Potentiometric and Conductometric Determination of Metal Complexes of Tenoxicam in Different Dosage Forms

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ABSTRACT

Potentiometric and conductometric methods were used to investigate the interaction of tenoxicam (TXM)with10 metal ions: Fe(III), Cr(III), La(II), Th(IV), Co(II), Mn(II), Pd(II), Ti(II), Sr(II), and Zr(II). The ionization constant of TXM as a ligand and the stability constants of the formed complexes were calculated at 25 ± 0.1 °C in 0.05 M $NaNO_3$ aqueous solution. Conductometric methods were used to confirm the stoichiometry of the complexes. The metal/ligand ratio was 1:2 or 1:3 depending on the nature of the ligand-metal bonding. The determination of TXM in pure form, and three different dosage forms (tablets, suppository, and injection) was carried out by the potentiometric method, which was simple, precise, rapid, and inexpensive. The quantification of TXM was performed by the well-known standard addition method. The typical limit of quantification was 4.50 mg L^{-1}. The proposed method showed excellent linearity in the range of 0.09–4.66 mg L^{-1}. No interference was observed in the presence of other components that were common in the dosage forms. The recovery of TXM from several tablet dosage formulations ranged from 96.66 to 101.21%.

Key Words: *Tenoxicam, Potentiometric, Conductometric, Tablets, Suppository, Injection.*

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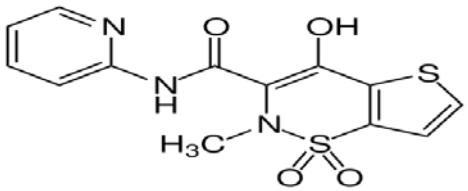
INTRODUCTION

Tenoxicam (TXM) is a nonsteroidal anti-inflammatory drug (NSAID) that is a part of the oxicam family, and it can be used as an effective analgesic and antipyretic agent [1, 2]. The chemical formula of TXM is $C_{13}H_{11}N_3O_4S_2$ (Scheme 1) and thepK_a = 4.50 and 3.73 (Scheme 1)



Scheme 1. Chemical structure of tenoxicam (4-hydroxy-2-methyl-N-(2-pyridinyl)-2H-thieno[2,3-e] [1,2] thiazine-3-carboxamide-1,1-dioxide)

The pharmacological effects of oxicam compounds are linked to the inhibition of cyclooxygenase, which catalyzes the production of cyclic endoperoxides and subsequent prostaglandin formation [3, 4]. The drug is commonly used for the treatment of rheumatic diseases [5, 6] and musculoskeletal and joint disorders [7]. The purity of TXM needs to be monitored because it often contains 2-aminopyridine (2-AP), which is a potential impurity that can be produced synthetically, or as a side product of acid cleavage [8]. According to the British Pharmacopoeia [8], a literature survey showed many different analytical methods for TXM determination, including high-performance liquid chromatography (HPLC) [9-11] and many spectrometric techniques (IR spectrophotometry [12], derivative spectrophotometry [11], flow-injection spectrophotometry [13], spectrofluorimetry [14, 15], and

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UV-vis spectrophotometry [16-19]). Different electrochemical methods such ascoulometry [20], polarography [21, 22] , and voltammetry [23-25] have also been used for TXM determination. However, the application of most of these techniques is usually restricted owing to time consuming processes, complicated operating procedures, high cost, and the need for sophisticated instruments, expensive reagents, and expertise.

Electrochemical methods could overcome the many disadvantages of these techniques. Among various electrochemical methods, the potentiometric method has been extensively used in many branches of solution chemistry because it is one of the most accurate and widely applicable techniques for studying the ionic equilibria of diverse complexes [26]. Potentiometric methods have been used for the study of binary and ternary complexes linked to biological molecules [27-35]. The potentiometric studies of complexes formed between drug compounds and metal ions have helped to elucidate how drug–metal interactions effect drug delivery to the target cells [36, 37]. Additionally, it has been suggested that the presence of metal ions in the composition may enhance the therapeutic action of the drug compounds [38]. Therefore, a large number of medications including TXM are prepared and characterized as metal complexes [39-42]. Such complexes have also been studied using spectrofluorimetric and polarographic techniques [43, 44].

Potentiometric methods have been widely used to quantify compounds in various samples. The Gran plot is a common method widely used to identify the equivalence point and K_a values in potentiometric titration based on linear approximations of the non-liner relationships between the electro-motive potential and the titrant volume [45]. Such a plot has some advantages over the more commonly used sigmoid logarithmic plot. Several applications of the Gran plot have been reported, such as the determination of fluoride by using a specific ion electrode [46], acid rain analysis [47], measuring the levels of strong acid in atmospheric aerosols [48], and the detection of nalidixic acid in pure forms and tablets [49].

Herein, for the first time, in the current study, a potentiometric method was developed for the direct determination of TXM in pure forms, tablets, suppositories, and injections. This method was based on the complexation equilibrium between TXM and different metal ions, and the equilibrium was quantitatively determined for 10 metal ions (Fe (III), Cr (III), La (II), Th (IV), Co (II), Mn (II), Pd (II), Ti (II), Sr (II), and Zr (II)) using Gran plot.

MATERIALS AND METHODS

Apparatus

All pH measurements were obtained with a pH meter (Jenway, UK) fitted with a combined glass electrode, and the total accuracy was 0.01 pH units. Conductometric titration measurements were carried out using a conductivity meter (Model 4320, Jenway, UK) equipped with an immersion cell. The H^+ concentration was used to calibrate the electrode system; therefore, all the equilibrium constants determined in this work were based on the concentration constants. The stoichiometry and stability constants were computed using Excel computer program [43].

Materials

Tenoxicam was purchased from (Sigma-Aldrich, St. Louis, MO, USA), and sodium hydroxide (BDH, Laboratory supplies, Poole, UK). All the other metal ion solutions (as nitrate and chloride salts) were of analytical grade (BDH, UK, Geneva), and used as purchased.

The following pharmaceutical formulations of TXM were analyzed: Mobiflex® (tablets containing 20 mg TXM each according to the label, Memphis Chemicals, Egypt), Tenoxicam® (suppositories containing 20 mg TXM each according to the label, Dar Al-daoa, Jordan), and Tenoxicam®(injections, containing 15 mg TXM per 3-mL ampoule, Micro Labs Limited, India).

Procedures

- **Metal Complexes of TXM**

The dissociation constant of the ligand (TXM) and the formation constant of its metal complexes at 25±0.1 °C in aqueous ethanol solution were obtained using the potentiometric method adapted from Calvin–Bjerrum's technique as used by Irving and Rossotti [50]. Three sets of solutions were prepared and titrated against 0.05 M carbonate-free NaOH solution (which was standardized against potassium hydrogen phthalate): (a) 0.005 M HNO_3 + 0.045 M $NaNO_3$, (b) Solution (a) + 0.001 M ligand, and (c) Solution (b) + 0.001 M metal nitrate solution. In each case, the total volume was adjusted to 50 mL by adding double-distilled water. The titration was performed at 25±0.1 °C, and different ionic strengths (I = 0.05, 0.15, and 0.25 M $NaNO_3$).

Conductometric titrations were carried out at room temperature by titrating each metal ion solution (25 mL, 1×10^{-3} M) against 1×10^{-2} M TXM solution in 0.5 mL increments. Correction for the dilution effect was performed by multiplying the values of the specific conductance by a factor of $\frac{(25+v)}{25}$, in which v was the volume of titrant added.

Determination of TXM

- **TXM in Pure Form**

A standard solution of TXM (1×10^{-2} M, 25 mL) was prepared by diluting the stock solution with absolute ethanol and adjusting the ionic strength to 0.5 M with $NaNO_3$. Then, a 15 mL aliquot of this solution was

transferred to a thermostated glass cell (25±1.0 °C). After that, the solution was titrated potentiometrically and conductometrically with a standard solution of NaOH (I = 0.1 M).

- **TXM in Tablets**

Ten tablets of Mobiflex®, each containing 20 mg of TXM according to the label, were weighed to calculate their average weight. The tablets were ground into a fine powder and homogenized. A portion of the powder equivalent to 100 mg of TXM was accurately weighed, dissolved in ethyl alcohol, and filtered. The filtrate was then diluted with double-distilled water, and its ionic strength was adjusted to 0.5 M with $NaNO_3$. Finally, 10 mL of this solution was diluted to 25 mL with double-distilled water, and analyzed using a procedure similar to that described in 3.3.2.1. The quantity of TXM per tablet was calculated from the standard calibration curve.

- **TXM in Suppositories**

Ten Tenoxicam®suppositories, eachcontaining 20 mg of TXM according to the label, were weighed to calculate their average weight. A portion of the mixed suppositories equivalent to 100 mg of TXM was accurately weighed and dissolved in 10 mL of ethanol. The resulting mixture was filtered, and its ionic strength was adjusted to 0.5 M with $NaNO_3$. Finally, this solution was diluted to 25 mL with double-distilled water, and analyzed using a procedure similar to that described in 3.3.2.1.

- **TXM in Injections**

The contents of 10 Tenoxicam® ampoules, each labeled to contain 15 mg TXM, were mixed thoroughly. A volume equivalent to one ampoule was accurately measured, diluted with double-distilled water, and its ionic strength was adjusted to 0.5 M with $NaNO_3$. Then, the solution was diluted again with double distilled water to 25 mL and analyzed using the same procedure as described in 3.3.2.1.

RESULT AND DISCUSSION

Formation Constants of TXM Complexes

- **Potentiometric Measurements of TXM with Metal Ions**

Potentiometric and conductometric measurements were carried out on the interaction of TXM with five metal ions: La(II), Ti(II), Sr(II), Fe(III), and Th(IV). In the potentiometric method, the ionization constant of the ligand and stability constant of the formed complex were calculated at 25±0.1°C in $NaNO_3$ aqueous solutions with different ionic strengths (I = 0.05, 0.15, and 0.25 M). The results are shown in Table 1.

Table 1: Protonation constant of TXM and stability constants of metal–TXM complexes at 0.05 M $NaNO_3$ and 25±0.1°C

Cation	Log K_1 (M:L)*	Log K_2 (M:L)*	Log K_3 (M:L)*	Ref.
H^+	5.00 5.29 (1:1)	…….	…….	Present work 43
Fe (III)	…….	8.70 9.40 (1:2)	6.57 8.90 (1:3)	Present work 43
Th (IV)	…….	7.79 (1:2)	5.97 (1:3)	Present work
La (II)	…….	7.83 (1:2)	6.00 (1:3)	Present work
Ti (II)	…….	7.74 (1:2)	5.81 (1:3)	Present work
Sr (II)	…….	7.81 (1:2)	5.82 (1:3)	Present work

(*) obtained from potentiometric and conductometric methods

- **Proton–TXM Stability Constants**

The potentiometric titration curves of TXM are shown in Fig. 1. Values of $\bar{n}A$ (average number of proton attached to each ligand) were determined according to Irving and Rossotti [50] as shown in Eq. (1):

$$\bar{n}A = Y + \frac{(V_1 - V_2)(N^\circ + E^\circ)}{(V^\circ + V_1)T_cL^\circ} \qquad (1)$$

WhereV_1 and V_2 are the volumes of alkali required to reach the same pH in a mineral acid (HNO_3) and (HNO_3+TXM) solutions, respectively. $T_cL°$ is the total concentration of the ligand, N° is the normality (concentration) of NaOH solution (0.1 M), and E° is the initial concentration of free HNO_3 in the solution. Calculations of proton–TXM association constants were carried out by plotting $\bar{n}H$ against pH, as shown in Fig. 2. The value of $LogK_1^H$(the first proton association constant of TXM) is the pH value corresponding to $\bar{n}H$ = 0.5. The obtained pK_avalues of TXM-metal complexes (Table 1) were in good agreement with that found in the literature [43].

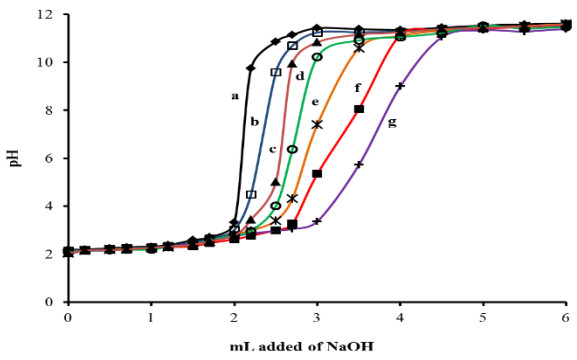


Fig. 1. Potentiometric titration curves of TXM in I = 0.5 M $NaNO_3$ and at 25±0.1 °C: (a) 0.1 M HNO_3, (b) a + 0.001 M TXM, (c) b + 0.001 M Ti (II), (d) b + 0.001 La (II), (e) b + 0.001 M Sr (II), (f) b + 0.001 M Fe (III), and (g) b + 0.001 M Th (IV)

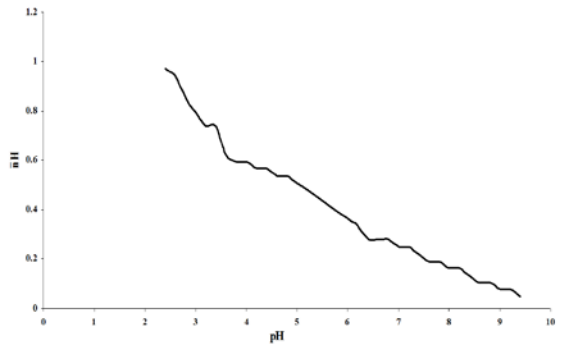


Fig. 2. Protonation constant curve of TEC in I = 0.5 M $NaNO_3$ and at 25±0.1 °C

- **Formation Constants of Metal–TXM Complexes**

The titration curves of the metal–TXM complex solutions (curves *c*–*g*) differed among themselves and were well separated from that of free ligand solution (curve *b*). Thus, the replacement of H^+ ion was due to complexation. Equations (2) and (3) were used to calculate the values of $\bar{n}$ (average number of ligand molecules attached per metal ion) and *pL* (free ligand exponent) as shown by Irving and Rossotti [50].

$$\bar{n} = \frac{(V_3 - V_2)(N^\circ + E^\circ)}{(V_\circ + V_2)\bar{n}HT_cM^\circ} \quad (2)$$

$$pL = Log\left[\frac{1+\beta_1[H^+]+\beta_2[H^+]^2}{(T_cl^\circ - \bar{n}T_cM^\circ)} \times \frac{V_\circ + V_3}{V_\circ}\right] \quad (3)$$

The $\bar{n}$ values were plotted against *pL* to obtain the formation curves of metal complexation equilibria (Fig. 3). From these curves, the stability constants were computed using the half-integral method [50]. For all of the metal–TXM complexes, the formation constants of the second and third complexes were obtained, but those of the first complex were not obtained owing to the chemical nature of TXM and the studied metal ions.

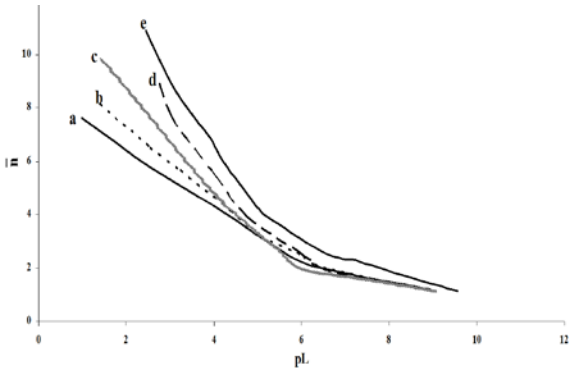
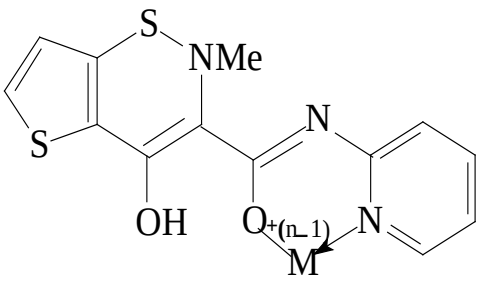


Fig. 3. Representative formation constant curves of binary metal ion-TXM complexes at I = 0.05 M: (a) La (II), (b) Th (IV), (c) Ti (II), (d) Sr (II), and (e) Fe (III)

The protonated amino group (–NH) in TXM was the active site in the complexation process. This site led to the formation of six-membered rings [43]. Furthermore, it was observed that in TXM, the oxygen of the amide group and the pyridyl nitrogen formed a bond with the metal cation, as shown below(Scheme 2):



Scheme 2: the oxygen of the amide group and the pyridyl nitrogen in TXM

The stability of the different metal–TXM binary complexes in this study could be ordered in a similar way to that reported by Irving and Williams [51] for binary metal–ligand complexes in 0.05 M $NaNO_3$:

Fe>La>Sr>Th>Ti

In addition, the effect of the ionic strength on the stability constant of metal–TXM complexes in aqueous solution at 25±0.1 °C was investigated. The ionic strength has been considered as the most important factor in electrolyte solutions, and has had a direct influence on the stability constants of the metal complexes. Five different metal ions, namely Fe (III), Th (IV), Ti (II), Sr (II), and La (II), were complexed with TXM. According to the relationship between $LogK_a$ and the ionic strength of these ions shown in Fig. 4, the stability constants of metal–TXM complexes decreased as the ionic strength increased.

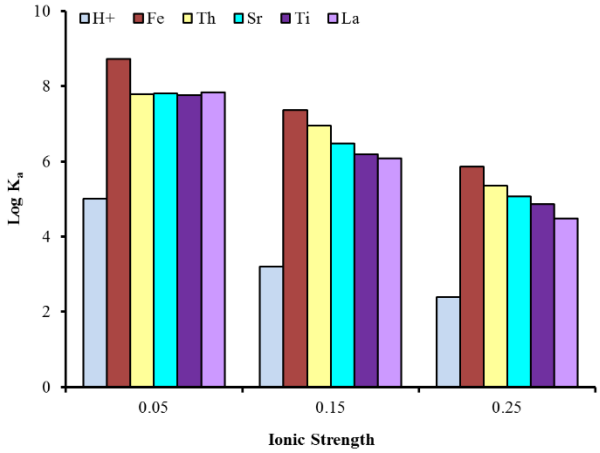


Fig. 4.Effect of ionic strength on the stability constants of some metal–TXM complexes

- **Conductometric Measurements**

The conductometric analysis was based on changes in the electrical conductivity of the solution as a result of complex formation. These changes were directly related to

the number of ions in the complex structures and their movements in the solution. Herein, the conductometric titration curves were used to trace the binary complex formation with different metal ions (Fe (III), Th (IV), La (II), Sr (II), and Ti (II)) at room temperature. The obtained results (Fig. 5) showed that the recorded conductance *vs.* the volume of titrant was proportional to the mobility of ions in the solution. This might be owing to the neutralization of H^+ during the formation of the M–TXM complex. The slow increase in conductance upon the addition of TXM to the metal ions might be attributed to the formation of the highly charged TXM anions of the relatively weak acid. Two well-defined breaks corresponding to the stoichiometric ratios of 1:2 and 1:3 (M/L) were also evident (Fig. 5).These results were comparable with those obtained by the potentiometric method (Table 1).

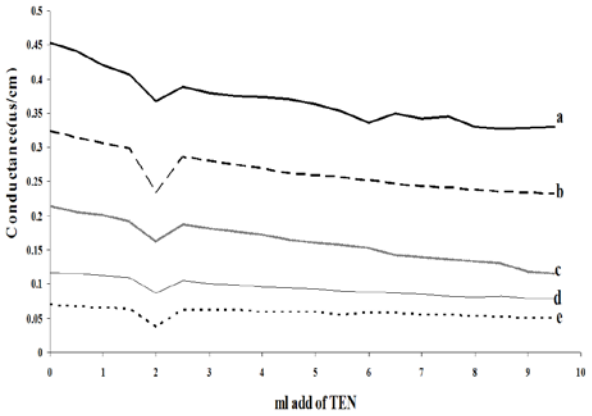


Fig. 5. Conductometric titration curves of metal ions (1×10^{-3} M, 25 mL) with 1×10^{-2} M TXM: (a) Fe (III), (b) Th (IV), (c) La (II), (d) Sr (II), and (e) Ti (II)

- **Species Distribution Diagrams of TXM**

The species distribution curve of TXM has been shown in Fig. 6. All the species had a wide protonation range (pH = 2.6–11.4). When the pH increased, the protonated ligands lost their protons and converted to the other forms, as shown in Fig.6. The HL species started to form at pH = 2.6 and the protonation state decreased up to pH = 7.8. The free ligand (L^-) was present from pH = 3.8 and reached its maximum concentration at pH = 11.4. The data obtained from studying the M–TXM complexes were evaluated using MS Excel® and SPSS® statistical software [43], and the obtained species distribution curves have been shown in Fig. 7. In this figure, the concentrations of various complexes formulated as ML_2 were very small, and depended on the pH and the type of medium.

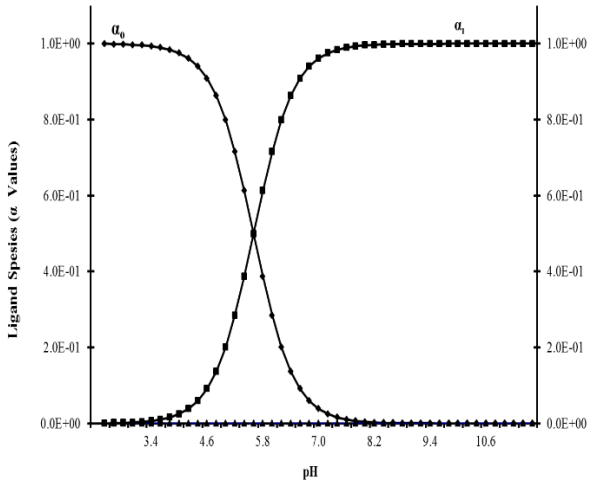


Fig. 6. Ionization equilibriaof TXM at different pH values

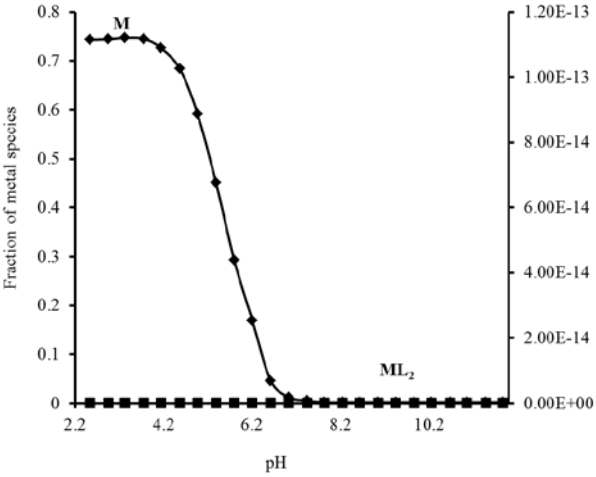


Fig. 7. Ionic equilibria of Fe–TXM at different pH values

Potentiometric Determination of Pure TXM

TXM is a weak acid with a dissociation constant $pK_1 = 5.0$ for the amino group. Because $K_1 = 1\times10^{-5}$, the titration curve was expected to present a clear inflection at the first point of the equivalence. Accordingly, Fig. 8 shows the potentiometric titration curve with only one inflection point. In our proposed method, the change at the titration end-point was clear, and the produced curve had a satisfactory shape for accurate and reproducible detection of the end-point. Curves (a) and (b) show the first derivative of the combined glass pH–electrode, and curve (c) is the second derivative.

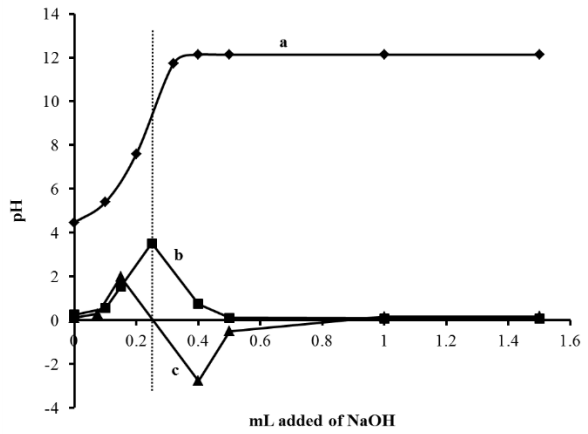


Fig. 8.Typical potentiometric titration curves of pure TXM in tablets (20 mg TXM per tablet): (a) normal titration curve, (b) first derivative, and (c) second derivative

- **Effect of Ionic Strength on the Determination of Pure TXM**

The effect of $NaNO_3$ ionic strength (0.5–1.5 M) on the potentiometric and conductometric data have been illustrated in Table 2. The best and highest recovery percentages (close to 100%) were obtained in 0.5 M $NaNO_3$. Thus, an ionic strength of 0.5 M was used for the determination of TXM in pure and dosage forms.

Table 2: Effect of ionic strength on the percentage recovery for pure TXM

Ionic Strength (M)	Added pure (mg)	Found (mg)	Recovery (%)
0.05	15 15	5.62 (5.59)	37.46 (37.26)
0.1	15 15	8.43 (8.41)	56.2 (56.07)
0.5	15 15	15.18 (15.14)	101.2 (100.93)
0.75	15 15	16.87 (16.75)	112.46 (111.66)
1	15 15	17.43 (17.39)	116.2 (115.93)
1.5	15 15	22.49 (22.44)	149.93 (149.6)

Data between parentheses are from the conductometric method

- **Analytical Performance**

Under the optimum conditions (I = 0.5 M $NaNO_3$), the percentage recoveries were close to 100%. The calculated percentage recoveries were obtained linearly in the ranges of 98.67–99.33 % and 96.43–98.00 % for the potentiometric and conductometric methods; respectively. The corresponding standard deviation (SD) ranges were 0.43–1.21 and 0.4–1.16; respectively, and the 95 % confidence levels were within 0.38–1.06 and 0.33–1.0; respectively for n = 5 replicates (Table 3). These results highlighted the accuracy and precision of the proposed method for TXM determination.

Table 3: Determination of pure TXM using potentiometric and conductometric methods in I = 0.5 M $NaNO_3$

Added pure (mg)	Found (mg)	Recovery %	SD (n=5)	Confidence (n=5 and α =0.05)
0.	0.0083 (0.0081)	98.81 (96.43)	1.21 (1.16)	1.06 (1.0)
0.015	0.0149 (0.0147)	99.33 (98.0)	0.60 (0.56)	0.52 (0.48)
0. 0075	0.0074 (0.099)	98.67 (97.29)	0.88 (0.82)	0.77 (0.70)
0.02	0.0198 (0.0195)	99.0 (97.75)	0.43 (0.40)	0.38 (0.33)

Data in parentheses are from the conductometric method

The detection limit was calculated as 3σ/b, in which σ is the slope of the calibration curve and b is the SD of the three measurements at the lowest point of the calibration line. The quantitative limit was also calculated as 10σ/b. [43] It was evident that TXM could be detected at 4.50 mg mL^{-1} with a highly linear relationship (R^2 = 0.9966) and SD = 2.46 for n = 5. TXM was successfully determined using the proposed method in the concentration range of 0.095 to 4.66 mg mL^{-1} (Fig. 9). In addition to the good analytical performance, the proposed method was easy and simple.

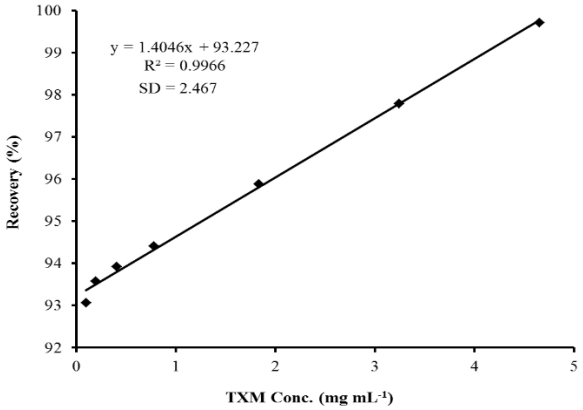


Fig. 9. Linearity range of pure TXM in I = 0.5 M $NaNO_3$

- **Effect of Interference**

To assess the efficiency and selectivity of the proposed method for TXM determination, a series of sample solutions were prepared containing a fixed amount of TXM, and spiked with common additives and excipients in drugs. The researchers considered the components that often accompanied TXM, such asD(+) lactose monohydrate, sodium chloride, and sodium acetate at concentrations at least 100 times higher than those of TXM. The experiments showed that under the optimum conditions, these common additives had no serious effects on the measurements. Therefore, the proposed method was suitable for highly efficient and selective determination of TXM.

- **Analytical Application**

To assess the applicability of the proposed method for the analysis of pharmaceutical formulations, the recovery test from real TXM samples was carried out for tablet, suppository, and injection formulations. In Fig. 10, curve (a) is the typical potentiometric titration curve with only one inflection point, whereas curves (b) and (c) are the first and second derivatives of (a); respectively.

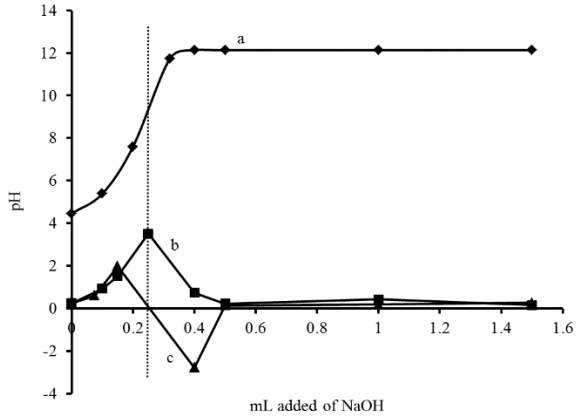


Fig. 10. Typical potentiometric titration curves of pure Meloxicam in injections (20 mg TXM/3 mL): (a) normal titration curve, (b) first derivative, and (c) second derivative

The results of the conductometric titration of TXM in pure and pharmaceutical preparations are shown in Fig. 11. The obtained data proved that this method could be used successfully for the analysis of such compounds in different dosage forms, and had the advantages of being simple, inexpensive, accurate, and reproducible.

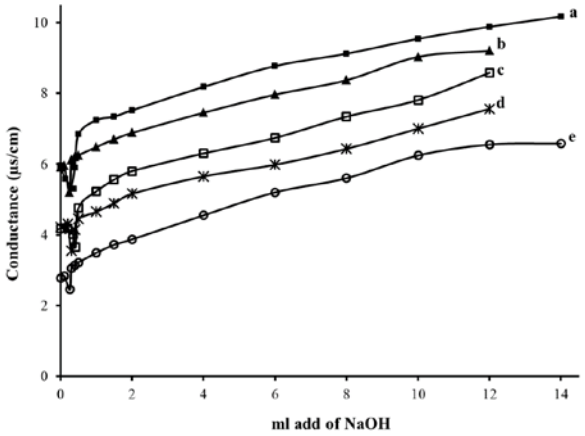


Fig. 11. Typical conductivity curves for the determination of TXM in pure and different dosage forms: (a) Meloxicam tablets (7.5 mg TXM/tablet), (b) Mexicam tablets (15 mg TXM/tablet), (c) Tenoxicam suppositories (20 mg TXM/suppository), (d) pure Tenoxicam (20 mg), and (e) Tenoxicam injection (15 mg TXM/3 mL)

The TXM in tablet, suppository, and injection dosage forms was determined by the proposed method. According to Table 4, the recovery percentage of the two procedures ranged from 96.66 to 101.21 %, with a SD = 0.31–0.78 and confidence limits of 0.28 to 0.68. These results were in good agreement with those determined by the spectrofluorimetric method (100.05± 1.2%) [43].

Although, several methods were described for the determination of TXM with low detection limit, but it still required high cost instruments, reagents and experience. But in the current work, a simple, precise, rapid, low–cost analytical method used for the determination of TXM with excellent recovery was represented as can be shown in Table 3 (in case of TXM determination in pure form) or Table 4 (in case of TXM determination in dosage forms).

Table 4: Recovery data for TXM determination in different dosage forms by potentiometric and conductometric methods

Dosage Forms	Label to content (mg)	Found (mg)	Recovery %	SD (n=5)	Confidence (n=5, α=0.05)
Tenoxicam(Suppositories)	20	19.91 (19.85)	99.55 (99.25)	98.4 (97.75)	19.68 (19.55)
Tenoxicam (Injection)	10	9.97 (9.91)	99.7 (99.1)	101.21 (100)	15.8 (15.0)
Mobiflex® (Tablet)	20	19.95 (19.85)	99.75 (99.25)	97.46 (96.66)	7.31 (7.25)

Data between parentheses are from the conductometric method

CONCLUSION

The complexation reaction between tenoxicam and 10 different metal ions (Fe (III), Cr (III), La (II), Th (IV), Co (II), Mn (II), Pd (II), Ti (II), Sr (II), and Zr (II)) was monitored using either potentiometric or conductometric methods. These methods allowed the identification of the formed complexes, as well as the determination of their stability constants. According to the both methods, the complexes had metal-to-ligand stoichiometric ratios of 1:2 or 1:3. Finally, the distribution of tenoxicamspecies and its metal complexes were found to vary across a wide pH range. Many current methods for the determination of tenoxicam require special instruments, reagents, and expertise, whereas the methods proposed here only involved a simple procedure with a fast response, low cost, and sufficient accuracy for pharmaceutical formulations. The recovery of tenoxicam in various dosage forms ranged from 96.66 to 101.21%, and no interferences were observed.

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