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Different kinetic spectrophotometric methods for the determination of Mefenamic Acid, Niflumic Acid, Mesalazine and Sulfasalazine in their pharmaceutical formulation

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ABSTRACT

The objective of this research was to develop simple and sensitive three kinetic methods for the determination of some anti-iflamatory drugs, mefenamic acid (MA), niflumic acid (NA), mesalazine (MS) and sulfasalazine (SS) in pure form and in their pharmaceutical formulations. The first method was based upon the kinetic investigation of the oxidation reaction of each drug (MA, NA, MS and SS) with alkaline potassium permanganate at room temperature for fixed time yielding a green color of manganate ion. The reaction is monitored by measuring the rate of change of absorbance of the resulting manganate species at 610 nm. The second method is based upon the reaction of carboxylic acid group of MA and NA with a mixture of potassium iodate (KIO_3) and potassium iodide (KI) at room temperature. The reaction is followed by measuring the increase in absorbance at 352 nm as a function of time. The third method is based upon the oxidation reaction of MS and SS with a mixture of iodine and potassium iodide (KI) at room temperature. The light brown color is followed by measuring the increase in absorbance at 496 nm as a function of time. The initial-rate and fixed-time methods were adopted for constructing all the calibration curves. The proposed methods are validated statistically and through recoveries studies to confirming that there is no significant difference between the proposed methods and the reference method.

Keywords: mefenamic acid, niflumic acid, mesalazine, sulfasalazine, Kinetic determination.

INTRODUCTION

Mefenamic acid, niflumic acid, mesalazine and sulfasalazine are non-steroidal anti-inflammatory drugs with anti-inflammatory, analgesic and anti-pyritic activity [1].

MA has been determined in pharmaceutical preparations using numerous methods but the most recently one can summarized as follow: colorimetric methods [2, 3], spectrofluorimetry [4], GC [5], TLC [6, 7] and HPLC in human serum [8, 9], in human plasma [10 11], in dosage form [12] and in urine [13].

NA has been determined in pharmaceutical preparations using spectrophtometry [14, 15], TLC [16, 17] and HPLC in human plasma [18] or in animal serum [19].

MS has been determined in pharmaceutical preparations using spectrophtometry [20], spectrofluorimetry [21], TLC [22], HPLC in biological fluid [23] or in pharmaceutical preparation [24].

The analytical methods reported for the determination of SS in pharmaceutical preparations included IR method, HPLC and capillary electrophoresis[25-27].

This work represents the first attempt at assaying each drug in pharmaceutical formulation by kinetic methods. Either oxidizing the drugs with alkaline $KMno_4$ or mixture of iodide-iodate or mixture of iodine-iodate resulting in the formation of green or yellow or light brown color, which absorb maximally at 610, 352 or 496 nm for the three methods, respectively.

EXPERIMENTAL SECTION

Apparatus

- Shimadzu UV-visible 1601 PC double beam spectrophotometer (Kyoto, Tokyo, Japan) with 1 cm quartz cuvettes, connected to a computer loaded with Shimadzu UVPC software.
-An ultrasonic, BANDELIN , sonorex TK 100 H.

Materials and reagents

All chemicals and reagents used were of analytical or pharmaceutical grade.

The following reagents were used:
1.potassium permanganate (Merck, Germany), 8mM aqueous solution.
2.sodium hydroxide (BDH, UK) , 0.5 M aqueous solution.
3.sodium hydroxide (BDH, UK) , 0.1 M aqueous solution.
4.potassium iodide (Merck, Germany), 0.15 M aqueous solution.
5.potassium iodate (Merck, Germany), 0.1 M aqueous solution.
6.Iodine solution (Merck, Germany), 0.1 M aqueous solution.
7.Mefenamic acid (purity 99.96 %) and ponstan ® capsules (B.N. 35038 E) (labeled to contain 250-mg mefenamic acid) were kindly supplied by EL-Nile company, Cairo, Egypt.
8. Niflumic acid (purity 100.03 %) and nifluma cream (B.N. 704 9003) (labeled to contain 2.5 gm% niflumic acid (500mg/20gm cream) were kindly supplied by El-Pharoania company, Cairo, Egypt.
9. Mesalazine (purity 99.87%) and salazine ® capsules (B.N. 532) (labeled to contain 500-mg mesalazine) were kindly supplied by EL-Pharoania company, Cairo, Egypt.
10.Sulfasalazine (purity 99.81%) and salazo-sulfa pyrine® tablets (B.N. 0711067) (labeled to contain 500-mg sulfasalazine) were kindly supplied by El-Kahera company, Cairo, Egypt.

Preparation of Standard stock solutions:

For methods (1, 3): Solutions of MA , NA, MS and SS (1mg/ml) were prepared by in water containing 10-ml of 0.1M NaOH for methods (1, 3)

For method (2): Solutions of MA and NA (1mg/ml) were prepared in methanol.

General procedure and linearity

a) method (1)

Aliquots of each prepared standard solutions equivalent to (0.1- 5 mg) were transferred into a series of 10-ml volumetric flasks, 1-ml of 0.5M NaOH were added to each flask, followed by the addition of 3-ml of 8 mM of $KMno_4$ solution. The content of each flask were mixed and the volumes were completed to the mark with water and allowed to stand for 30 min for MA and NA, 25 min. for MS and SS at ambient temperature (25^oC). The absorption spectrum was recorded at 610 nm against a reagent blank solution.

The following regression equations (1, 2, 3, 4) were computed.

$A= 0.0575x\ C_{(\mu g/ml)}+0.0874$ $r^2 = 0.9992$ MA……(1)

$A= 0.0473xC_{(\mu g/ml)}+0.0119$ $r^2 = 0.9992$ NA…….(2)

$A= 0.0746x\ C_{(\mu g/ml)}+0.0518$ $r^2 = 0.9994$ MS…....(3)

$A= 0.0486xC_{(\mu g/ml)}+0.0107$ $r^2 = 0.9993$ SS……..(4)

Where *A* is the absorbance value. *C* is the concentration in (µg/ml) and r^2 is the regression coefficient.

b) Method (2)

Aliquots of MA and NA standard solutions equivalent to (0.1-4 mg) were transferred into 10-ml volumetric flasks, 2.5 ml 0.15M KIO_3 followed by 3.5-ml of 0.15M KI were added and then diluted to volume with distilled water and allowed to stand for 10 min. The increase in absorbance at 352 nm was recorded as a function of time against a reagent blank prepared similarly.

The following regression equations (5 and 6) were computed.

$A= 0.0255C_{(\mu g/ml)} - 0.0052$ $r^2 = 0.9993$ MA……(5)

$A= 0.0384xC_{(\mu g/ml)}+0.0437$ $r^2 = 0.9992$ NA…….(6)

Where A is the absorbance value. *C* is the concentration in (µg/ml) and r^2 is the regression coefficient.

c) Method (3)

Aliquots of MS and SS standard solutions equivalent to (0.1-7mg) were transferred into a series of 10-ml volumetric flasks, 0.5-ml of 0.1N I_2 for MS or 2-ml for SS were added to each flask, followed by the addition of 1-ml of 0.15M KI and then diluted to volume with distilled water and allowed to stand for 10 min. The absorption spectrum at 496nm was recorded against a reagent blank solution prepared similarly.

The following regression equations (5 and 6) were computed.

$A= 0.015x\ C_{(\mu g/ml)}-0.0249$ $r^2 = 0.9992$ MS……(7)

$A= 0.0224x\ C_{(\mu g/ml)}+0.0011$ $r^2 = 0.999$ SS…….(8)

Where *A* is the absorbance value. *C* is the concentration in (µg/ml) and r^2 is the regression coefficient.

Procedure for pharmaceutical preparations

An accurately weighed amount of finely powdered ponstan capsules, salazine capsules and salazo sulfa-pyridine tablets equivalent to 10 mg of MA, MS and SS, respectively, were transferred into a 100-ml volumetric flask, followed by 80-ml distilled water containing 10-ml 0.1N sodium hydroxide and sonicated for 15 min to dissolve the drug. The volume was made up to 100-ml with appropriate solvent for methods (1 and 3).

An accurately weighed amount of finely powdered ponstan capsules equivalent to 100 mg of MA were transferred into a 100-ml volumetric flask, followed by the addition of 80-ml methanol and sonicated for 15 min to dissolve the drug. The volume was made up to 100-ml with methanol, for method (2).

An accurately weighed 0.4gm of cream equivalent to 10mg NA were placed in 100 ml beaker, add 10 ml solvent (0.1N NaOH for method (1) or methanol for method (3)) and gently heat on water bath at 40-50^{o}C just melt the base with continuous stirring for 10 min., allow to cool to solidify the base, decant the aqueous layer into 100 ml volumetric flask, the extraction procedure was repeated three times. The solution was filtered each time into 100 ml volumetric flask and the volume was completed to the mark with the solvent (water for method (1) and methanol for method (3).

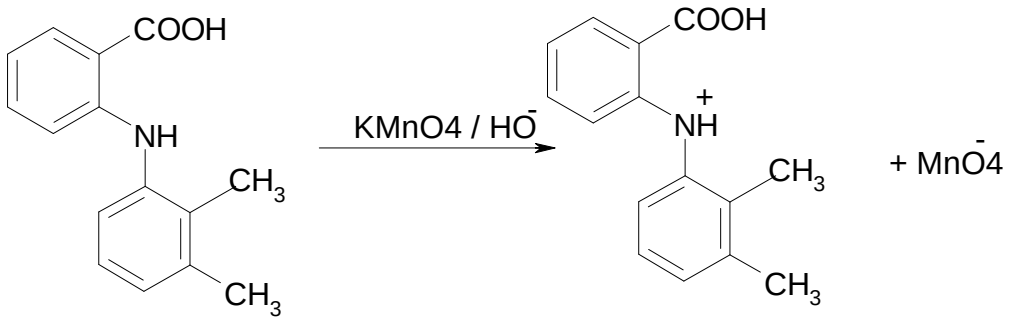
The all above solutions were filtered through a dry funnel and a dry filter paper. The first 10-ml of the filterate was rejected. Different aliquots of this solution were transferred into a series of 10-ml volumetric flasks and proceed as mentioned under general recommended procedures. The absorbance intensity of the resulted solution was measured at specific wavelength for each procedure. The nominal content of the tablets and capsules was calculated either from a previously plotted calibration graph or using the regression equation.

RESULTS AND DISCUSSION

Mechanism of the color reaction.

a) Method (1)

Based on kinetic investigation of the oxidation reaction of four drugs by loss of the lone pair of electron on NH group with alkaline $KMno_4$ at room temperature. The absorbance of the reduction product, manganate ion was measured at different time intervals at 610 nm, **scheme (1)**. As the intensity of the color increase by time, this was used for kinetic determination of these drugs in bulk and in pharmaceutical preparations.



Scheme (1): Proposed reaction between MA and potassium permanganate in alkaline medium.

b) Method (2)

The second procedure depend on that acidic compounds liberate iodine from solution containing both KIO_3 and KI according to the reaction [28] :

$5I^- + IO_3^- + 6H^+ \rightarrow 3H_2O + 3I_2$

A yellowing of the solution reveals the occurrence of the reaction due to the formation of I_2 which immediately converted into triiodide ions in the presence of iodide ions ($I_2 + I^- \rightarrow I^-_3$) exhibiting absorption maxima at 290 and 360 nm [29]. MA and NA as a drugs possesse –COOH group in their moiety and hence undergoes a similar reaction with iodide-iodate mixture resulting in the evolution of iodine. The librated iodine immediately reacts with potassium iodide to give triiodate ions showing absorption maxima at 298 and 352 nm. The confirmatory test for the presence of iodine in the final solution of the drugs were established by the blue color, which appears on addition of starch solution [30].

c) Method (3)

The third procedure depend upon reaction of MS and SS with iodine in the presence of KI to give brown color measure at 496nm, fig (3) as follow:

Drug + KI + $I_2 \rightarrow$ oxidized drug + KI_3

Optimization of the reaction conditions

Preliminary experiments were performed to determine the optimum conditions of the variables used in the estimation of drugs.

The effect of different solvent was also studied. Water was used to dissolve the drug since $KMnO_4$ oxidizes other solvents with the production of green manganate ions.

At room temperature, the reaction rate increases substantially as the color development increases. Therefore, room temperature was selected as the optimum temperature. Heating the solution was found to increase the rate of the reaction but MnO_2 was precipitate.

The reaction rate and maximum absorbance increases with time, and with increasing $KMnO_4$ concentration. It was found that 3-ml of 8mM of $KMnO_4$ solution and 1-ml of 0.5 M NaOH was adequate for the maximum absorbance for method (1).

The influence of the volume of 0.1 M KIO_3 and 0.15 M KI on the rate of reaction was investigated in different range. It was found that 2.5 ml of 0.1 M KIO_3 and 3.5 ml of 0.15 M KI were recommended for method (2).

Studying the effect of 0.1M iodine and 0.15 M KI concentrations revealed that maximum color intensity was attained using 0.5 ml and 2-ml of 0.1M iodine for MS and SS, respectively and 1.0 ml of 0.15 M KI for method (3).

The calibration graphs were linear over the concentration range of 2-20, 2-20, 1.5-15 and 2.5-25 (μg/ml) for MA, NA, MS and SS using $KMno_4$, respectively, while 4-40 and 2.5-30 (μg/ml) for MA and NA using KIO_3/KI, respectively, finally 10-70 and 5-50 (μg/ml) for MS and SS using I_2/KI, respectively. Regression analysis indicates linear relationships with negligible intercepts.

3.3. Kinetic study of the reactions

Under the optimized experimental conditions, the assay of each drug was performed in presence of excess concentration of $KMno_4$ and NaOH or KIO_3 and KI or I_2 and KI with respect to drug

concentration. Therefore, a pseudo zero order reaction condition was worked out with respect to the concentration of reagents. The kinetic plots, **(Figs. 1, 2, 3)** are all sigmoid in nature and therefore, the initial rate of reaction was obtained by measuring the slope (tan α = dA /dt) of the initial tangent to the absorbance-time curves at different concentrations of the drug. The order with respect to drug was evaluated by plotting the logarithm of the initial rate of reaction vs logarithm of the molar concentration of drug and was found to be one.

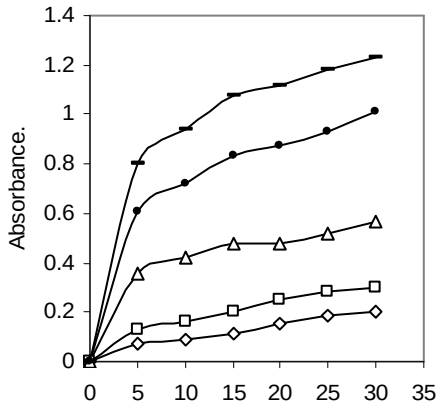


Fig (1): Absorbance versus time graphs for the reaction betw een MA(2-20 ug/ml) and $KMNO_4$.

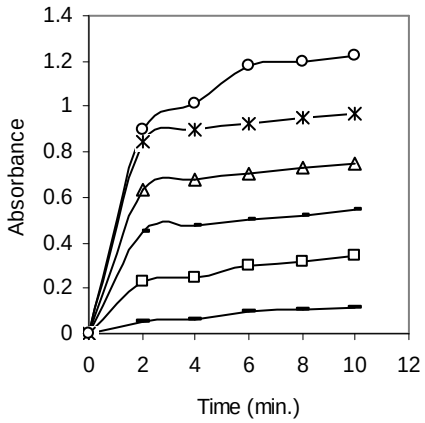


Fig. (2): Absorbance versus time graphs for reaction betw een MA (5-40ug/ ml) and periodate

The initial rate of reaction would follow a pseudo first order and obeyed the following rate equation:

$V = K\,[C]^{n}$ (9)

Where *V* is the rate of the oxidation reaction and *K* is the conditional rate constant, *[C]* is the molar concentration of drugs and n is the order of reaction. Taking logarithms of rates and concentrations, therefore:

$\text{Log } V = \text{Log } \Delta A/\Delta t = \log K + n \text{ Log } [C]$ (10)

The rate of the reaction (ΔA/Δt) may be estimate by the variable time method measurement[31], where *A* is the absorbance and *t* is the time in seconds.

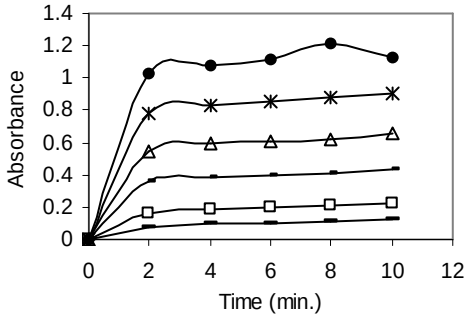


Fig. (3): Absorbance versus time graphs for reaction betw een MS (10-70 ug/ml) and iodine

Regression of log *V* versus log [C] gave the regression equations:
Log rate = 0.8011 log C + 0.0928 (R^2=0.9946) for MA-$KMno_4$

Log rate = 0.9401 log C + 0.4267 (R^2=0.9992) for NA-$KMno_4$
Log rate = 0.8696 log C + 0.37 (R^2=0.9994) for MS-$KMno_4$
Log rate = 0.9645 log C + 0.9606 (R^2=0.9996) for SS-$KMno_4$

Hence K = 1.238, 2.671, 2.344 and 9.132 Sec $^{-1}$ for MA, NA, MS and SS and the reaction is pseudo first order (n ≈ 1) with respect to MA, NA, MS and SS concentration, respectively.
Log rate = 1.0094 log C + 1.044 (R^2=0.9994) for MA-KIO_3
Log rate = 0.8505 log C + 0.6589 (R^2=0.9916) for NA-KIO_3
Log rate = 00.9558 log C+ 0.4458 (R^2=0.9995) for MS-I_2
Log rate = 00.966 log C + 1.0303 (R^2=0.9987) for SS-I_2

Hence K = 11.066, 4.559, 2.791 and 10.723 Sec $^{-1}$ for MA, NA, MS and SS and the reaction is pseudo first order (n ≈ 1) with respect to MA, NA, MS and SS concentration, respectively.

Evaluation of the kinetic methods

The quantitative of MA, NA, MS and SS under the optimized experimental conditions outlined above would results in a pseudo-first order reaction with respect to the drugs concentration and the rate equation as follows:

Rate = K [drug] (11)

Where K is the pseudo-first order constant

Several experiments can be carried out to obtained drug concentration from the rate data according to equation (11) such as: fixed time method, rate constant method and fixed absorbance method [32, 33]. fixed time method was tried as follow:

Table (1): Calibration equations at different fixed time for MA and NA (2-20µg/ml)at room temperature at 610 nm.

Time (min.)	Regression equation for MA	R^2	Regression equation for NA	R^2
5	0.0398 C -0.0028	0.9914	0.0376 C - 0.022	0.9925
10	0.0464 C +0.0032	0.9935	0.0409 C - 0.0157	0.9936
15	0.0531 C +0.0092	0.9948	0.0449 C - 0.0203	0.9968
20	0.0532 C +0.0415	0.9988	0.0453 C + 0.0025	0.999
25	0.0548 C +0.0707	0.9991	0.0463 C +0.0037	0.999
30	0.0575 C +0.0874	0.9992	0.0473 C +0.0119	0.9992
35	0.0572 C +0.0744	0.9991	0.0472 C +0.0013	0.998

Table (2): Calibration equations at different fixed time for MS (1.5-15 µg/ml) and SS (2.5-25 µg/ml) at room temperature at 610 nm.

Time (min.)	Regression equation for MS	R^2	Regression equation for SS	R^2
5	0.0671 C - 0.0193	0.9875	0.0397 C + 0.0047	0.9292
10	0.0716 C - 0.0082	0.9954	0.0435C + 0.0096	0.9986
15	0.0743 C + 0.0077	0.998	0.0447 C+ 0.0148	0.9975
20	0.0744 C + 0.0309	0.9987	0.0464 C + 0.0114	0.997
25	0.0746 C + 0.0518	0.9994	0.0486 C + 0.0107	0.9993
30	0.0717 C + 0.0542	0.9993	0.0467 C + 0.011	0.9977

Fixed-time method

Reaction rates were determined for different concentrations of drugs at a preselected fixed-time, which was accurately determined, the absorbance versus initial concentration of drugs were

established at fixed times of 5, 10, 15, 20, 25, 30 and 35min. for MA and NA, while 5, 10, 15, 20,25 and 30 min for or MS and SS for method (1) with the regression equations assembled in **tables (1, 2).**

The absorbance versus initial concentration of drugs were established at fixed times of 2, 4, 6, 8, 10 and 12min. for MA, NA using method (2) also for MS and SS using method (3) with the regression equations assembled in **tables (3, 4).**

Table (3): Calibration equations at different fixed time for MA (5-40 µg/ml) and NA (2.5-30 µg/ml) at room temperature at 532nm.

Time (min.)	Regression equation for MA	R^2	Regression equation for NA	R^2
2	0.0249 C -0.0413	0.9982	0.0374 C +0.0107	0.9983
4	0.025 C -0.0305	0.9987	0.0378 C - 0.014	0.9984
6	0.025 C - 0.0196	0.9991	0.0381 C - 0.022	0.999
8	0.0251 C – 0.097	0.9992	0.0382 C + 0.0334	0.999
10	0.0255 C + 0.0052	0.9993	0.0384 C +0.0437	0.9992
12	0.0252 C +0.0068	0.9991	0.03284 C +0.0295	0.999

Table (4): Calibration equations at different fixed time for MS (10-70 µg/ml) and SS (5-50 µg/ml) at room temperature at 496nm.

Time (min.)	Regression equation for MS	R^2	Regression equation for SS	R^2
2	0.0142 C - 0.0026	0.9939	0.0209 C - 0.0469	0.9962
4	0.0l43 C - 0.012	0.9967	0.0218 C - 0.034	0.997
6	0.0144 C + 0.02	0.9967	0.0221 C - 0.0241	0.9977
8	0.0147 C + 0.0147	0.999	0.0222 C - 0.0145	0.9989
10	0.0150 C – 0.015	0.9992	0.0224 C - 0.0011	0.999
12	0.0143 C - 0.0326	0.9953	0.0223 C - 0.0179	0.9965

It is clear that the slope increase by time and the most acceptable values of the correlation coefficient (R^2) and the intercept were obtained for a fixed time of 30 min. for MA and NA and 25 min. for MS and SS using method (1), while 10min. for MA and NA using method (2), also 10 min. for MS and SS using method (3) which therefore chosen as the most suitable time interval for measurement.

Application

Determination of MA, NA,MS and SS in bulk using the proposed methods.

Aliquots of each prepared working standard solutions of MA, NA, MS and SS equivalent to 25 – 200.00 µg were transferred into a series of 10-ml volumetric flasks. The same procedure mentioned under "General procedure and linearity" for method (1) was repeated. The recovered concentrations of the four drugs were calculated using the regression equations (1-4).

Aliquots of prepared working standard solutions of MA or NA equivalent to 50.00 – 400µg were transferred into a series of 10-ml volumetric flasks. The same procedure mentioned under "General procedure and linearity" for method (2)was repeated. The recovered concentrations of MA and NA were calculated using the regression equations (5, 6).

Aliquots of prepared working standard solutions of MS or SS equivalent to 100-350µg were transferred into a series of 10-ml volumetric flasks. The same procedure mentioned under "General procedure and linearity" for method (3) was repeated. The recovered concentrations of MS and SS were calculated using the regression equations (7, 8).

The results in **table (5)** shows that the mean recoveries and standard deviations were 99.85 ± 0.70, 99.74± 0.63, 99.84 ± 0.36 and 100.04 ± 0.61 for MA, NA, MS and SS, respectively, using method (1**)** and 100.08 ± 0.61 and 99.95± 0.42 for MA and NA, respectively using method(2) while 100.02 ± 0.60 and 99.15 ± 0.64 for MS and SS, respectively using method (3).

Determination of MA, NA,MS and SS in their pharmaceutical formulations using the proposed methods.

Accurately different aliquots of the prepared pharmaceutical dosage forms solutions were transferred into a series of 10-ml volumetric flasks and the volumes were completed with the appropriate solvent. The procedures mentioned under "General procedure and linearity " were repeated.

The same experiments were repeated applying the standard addition technique and the recovered concentrations of labeled and added amount of both drugs were calculated using the above regression equations (1-8).

Table (5): Determination of mefenamic acid, niflumic acid, mesalazine and sulfasalazine using the three proposed kinetic methods.

Item	MA		NA		MS		SS	
Recovery % ± SD of:	method (1)	method (2)	method (1)	method (2)	method (1)	method (3)	method (1)	method (3)
-in bulk powder	99.85 ± 0.70	100.08 ± 0.61	99.74± 0.63	99.95± 0.42	99.84 ± 0.36	100.02 ± 0.60	100.04 ± 0.61	99.15 ± 0.64
-Dosage form	100.40 ± 0.41	100.16±0. 44	99.93 ± 0.5	100.06 ± 0.53	100.20 ± 0.54	99.92 ± 0.26	99.75 ± 0.59	99.79 ± 0.59
-Added authentic	99.64 ± 0.64	100.61 ± 0.37	100.51± 0.46	100.23± 0.43	100.06 ± 0.72	99.97 ± 0.46	100.07 ± 0.41	99.60± 0.49

Table (6): Statistical analysis for the determination of MA, NA, MS and SS using the three proposed methods compared with official or reported methods.

		Proposed methods				Official or reported methods	
Formulations		Recovery %	RSD %	t-value	F-value	Recovery %	RSD %
Ponstan capsules (500-mg-MA)	$KMno_4$ method	100.40	0.41	1.44	2.27	99.92	0.62
	KIO_3 method	100.16	0.44	0.71	1.99		
Niflumu cream (2.5%NA)	$KMno_4$ method	99.93	0.50	0.27	1.74	99.83	0.66
	KIO_3 method	100.06	0.53	0.61	1.55		
Salazin capsules (500-mg-MS)	$KMno_4$ method	99.79	0.59	1.64	1.18	100.35	0.49
	I_2 method	99.92	0.26	1.73	3.55		
Salazo-sulfa pyrin tablets(500 mg-SS)	$KMno_4$ method	99.77	0.59	1.37	2.06	100.21	0.41
	I_2 method	99.69	0.56	1.68	1.87		

Theoretical t-value (v = 8) and F-value (v = 4,4) at 95% confidence level are 2.306 and 6.39, respectively.

The mean percentage recoveries of the labeled amount were 100.40 ± 0.41, 99.93 ± 0.50, 100.20 ± 0.54 and 99.75 ± 0.59 for MA, NA, MS and SS, respectively, using method (1**)** and 100.16 ±

0.44 and 100.06 ± 0.53 for MA, NA using method (2), while 99.92 ± 0.26 and 99.79 ± 0.59 for MS and SS using method (3), **table (5).**

The mean percentage recoveries of the added amount were 99.64 ± 0.64, 100.51± 0.46, 100.06 ± 0.72 and 100.07 ± 0.41 for MA, NA, MS and SS, respectively, using method (1**),** and 100.61 ± 0.37 and 100.23± 0.43 for MA, NA using method (2), while 99.97 ± 0.46 and 99.60± 0.49 for MS and SS using method (3), **table (5).**

The applicability of the proposed methods for the determination of four drugs has been tested on commercially available pharmaceutical formulations. The results of the proposed methods were compared with those obtained by the official methods for MA[34], MS[34], SS [35] and reported method for NA [36] using point hypothesis test. The student t- and F- values **(table 6)** at 95% confidence level did not exceed the tabulated t- and F-value, confirming no significant difference between the performance of the proposed methods and the official methods.

CONCLUSION

The data given above reveal that the suggested methods are simple, accurate, sensitive with good precision and accuracy and suitable for analysis of the cited drugs with low cost and available reagents also with simple equipements and simple procedures with not consuming time. The determination can be done for each drug in pure form and in their pharmaceutical preparation without interference from any excipients.

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