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A Sensitive Kinetic Spectrophotometric Determination of Cefprozil and Dropropizine in Bulk and in Dosage Forms

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A SIMPLE, accurate and sensitive kinetic spectrophotometric method is described for analysis of cefprozil and dropropizine. The method is based on kinetic investigations of the oxidation reaction of the drugs with alkaline potassium permanganate ($KMnO_4$) at room temperature. The reaction is monitored spectrophotometrically by measuring the rate of change of absorbance of the resulting manganate species at 610 or 608 nm for cefprozil or dropropizine, respectively, with time. The two calibration curves at fixed-time method for the two drugs are utilized for the assay of drugs in the concentration ranges of 1.0-8.0 and 0.2-2.0 μg ml^{-1} for cefprozil and dropropizine, respectively. The results are optimized and validated statistically and through recovery studies. The method has been successfully applied to the determination of cefprozil and dropropizine in pharmaceutical preparations. The results obtained are compared statistically with those given by the reference method. A proposal of the oxidation reaction pathway is postulated.

Keywords: Cefprozil, Dropropizine, Potassium permanganate, Kinetic spectrophotometry and Pharmaceutical analysis.

Cefprozil (Scheme 1), (6R, 7R)-7-[(R)-2-amino-2-(p-hydroxyphenyl) acetamido]-8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, is a semisynthetic oral second generation cephalosporin consists of 90:10 Z/E isomeric mixture with a wide antibacterial spectrum of activity[1,2]. The drug is the subject of a monograph in the United States Pharmacopoeia, USP 27[3]. Few methods have been reported for determination of cefprozil in pure form and in pharmaceutical preparations or in biological fluids. Chromatographic[4,5], flow-injection chemiluminescent[6] and spectrophotometric[7-10] methods have been reported. Saleh *et al*. [9] described a spectrophotometric method for determination of cefprozil. This method is based on the reaction of the drug as n-donor with chloranilic acid as a π-acceptor and the colored radical anion was measured at 520 nm. This method is used as a reference method for validation of the proposed method.

Dropropizine (Scheme 1), 3-(4-phenyl-1-piperazinyl)-1,2-propanediol, is a cough suppressant reported to have a peripheral action in non-productive cough[11]. The drug is listed in Clark's, Analysis of Drugs and Poisons[12]. Studies on the human metabolism and the toxicological detection of the cough suppressant dropropizine in urine[13,14] and plasma[15] using gas chromatographic-mass spectrometric methods are described.

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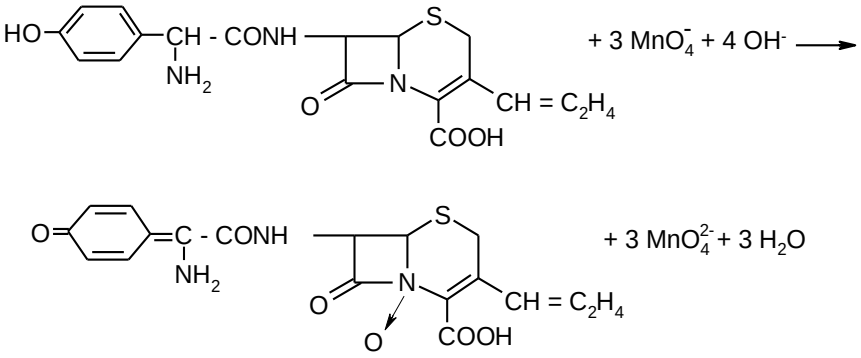
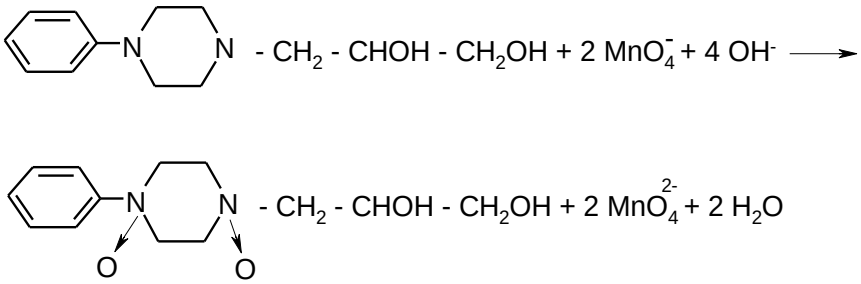
Cefprozil;



Dropropizine;



Scheme 1

Kinetic methods are becoming of great interest in chemical analysis. Various kinetic methods have been applied to the determination of many inorganic and organic species[16]. Some kinetic spectrophotometric methods have been used for the determination of some drugs in pharmaceutical compounds through the reaction of these drugs with alkaline potassium permanganate whereby a green color peaking at 610-612 nm is produced[17-22].

No attempts have yet been made to determine cefprozil or dropropizine by any kinetic spectrophotometric method. This work represents the first attempt at assaying cefprozil and dropropizine in pharmaceutical preparations by use of kinetic method. The method is based on oxidizing the drugs with alkaline potassium permanganate. The reaction is followed up spectrophotometrically and the rate of change of absorbance at 610 and 608 nm for cefprozil and dropropizine, respectively, is measured. The fixed-time method is adopted after full investigation and understanding of the kinetics of the reaction. The proposed method is simple, accurate and sensitive. The mechanism of oxidation of drugs with alkaline $KMnO_4$ is suggested in order to throw more light on the nature of the oxidation product formed.

Experimental

Apparatus

All spectral and absorbance measurements were made on a Shimadzu UV-visible 1601 spectrophotometer (Japan) with matched quartz cells of 1-cm optical path length.

Reagents and materials

All chemicals were of analytical grade and all of the solutions were prepared with double distilled water. Freshly prepared solutions were always used. Aqueous solutions of 1.5 x 10^{-2}M potassium permanganate (Merck, Germany) and 0.5 M sodium hydroxide (BDH, UK) were prepared.

Cefprozil anhydrous (Bristol-Myers Squibb, Co., USA) and dropropizine (Eva Pharma, Egypt) were of pharmaceutical grade. Pharmaceutical preparations of these compounds were obtained from commercial sources. Cefzil tablets and powder for oral suspension (Bristol-Myers Squibb Co., Egypt) labeled to contain 250 mg of cefprozil anhydrous per tablet and 125 mg of cefprozil anhydrous per 5 ml of powder for oral suspension. Tussipine lozenges (Eva Pharma, Egypt) labeled to contain 20 mg dropropizine per lozenge.

Preparation of standard solutions

Stock solutions (100 μg ml^{-1}) of cefprozil and dropropizine were prepared by dissolving 10 mg of drug in 100 ml distilled water in 100 ml calibrated flasks. These solutions are stable for 7 days if were kept in the refrigerator. More dilute solutions, whenever required were obtained by appropriate dilution with water.

General procedure

Procedure for the determination of cefprozil and dropropizine

Aliquots of 1.0 ml $KMnO_4$ (1.5 x 10^{-2}M) and 1.0 ml of 0.5 M NaOH solutions were placed in 10-ml calibrated flasks. Accurate volumes of working standard solution of cefprozil (0.2-1.6 ml of 50 μg ml^{-1}) or dropropizine (0.2-2.0 ml of 10 μg ml^{-1}) were added, and the solutions were mixed well and diluted to volume with water. At a fixed time of 40 min, the absorbance was measured directly at 610 or 608 nm for cefprozil or dropropizine, respectively, against a reagent blank. The calibration graph was constructed by plotting the final concentration of the drug against the absorbance values, measured at a fixed time of 40 min. Alternatively, the corresponding regression equation was derived.

Procedure for tablets or lozenges

Ten tablets or lozenges were weighed and finely grounded. A weighed amount of the fine powder equivalent to 10 mg of cefprozil anhydrous or dropropizine was dissolved in 20 ml of methanol or dichloromethane, respectively, stirred for 10 min and filtered through a Whatman No. 42 filter paper. The residue was washed well with methanol or dichloromethane for cefprozil or dropropizine, respectively. The filtrate and washings were evaporated to dryness and the left drugs were dissolved in distilled water and diluted to 100 ml with distilled water in 100-ml calibrated flasks. These solutions labeled to contain 100 μg ml^{-1} of drug. More dilute solutions equivalent to 50 μg ml^{-1} of cefprozil anhydrous and 10 μg ml^{-1} of dropropizine were obtained by appropriate dilution with distilled water. These solutions were analyzed by the above procedure. Nominal content of Cefzil tablets or Tussipine lozenges was calculated either from previously plotted calibration graph or by using the regression equation.

Procedure for oral suspension

In a 100 ml conical flask, place a quantity of oral suspension powder equivalent to 10 mg of cefprozil anhydrous and dissolve in 20 ml of methanol. Complete the procedure as described under procedure for tablets and lozenges. Then the nominal content of Cefzil powder for oral suspension was calculated from the regression equation.

Results and Discussion

Kinetics and optimization of the reaction conditions by using $KMnO_4$

The reaction between cefprozil or dropropizine and $KMnO_4$ in alkaline medium yields a green color due to the production of manganate ion (MnO_4^{2-}), which absorbs at 610 or 608 nm for cefprozil or dropropizine, respectively. The intensity of the color produced increases gradually reaching its maximum after 40 min for two drugs, when it remains stable for at least one hour for cefprozil and 40 min for dropropizine. As the intensity of the color increases with time, it was deemed useful to elaborate a kinetically based method for the determination of cefprozil or dropropizine.

At room temperature, the reaction increased substantially with time, as revealed by the intensification of the developed color and subsequence increases in the slope of the calibration graph (Table 1), indicating higher analytical sensitivity. Heating the solution was found to increase the rate of the reaction but MnO_2 was precipitated, therefore room temperature was selected as the optimum temperature.

TABLE 1. Calibration equations at different fixed times for cefprozil and dropropizine over the ranges $0.25 \times 10^{-5} - 1.75 \times 10^{-5}$ M and $1 \times 10^{-6} - 8 \times 10^{-6}$M, respectively, at constant concentration of NaOH (0.05 M) and $KMnO_4$ (1.5×10^{-3} M) at room temperature (25 ± 1°C).

Time, min	Regression equation	Correlation coefficient (r)
Cefprozil, λ = 610 nm		
10	$A = 0.002 + 3.52 \times 10^4 C$	0.9953
20	$A = 0.000 + 3.96 \times 10^4 C$	0.9994
30	$A = 0.002 + 4.80 \times 10^4 C$	0.9997
40	$A = 0.003 + 5.00 \times 10^4 C$	0.9999
50	$A = - 0.004 + 5.00 \times 10^4 C$	0.9998
Dropropizine, λ = 608 nm		
10	$A = - 0.020 + 7.00 \times 10^4 C$	1.0000
20	$A = - 0.006 + 8.30 \times 10^4 C$	0.9999
30	$A = - 0.008 + 9.60 \times 10^4 C$	0.9999
40	$A = 0.009 + 10.27 \times 10^4 C$	0.9999
50	$A = - 0.005 + 9.93 \times 10^4 C$	0.9998

The reaction rate and maximum absorbance increased with increasing $KMnO_4$ concentration. It was found that 1.0 ± 0.1 ml of 1.5 x 10^{-2} M $KMnO_4$ in the total volume of 10 ml was adequate for the maximum absorbance (using 8 μg ml^{-1} for cefprozil and 2 μg ml^{-1} for dropropizine in the total reaction mixture).

The influence of NaOH concentration on the reaction rate was also studied using 0.1-2.0 ml of 0.5 M NaOH. It was found that increasing the volume of 0.5 M NaOH would increase the absorbance of the reaction product up to 1.0 ml, after which further increase in the volume of 0.5 M NaOH resulted in no change in the absorbance of the reaction product, thus 1.0 ml of 0.5 M NaOH was found to be the most suitable concentration for maximum absorbance. Trials were made to determine cefprozil or dropropizine through oxidation with $KMnO_4$ in neutral and acidic media, but no oxidation of drug was observed.

The rate of reaction was also found to be concentration-dependent. The rate of reaction was followed at room temperature (25 ± 1°C) with various concentrations of the drug in the range 0.25 x 10^{-5} – 1.75 x 10^{-5} M for cefprozil and 1.0 x 10^{-6} – 8.0 x 10^{-6} M for dropropizine, keeping $KMnO_4$ and NaOH concentrations constant (Fig.1& 2). The reaction rate was found to obey the following equation:

$$\text{Rate} = K^{-}[\text{drug}]^{n} \quad (1)$$

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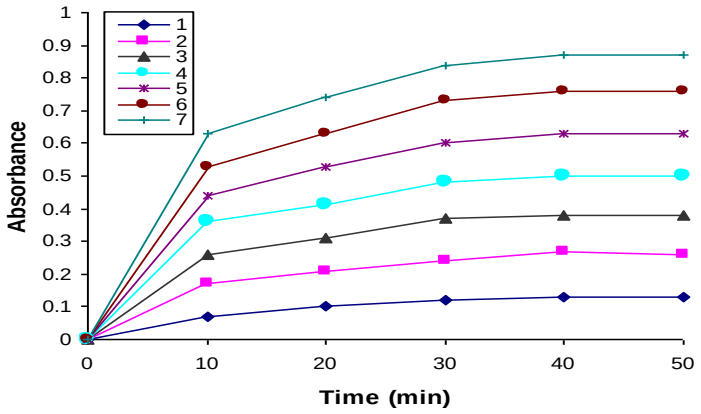

Fig. 1. Absorbance versus time graphs for the reaction of cefprozil and alkaline $KMnO_4$ at 25°C. Cefprozil concentration: 0.25 x 10^{-5} (1), 0.50 x 10^{-5} (2), 0.75 x 10^{-5} (3), 1.00 x 10^{-5} (4), 1.25 x 10^{-5} (5), 1.50 x 10^{-5} (6) and 1.75 x 10^{-5} M (7), λ = 610 nm.

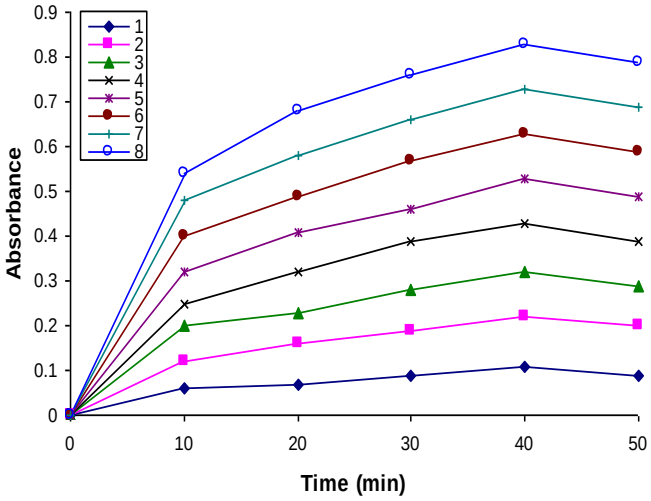

Fig. 2. Absorbance versus time graphs for the reaction of dropropizine and alkaline $KMnO_4$ at 25 ºC. Dropropizine concentration: 1 x 10^{-6} (1), 2 x 10^{-6} (2), 3 x 10^{-6} (3), 4 x 10^{-6} (4), 5 x 10^{-6} (5), 6 x 10^{-6} (6), 7 x 10^{-6} (7), 8 x 10^{-6} M (8), λ = 608 nm.

The rate of the reaction may be estimated by the variable-time method measurement[23], as ΔA/ Δt, where A is the absorbance and t is the time in seconds. Taking logarithms of rates and concentrations of drug, Equation (1) is transformed into:

$$\log (\text{rate}) = \log \frac{\Delta A}{\Delta t} = \log K^{-} + n \log [\text{ drug}] \quad (2)$$

Regression of log (rate) versus log [cefprozil] or log [dropropizine] by the least squares method gave the regression equation:

$$\log \frac{\Delta A}{\Delta t} = 1.04 + 0.96 \log [\text{cefprozil}] \qquad (r = 0.9996).$$

$$\log \frac{\Delta A}{\Delta t} = 1.525 + 0.98 \log [\text{dropropizine}] \quad (r = 1.0001).$$

Hence K^{-} = 10.96 and 33.5 sec^{-1} and the reaction is first order (n = 0.96 and 0.98 ≃ 1.0) for cefprozil and dropropizine, respectively.

Evaluation of the kinetic methods

The quantitation of cefprozil and dropropizine under the optimized experimental conditions outlined above, would result in a pseudo-first order with respect to their concentrations keeping $KMnO_4$ and NaOH constant at high concentration. However, the rate of reaction will be directly proportional to cefprozil or dropropizine concentration in a pseudo-first order rate equation as follows:

$$\text{Rate} = K^{-}[\text{drug}] \quad (3)$$

where K^{-} is the pseudo-first order rate constant. Equation (3) was the basis for several experiments, which were carried out to obtain cefprozil or dropropizine concentration. Initial-rate, rate-constant, fixed-absorbance and fixed-time methods[24,25], were tried and the most suitable analytical method was selected taking into account the applicability, the sensitivity (*i.e*., the slope of the calibration graph), the intercept and the correlation coefficient (r).

Rate-constant method

Values of log absorbance versus time for drug concentration in the range 0.25×10^{-5}– 1.75×10^{-5} M for cefprozil and 1×10^{-6} – 8×10^{-6} M for dropropizine were plotted and all appeared to be rectilinear.

Pseudo-first order rate constants (K^{-}) corresponding to different drug concentrations (C) were calculated from the slopes (log A vs.t) multiplied by -2.303. The regression of K^{-} versus C gave the equation:

$$K^{-} = 0.0004 + 10.24\ C \quad (r = 0.9690) \text{ for cefprozil}$$
$$K^{-} = -\ 0.0001 + 22.00\ C \quad (r = 0.9579) \text{ for dropropizine}$$

The values of r are indicated of poor linearity probably because of inconsistency of K.

Fixed-absorbance method

A preselected value of the absorbance (0.5 for cefprozil and 0.4 for dropropizine) was fixed and the time was measured in seconds. The reciprocal of time (1/t) versus initial concentration of drug (C) was plotted and the following equation of the calibration graph was obtained:

$$1/t = 0.0011 + 3.78 \times 10^{2}\ C \quad (r = 0.9907) \text{ for cefprozil}$$
$$1/t = -\ 0.0051 + 1.168 \times 10^{3}\ C \quad (r = 0.9903) \text{ for dropropizin}$$

The ranges of drug concentration giving the most acceptable calibration graph with the above equations were limited (4.07-7.12 μg ml^{-1} of cefprozil and 1.2 – 1.9 μg ml^{-1} of dropropizine), which could be adisadvantage.

Fixed-time method

Reaction rates were determined for different concentrations of cefprozil and dropropizine. At a preselected fixed time, which was accurately determined, the absorbance was measured. Calibration graphs of absorbance versus initial concentration of drug were obtained at fixed times of 10, 20, 30, 40 and 50 min with the calibration equations shown in Table 1.

It is clear that the slope of the calibration graph increases with time. The most suitable values of the correlation coefficient (r) and the intercepts were obtained for a fixed time of 40 min for both drugs, which was therefore chosen as the most suitable time interval for measurement.

Reaction mechanism

The stoichiometry of the reaction was studied adopting by continuous variation method[26]. The results show the molar ratio of drug to $KMnO_4$ was 1:3 or 1:2 (Fig.3) for cefprozil or dropropizine, respectively, as indicated in Scheme 1.

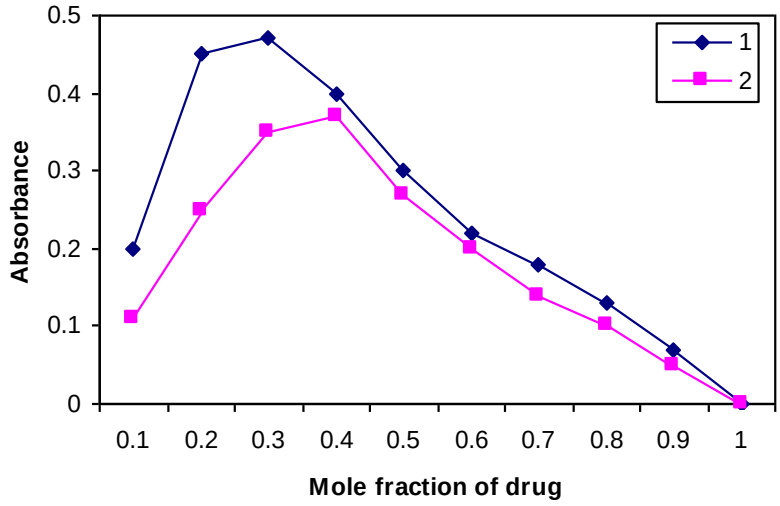

Fig.3. Continuous variation plots for oxidation of (1) cefprozil ($1x10^{-3}$M), (2) dropropizine ($5x10^{-4}$M) with $KMnO_4$, λ = 610 and 608 nm for 1 & 2, respectively. Total molar concentration = $2x10^{-4}$ and $1x10^{-4}$ M for 1 & 2, respectively.

The oxidation of phenolic group on cefprozil containing a -CH moity in the para substituent can be consisted of the generation of free phenoxy radical which can be stabilized by the formation of a quinone through the delocalization of the unpaired electrons over the aromatic ring[27]. Besides, the nitrogen of the β-lactam ring can be included in the oxidation reaction of cefprozil[28] (Scheme 1).

In case of dropropizine, the oxidation reaction can be explained that N-substituted piperazine group, owing to its higher basicity, nitrogen atom is the side of the reaction with alkaline $KMnO_4$[22] as indicated in Scheme 1.

Analytical parameters

After optimizing the reaction conditions, the fixed-time method was applied to the determination of cefprozil or dropropizine in pure form over the concentration range 1.0-8.0 or 0.2 – 2.0 μg ml^{-1}, respectively. Analysis of the data gave the following regression equations:

$$A = 0.005 + 0.124\ C, \quad r = 0.9999 \text{ for cefprozil}$$
$$A = 0.009 + 0.435\ C, \quad r = 1.0002 \text{ for dropropizine}$$

where A is the absorbance at 610 and 608 nm for cefprozil and dropropizine, respectively, and C is the concentration in μg ml^{-1}. The correlation coefficients (r) are approximately equal 1.0000, indicating good linearity and conformity to Beer's law for the proposed method.

Ringbom plots[29] for optimum concentration ranges can be obtained by plotting the photometric data of percent transmittance as ordinate against logarithm of concentration as abscissa; from which the linear portion of the curve gives accurate range of microdetermination of the drugs under investigation and represented in Table 2. The low values of the detection (LOD) and the quantitation (LOQ) limits are evidence for the sensitivity of the method. The molar absorptivities calculated from the linear regression coefficients together with the Sandell sensitivities are listed in Table 2.

TABLE 2. Analytical parameters for determination of cefprozil and dropropizine in the pure form by applying the $KMnO_4$ method (using the fixed-time method, 40 min).

Parameters	Cefprozil	Dropropizine
λ_{max} (nm)	610	608
Beer's law limits (μg ml^{-1})	1.0-8.0	0.2-2.0
Ringbom optimum concentration range (μg ml^{-1})	1.4-7.6	0.3-2.0
Molar absorptivity (l mol^{-1} cm^{-1})	4.88×10^4	1.05×10^5
Sandell sensitivity (ng cm^{-2})	8.00	2.25
Slope (b) (specific absorptivity)	0.124	0.435
Intercept (a)	0.005	0.009
Correlation coefficient (r)	0.9999	1.0002
Relative standard deviation (%, n=6)	0.85	0.98
LOD (μg ml^{-1})	0.21	0.07
LOQ (μg ml^{-1})	0.68	0.22
Intraday precision	100.30 ±0.20	100.50 ±0.32
Interday precision	100.03 ±0.22	100.20 ±0.46

Validation of the proposed method

Accuracy and precision

In order to study the accuracy and precision of the proposed method, three concentration levels of cefprozil and dropropizine within the linearity range of Beer's law were selected. The short-term precision (intraday assay) was performed by measuring five independent analyses at each concentration level within one day.

The daily precision (interday assay) was evaluated by measuring the cefprozil or dropropizine content at each level on five consecutive days by fixed-time method. The mean percent recoveries and relative standard deviations (RSD) obtained in intraday and interday assays (Table 2) can be considered to be very satisfactory and thus, the proposed method is very effective for the determination of cefprozil or dropropizine in drug formulations.

Analytical recovery and interference liabilities

The accuracy of the proposed method was checked by performing recovery experiments using the standard additions method[30]. Known amounts of the pure drug (cefprozil or dropropizine) were added to preanalyzed cefprozil tablets or oral suspension and dropropizine lozenges, and then determined by the recommended procedure. The obtained mean recoveries and relative standard deviations were in the

range 99.98-100.65% and 0.26 – 0.41% for cefprozil or 99.94 – 100.25% and 0.46 – 0.63% for dropropizine.

These results prove the accuracy of the proposed method and absence of interference from the common excipients. The extraction of cefprozil with methanol from tablets or oral suspension and dropropizine with dichloromethane from lozenges could eliminate the interference from the common excipients. The obtained good recoveries ensured the suitability of the method for the analysis of cefprozil or dropropizine in its dosage forms without interference from the common reducing excipients. The great sensitivity of the method that necessitated the dilution of the sample, and consequently the excipients beyond interference capability.

Application of the proposed method

The fixed-time method was applied for the determination of cefprozil and dropropizine in pharmaceutical preparations. The concentration of the drug was calculated using the corresponding calibration equation in Table 2 at a fixed time of 40 min for both drugs. The results obtained for the analysis of drug in pharmaceutical preparations compared with the reference method[9] (Table 3). The Student's t-test and F-test values of 95% confidence level did not exceed the theoretical values of 2.306 and 6.39 for t-and F-tests, respectively, indicating no significant difference between the proposed method and reference method with regarding to accuracy and precision. However, the principal advantage of the proposed method is its suitability for the routine quality control of the drug alone and in its dosage forms without fear of interference caused by the excipients expected to be present in tablets, lozenges or oral suspension.

TABLE 3. Application of the proposed kinetic method to the determination of cefprozil and dropropizine in their pharmaceutical formulations .

Drug	Pharmaceutical formulations	Found ± SD % [a]	
		Proposed method	Reference method[9]
Cefprozil	Cefzil tablets (250 mg/tablet)	99.92±0.51 t = 1.11 F = 3.40	99.39±0.94 (2.306)[b] (6.39)[b]
	Cefzil oral suspension (125 mg/5ml)	100.35 ± 0.46 t = 0.50 F = 4.82	100.10±1.01
Dropropizine	Tussipine lozenges (20 mg/lozenge)	99.73±0.39	

[a] Mean and standard deviation for five determinations.
[b] The tabulated values of t- and F-tests at 95% confidence limit.

Conclusion

The kinetically-based method proposed in this work for the quantitative analysis of cefprozil and dropropizine is direct method and more sensitive than the reference

method[9]. Further more the proposed method do not need the elaborate treatment and tedious extraction required in chromatographic method[4,5]. The data given above reveals that the proposed method is accurate and sensitive with good precision and accuracy. With this method, one can do the analysis at low cost without losing accuracy. This method is useful and convenient for quality control and routine determination of drugs in bulk and in dosage forms.

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طريقة طيفية حركية حساسة لتعيين السيفبروزيل و الدروبروبيزين في المادة الخام و المستحضر الصيدلي

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أمكن دراسة حركية تفاعل سيفبروزيل و دروبروبيزين مع برمنجنات البوتاسيوم في الوسط القاعدي و تم دراسة العوامل المؤثرة المختلفة على عملية الأكسدة. أمكن قياس معدل التغير في امتصاص أيون البرمنجنات الثنائي الشحنة و الذى يتميز باللون الأخضر عند طول موجة ٦٠٨-٦١٠ نانوميتر. أمكن الحصول على المنحيات القياسية عند وقت ثابت فى مدى تركيز ١-٨ ميكروجرام/مل للسيفبروزيل، ٢، - ٢ ميكروجرام/مل للدروبروبيزين. أمكن تعيين النسب المولارية للتفاعل مع افتراض آلية أكسدة هذه المواد بواسطة برمنجنات البوتاسيوم في الوسط القاعدي.

تم تطبيق هذه الطريقة في تعيين مركبات سيفبروزيل و دروبروبيزين في صورها النقية و في المستحضرات الصيدلية و قد أجريت الاختبارات الاحصائية لتباين مدى التوافق بين هذه الطريقة و الطرق المنشورة و قد أعطيت نتائج طيبة.