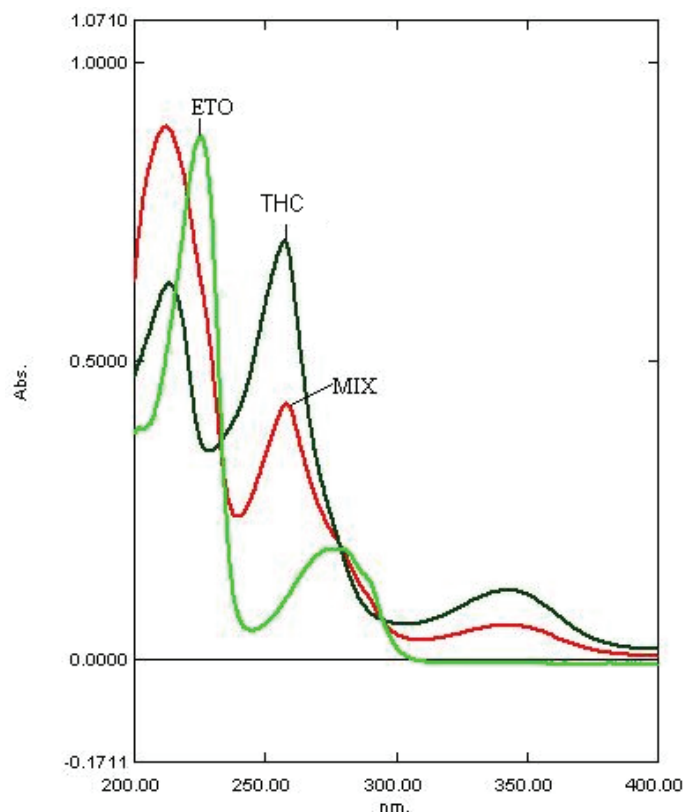
Figure 4. Overlain spectra of ETO and THC and their mixture.

volume of solution was further diluted with water to obtain concentrations 4 µg/mL of ETO and 4 µg/mL of THC. Absorbance of sample solution was recorded at 223, 236 and 259.6 nm and the concentrations of two drugs in the sample were determined using Eqs. (3) and (4) (Method-I) and (5) and (6) (Method-II). The analysis procedure was repeated for six times with tablet formulation. The results of analysis are mentioned in Table 3.

Percentage recovery studies

The accuracy of the proposed analytical method was determined by recovery experiments. The recovery studies were carried out at three different concentration levels. A known amount of drug was added to pre-analysed tablet formulation at 80, 100 and 120%, and percentage recoveries were calculated. The results of recovery studies were satisfactory and are presented in Table 4.

Table 2. E (1%, 1 cm) value of ETO and THC at 223, 259.4 and 236 nm

Parameter	(E 1%, 1cm) at 223 nm		(E 1%, 1cm) at 259.4 nm		(E 1%, 1cm) at 236 nm	
	ETO	THC	ETO	THC	ETO	THC
Mean	1383.17	509.67	262.67	433.16	397.66	397.83
SD	1.83	1.51	1.84	1.94	1.58	1.60
RSD / %	0.13	0.29	0.69	0.44	0.39	0.40

Table 3. Results of analysis of tablets by the proposed methods and statistical comparison of the results with the reference method

Method	Tablet content	Label claim, mg	Found, label claim±*SD*, % (*n* = 6)	
			Reference method [33]	Proposed method
I	ETO	200	99.60±0.0032	99.25±0.29, *F* Test: 0.0011, *t* Test: 0.179
	THC	4	104.50±0.0018	98.45±0.55, *F* Test: 1.542, *t* Test: 0.002
II	ETO	200	99.10±0.0021	101.71±0.92, *F* Test: 1.496, *t* Test: 0.038
	THC	4	103.25±0.0031	99.00±0.56, *F* Test: 4.865, *t* Test: 0.0056

Table 4. Results of recovery studies

Level of recovery, %	Amount of drug added, µg/mL	Drug	Recovery, %	
			Method-I	Method-II
80	3.2	ETO	100.55	100.42
	3.2	THC	99.86	99.72
100	4	ETO	99.87	101.12
	4	THC	99.75	99.87
120	4.8	ETO	99.77	100.68
	4.8	THC	99.54	100.34

Precision

Precision of an analytical procedure expresses the closeness of agreement between a series of measurements obtained from multiple samplings of the same homogenous samples under the prescribed conditions. The precision of the method was verified by intra-day, inter-day and repeatability studies. Intra-day precision was determined by analyzing three different concentrations (4, 5 and 6 µg mL^{-1}) of ETO and THC, for three times in the same day. Day-to-day variability was evaluated using the three concentrations listed above and analyzed on three different days. Repeatability of the sample solution was measured by taking absorbances of a homogenous sample of 4 µg mL^{-1} of ETO and 4 µg mL^{-1} of THC six times.

Sensitivity

Sensitivity of the methods for drugs was individually determined by calculating the LOD, LOQ and Sandell's sensitivity (µg/cm^2), which can be defined as the smallest weight of substance that can be detected in the column of solution of unit cross section.

Analysis of ETO and TCH in human urine

From stock solutions of ETO and THC, 0.4 mL of sample was spiked in 5 ml of human urine and centrifuged at 3000 rpm, 4 °C for 10 min, then the supernatant was collected and the volume was made up with methanol to 10 ml, followed by sonication for 5 minutes to obtain concentrations of 4 µg/mL of ETO and 4 µg/mL of THC. The absorbance was measured directly at 223, 236 and 259.6 nm and the concentrations of two drugs in the spiked urine sample [33-35] were determined using Eqs. (3) and (4) (Method-I) and (5) and (6) (Method-II).

Stress degradation studies

The ICH guidelines require stability testing of new drug substances and products that to reveal the inherent stability characteristics of the active substance. The aim of the present study was to perform the stress degradation studies on ETO and THC using the developed method.

Conduct of stress studies

Acid and base-induced degradation was attempted by adding 10 mg of ETO and THC in 10 mL each of 0.1 M HCl and 0.1 M NaOH solutions. The solutions were kept for 8 h at room temperature in the dark in order to exclude the possible degradative effect of light. The solutions were neutralized and diluted with methanol. The absorbances were measured directly at 223, 236 and 259.6 nm. For oxidative degradation, 10 mg of ETO and THC was added to 10 mL of 10% (v/v) hydrogen peroxide solution. The mixtures were kept for 8 h. The solutions were diluted with methanol and treated as described for acid and base-induced degradation. Photodegradation was studied by exposing 1 mg/mL solution in methanol to sunlight for 72 h. The resulting solutions were diluted with methanol and analyzed using the methods described above.

RESULTS AND DISCUSSION

Etodolac and thiocolchicoside followed linearity in the concentration ranges of 1-6 µg/mL and 4-24 µg/mL, respectively, and results are shown in Table 1 and Figures 5 and 6. The marketed brand of tablet was analyzed and recovery for ETO and THC determined by proposed methods I and II was found to be 99.25 and 101.71% for ETO and 98.45 and 99.00% for THC, respectively. The recoveries range from 99.54 to 101.12% for ETO and THC in Method-I and -II, respectively. The results of the proposed method were statistically compared with those obtained by the reference method [27]. Statistical analysis of the results, using Student's *t*-test and *F*-test revealed no significant difference between the performance of the proposed and reference method at 95% confidence level (Table 3). The advantage of the present method over the reference method [27] is that the author had used 0.1 M NaOH which may be responsible for the
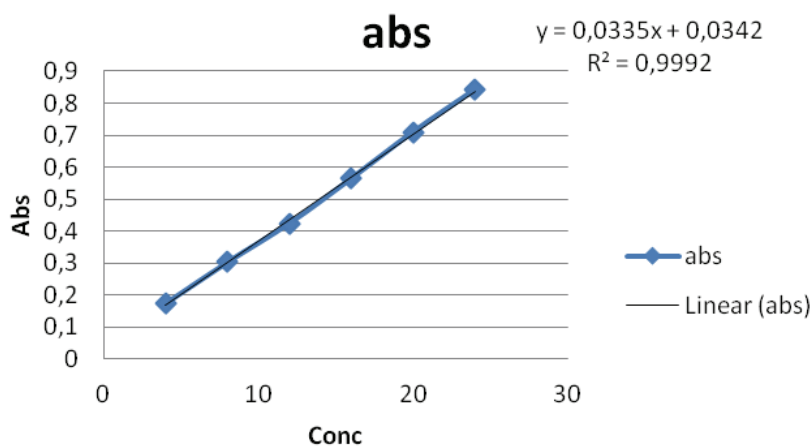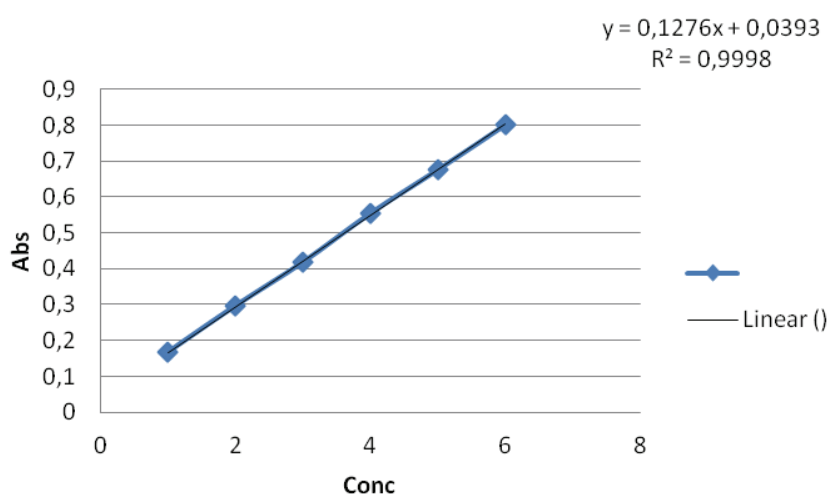
Figure 5. Calibration curve of THC.

Figure 6. Calibration curve of ETO.

degradation of thiocolchicoside. Linearity study was carried out with good precise range in accordance with the dose ration of both drugs in used formulation, which were not reported in the reference method. The proposed methods are more sensitive because of low values of LOD and LOQ and additionally Sandell's sensitivity, as compared to the reference method. Percentage label claim of both drugs by the proposed methods were found to be equivalent and more precise over previously published spectrophotometric methods. The proposed methods can be applied to the determination of ETO and THC in spiked human urine. Precision was calculated as inter and intraday variations (*RSD* is less than 2%) for both drugs and as repeatability (*RSD* is less than 2%) and are presented in Tables 5 and 6. LOD, LOQ and Sandell's Sensitivity of ETO and TCH were found to be sufficiently low (Table 7), showing that much lower amounts of both drugs can be effectively detected by these methods. Ruggedness for these drugs was carried out using two different laboratories and different analysts; no significant difference was obtained between the results in the present study. The specificity and selectivity of the method was investigated by observing any interference encountered from the common tablet excipients such as talc, lactose, starch and magnesium stearate. These excipients did not interfere with the proposed method.

Additionally, the developed methods were applied to determine ETO and THC in spiked urine sample. The recoveries of ETO and THC from spiked human urine sample were found to be satisfactory. As shown in Table 8, the percentage recovery values in the range 90.26 to 94.72 for Method-I as well as Method-II with relative standard deviation values of less than 2 proved that the accuracy and reproducibility of the proposed method for the determination of both the drugs simultaneously in spiked human urine. The UV spectrum obtained from action of acid, alkali, hydrogen peroxide, and light showed that THC was

Table 5. Results of precision studies

Precision (*RSD* / %)	Method-I		Method-II	
	ETO	THC	ETO	THC
Intra-day (*n* = 3)	0.14	0.15	0.37	0.25
Inter-day (*n* = 3)	0.25	0.14	0.14	0.29

Table 6. Results of repeatability study

Method	Drug (4 µg/mL)	Amount found in µg/mL (*n* = 6)	*RSD* / %
I	ETO	3.98	0.25
	THC	3.96	0.15
II	ETO	3.99	0.14
	THC	3.97	0.21

Table 7. Sensitivity

Parameter	ETO	TCH
LOD / µg mL^{-1}	0.088	0.129
LOQ / µg mL^{-1}	0.291	0.949
Sandell's sensitivity, µg/cm^2	0.00723	0.0230

Table 8. Analysis in human urine; amount spiked in urine: 4 µg/mL

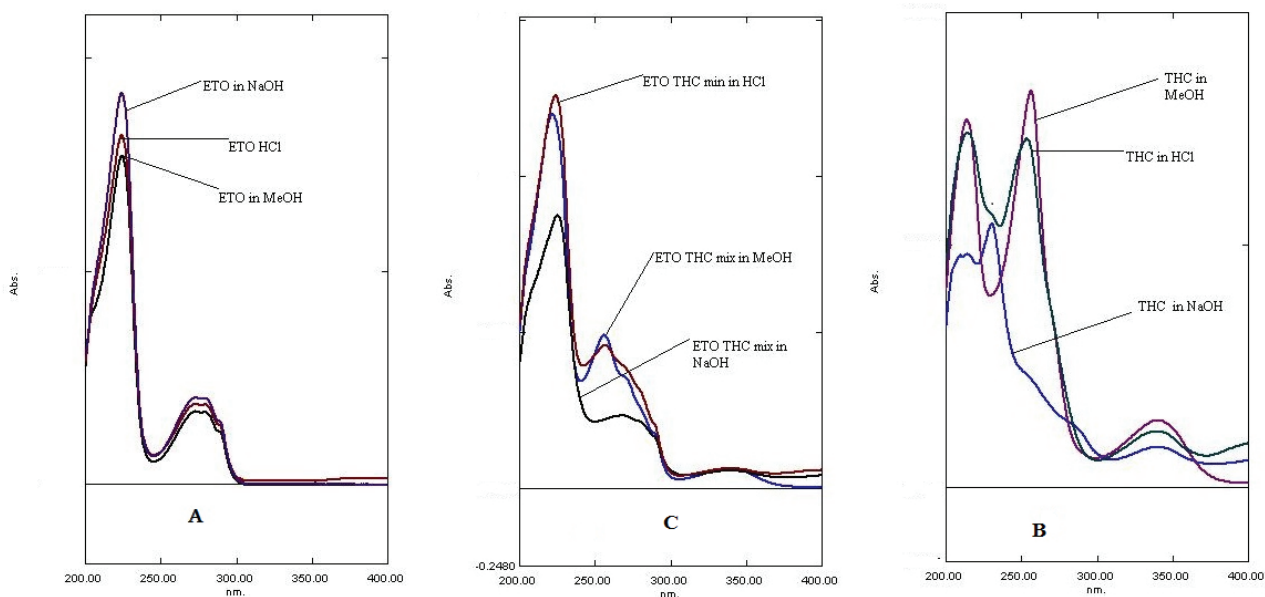| Method	Drug	Amount found, % (*n* = 5)	*RSD* / %
I	ETO	92.88	2.86
	THC	94.72	1.98
II	ETO	90.26	2.04
	THC	93.24	2.42

Figure 7. A) ETO in methanol, 0.1 M HCl and 0.1 M NaOH; B) THC in methanol, 0.1 M HCl and 0.1 M NaOH; C) ETO and THC mix in methanol, 0.1 M HCl and 0.1 M NaOH.

Table 9. Stress degradation studies of ETO and THC

Sample-exposure condition	λmax / nm		Recovery, %	
	ETO	THC	ETO	THC
0.1 M HCl, 8 h	223	259.6	98.52	99.08
0.1 M NaOH, 8 h	223	241.2[a]	98.69	42.84
10% H_2O_2, 8 h	223	259.6	100.21	99.58
Sunlight, 8 h	223	259.6	100.54	100.20

[a]Change in λmax of THC indicates that THC is susceptible to alkali condition and it does some transformation in THC structure

degraded only by alkali hydrolysis (Figure 7) because of change in λmax of THC and there was no effect of other stress conditions on THC as well as ETO. The amount remaining (%) and recovery (%) were calculated for ETO and THC in stability samples by using Eqs. (3) and (4) (Method-I) and (5) and (6) (Method-II), Table 9.

CONCLUSION

The developed methods were found to be simple, accurate and rapid for the routine estimation of ETO and THC in tablet formulation as well as in human urine. Degradation products resulting from stress studies did not interfere with the simultaneous estimation of ETO and THC except alkali conditions. The methods were validated according to ICH guidelines. The method, suitable for routine quality control, has been successfully applied to the determination of both drugs in commercial brands of tablets.

Acknowledgements

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NAUČNI RAD

SIMULTANO ODREĐIVANJE ETODOLAKA I TIOKOLČIKOZIDA U FARMACEUTSKOJ SUPSTANCI I TABLETAMA

*U radu su razvijene dve jednostavne, brze i reproduktivne spektrofotometrijske metode za simultano određivanje etodolaka (ETO) i tiokolčikozida (THC) u tabletama koje sadrže obe aktivne supstance. Metode uključuju rešavanje sistema jednačina uz korišćenje rezultata merenja apsorbanci na 223 nm (λ*max* za ETO), 259,4 (λ*max* za THC) i 236 nm (izo-apsorptivna tačka). Nađeno je da pod optimalnim uslovima za reakcije važi Berov zakon u opsegu koncentracija 1-6 μg/mL, odnosno 4-24 μg/mL za THC, odnosno ETO, a odgovarajući koeficijenti korelacije su 0,9998 i 0,9992. Količine određenih aktivnih supstanci su u odličnom slaganju sa količinama koje su označene na etiketi leka. Takođe, metode su uspešno primenjene za određivanje ETO i THC u ljudskom urinu. Ispitana je degradacija ETO i THC u uslovima kisele i bazne hidrolize i foto i oksidacione degradacije. Nastali degrdacioni produkti su analizirani razvijenom metodom. Nađeno je da se tiokolčikozid intenzivno razgrađuje u uslovima bazne hidrolize, a da je otporan na druge ispitivane uslove, dok je etodolak stabilan na sve ispitivane uslove. Metode su validirane u skladu sa ICH smernicama. Metoda je uspešno primenjena za određivanje obe aktivne supstance u tabletama i pogodna je za rutinsku kontrolu.*

Ključne reči: etodolak, tiokolčikozid, simultana metoda, Q-apsorpciona metoda, ljudski urin, forsirane degradacije leka.

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