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Spectrophotometric Estimation of Drugs Using Potassium Permanganate and Saffranin-O Dye Couple

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Abstract: *Simple, accurate and precise UV- Visible spectrophotometric methods have been developed for the estimation of five drugs viz., Gemifloxacin mesylate(GEM),Moxifloxacin hydrochloride (MOX), Olmesartan medoxomil (OLM), Sumatriptan succinate(SUM), Trimetazidine dihydrochloride(TMZ). The method is based on the oxidation of drugs with acidic Potassium permanganate (excess), and subsequent estimation of unreacted Potassium permanganate ($KMnO_4$) by using Saffranin – O (S-O) as an analytical reagent. The proposed methods were found to be successful for the estimation of these drugs in bulk and its pharmaceutical formulations. The results of analysis have been validated statistically for linearity, accuracy, precession, LOD, LOQ, robustness and ruggedness.*

Keywords: *Gemifloxacin mesylate(GEM),Moxifloxacin hydrochloride (MOX), Olmesartan medoxomil (OLM), Sumatriptan succinate(SUM), Trimetazidine dihydrochloride(TMZ), Potassium permanganate – Saffranin – O, UV-Visible spectrophotometry and validation.*

I. Introduction

1.1.Gemifloxacin (GEM),(Fig.1a):

It is chemically known as 7-[(4Z)-3-(Aminomethyl)-4-methoxyimino-pyrrolidin-1- yl]-1-cyclopropyl-6-fluoro-4-oxo- 1, 8-naphthyridine-3-carboxylic acid. It is used to treat a variety of bacterial infections [1]. This medication belongs to a class of drugs called quinolone antibiotics. Because of its physiological significance the drug has been quantitatively analyzed by different methods. A few analytical methods like HPLC [2-5], Spectrophotometry [6, 7], Spectrofluorimetry [8, 9] , LC-MS [10], and Chemiluminisence method [11] developed for the estimation of GEM are mention worthy.

1.2.Moxifloxacin (MOX),(Fig.1b):

It is chemically known as 1-cyclopropyl-7-[(1S, 6S)-2,8-diazabicyclo [4.3.0]non-8- yl]-6-fluoro-8-methoxy-4-oxo-quinoline-3-carboxylic acid. It is an advanced-generation, 8-methoxyquinolone derivate of fluoroquinolone antibacterial agent that is synthetic. It was discovered in 1999. Moxifloxacin is a broad-spectrum antibiotic [12] that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerases, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication. Various methods cited in literature for its determinations involve, high performance liquid chromatography [13-15], liquid chromatography [16-18], voltammetry [19,20], spectrophotometry [21,22]. However, most of these methods involve time-consuming procedures, derivatization and/ or sophisticated instruments. Due to the fact that MOX is a compound of great pharmacological and analytical importance, in recent years, there has been an increased interest to develop accurate analytical methods which are valid for quantification of MOX in biological and pharmaceutical samples.

1.3.Olmesartan medoxomil (OLM),(Fig.1c):

It is chemically known as 2H-1,3-dioxol-4-yl) methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2H-1,2,3.4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-imidazole-5-Carboxylate.OLM blocks the vasoconstrictor effects of angiotensin 2 by selectively blocking the binding ofangiotensin 2 to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of thepathways for angiotensin 2 synthesis. Liquid chromatography [23,24], UV spectrophotometry [25] and Capillaryelectrophoresis [26,27] are reported in the literature. Combination methods are reported for determination of OLMwith Ramipril [28] and HPTLC [29] method for Hydrochloro thiazide and OLM.

1.4.Sumatriptan succinate (SUM), (Fig.1d):

It is most frequently prescribed anti-migraine drug of triptan class. It is chemically known as 3-[2-(Dimethylamino) ethyl]-N-methyl-1H indole-5-methane sulphonamide succinate (1:1) base. SUM is a specific and selective 5-hydroxy tryptamine receptor [5HT1D] agonist with no effect on the other 5HT receptor [5HT2-5HT7] sub types. It is widely used for acute relief of migraine attack. SUM undergoes an extensive

biotransformation mainly through Mono amino oxidase-A. Several analytical techniques like spectrophotometric methods [30.31], Extractive spectrophotometry [32,33], HPLC [34,35] and voltammetry [36] have been reported for SUM in combination with other drugs.

1.5.Trimetazidine di hydrochloride(TMZ)),(Fig.1e):

It is chemically known as 1-[(2, 3, 4- trimethoxyphenyl)methyl]piperazine dihydrochloride.It is a clinically effective antianginal agent that has been used in the prophylaxis and management of angina pectoris, and in ischemia of neurosensorial tissues as in Meniere's disease. Trimetazidine exhibits some cytoprotective effects on myocardial energy metabolism and exerts an anti angina effect in the absence of significant hemodynamic effects. Trimetazidine dihydrochloride has been determined in pharmaceutical formulations and biological fluids by high performance thin-layer chromatography [37], liquid chromatography [38-40].

Therefore this method was made to develop a simple spectrophotometric method for the estimation of above mentioned drugs in pharmaceutical formulation.

II. Methods And Materials:

The pharmaceutical grade drugs were supplied by Arabindo pharmaceuticals and Hetero drugs Pvt. Ltd, Hyderabad. Saffranin-O, potassium permanganate (KMnO4) were purchased from S.d fine chem. Pvt. Ltd, Mumbai,India. Sulphuric acid (H2SO4) is purchased from SRL chemicals, Mumbai, India. Whatman filter paper no.42 was used for filtration purpose. All the reagents used were of analytical-reagent grade and triple distilled water was used throughout the investigation.Tablets were purchased from the local market.All absorbance measurements were recorded on Shimadzu 140 double beam spectrophotometer as well as on Thermo Nicolet 100 & Elico 159 UV-Visible single beam spectrophotometers using matched pair of Quartz cells of 10mm path l0mm path length.

2.1. Preparation of standard stock solutions:

KMnO4 (7.6x10-2M): Stock solution was prepared by dissolving 0.1209gm of KMnO4 in 100mL standard flask with double distilled water. Stock solution was further diluted to the concentration of 161.5µg mL.

Saffranin-O (1x10-3M): Stock solution was prepared by dissolving 35mg of Saffranin-O in 100mL standard flask with double distilled water. Stock solution was further diluted to the concentration of 140 µg mL-1.

Standard stock solutions of drugs were prepared by dissolving accurately weighed 40mg drug in separate 100 mL flasks. The stock solutions of GEM,MOX,OLM,SUM and TMZ were diluted with water to obtain 30µg mL-1, 24µg mL-1, 15µg mL-1, 16µg mL-1 and 16µg mL-1 respectively.

H2SO4: concentrared sulphuric acid (H2SO4) diluted appropriately with triple distilled water to get 0.2M acid solution.

2.2. Construction of calibration curve: Aliquots of pure drug solution (1.0-7.0mL) were transferred into a series of 10mL calibrated flasks. To each flask 1mL of 0.2M H2SO4 acid was added followed by 1.0mL of KMnO4 solution. The flasks are stoppered and contents were mixed and the flasks were heated for 10 min.These were cooled and finally, 1.0 mL of Saffranin-O solution was added to each flask and the volume was adjusted to the mark with water and mixed well. The absorbance of each solution was measured at 520 nm after 5 min.

A standard graph was prepared by plotting the absorbance versus the concentration of drugs. The concentration of the unknown were read from the calibration graph or computed from the regression equation derived using Beer's law data. Calibration curve for each drug was drawn in (Fig.2).

2.3. Analysis of commercial dosage forms: A quantity of finely ground tablets powder equivalent to10 mg of drug GEM (Gemistar-320mg), MOX(Moxif-400mg), OLM (Benicar-20 mg), SUM(Sumitrex -25 mg) and TMZ (Cardimax-SR-60mg) were accurately weighed and taken in 60 mL distilled water in 100 mL volumetric flask and left for 10 min for complete dispersion and then filtered through Whatman No.42 filter paper. The residue was washed well with distilled water for complete recovery of the drug. First 10 mL portion of the filtrate was rejected and a convenient aliquot of filtrate was further diluted for the analysis within the limits of Beer's law.

Drug+known excess of KMnO4 Reaction product of the drug+Unreacted KMnO4

Unreacted KMnO4 + Fixed amount of S-O Absorbance of S-O measured at 520nm.

2.4. Method validation: The proposed methods were validated according to guidelines of international conference on Harmonization (ICH). Under the described experimental conditions,standard experimental conditions, standard calibration curves for the studied drugs were constructed by plotting absorbance versus

concentration. Conformity with Beer's law was evident in the concentration range cited in Table-2.The linear regression equations, molar absorptivity, Sandell's sensitivity, limits of detection (LOD) and limits of quantification (LOQ) were listed in the same Table. Standard deviation, relative standard deviation, variance and standard error were calculated.

The accuracy of the method was established by analyzing the pure drug at three levels (within working limits) and the precision was ascertained by calculating the relative standarddeviation(RSD) of six replicate determinations on the same solution containing the drug at three levels in Table-3. The analytical results for accuracy and precision showed that the proposed methods have good repeatability and reproducibility.

The percentage recoveries of the pure drugs using the proposed methods compared with that given by reference methods are illustrated in Table-4. The validity of the proposed method in literature is evaluated by statastical analysis between the results obtained and that of reference methods. student's t-test and variance ratio F-test are chosen for the comparision of the results.

Values are within the permissible range reported in literature.

III. Results And Discussion

The calibration curves for GEM, MOX,OLM,SUM and TMZ, over a concentration range of 3.0-21.0 µg/mL, 2.4-16.8 µg/mL, 3.0-21.0 µg/mL, 3.2-22.4 µg/mL and 1.6-11.2 µg/mL respectively, were plotted and molar absorptivity for drugs were calculated at the wavelength of 520nm. The regression characteristics were reported in Table-2.The result of assay is reported in Table-3.The accuracy of the proposed method was evaluated by percentage recovery studies of the drugs.

The %RSD was less than 2% , showing high degree of precision of the proposed method. The results of the method lie within the prescribed limit, showing that method is free from interference from excipients.

IV. Conclusion

The obtained results from the method for the determination of mentioned drugs indicates that method is simple, accurate and precise. The method is economical compared to other sophisticated analytical instruments.Hence can be used for routine analysis of commercially available formulations.The method is suitable for the determination of these drugs in tablet formulation without interference from commonly used excipients.The solvents used for the method are inexpensive and simple to prepare, and could be used in a quality control laboratory for routine drug analysis.

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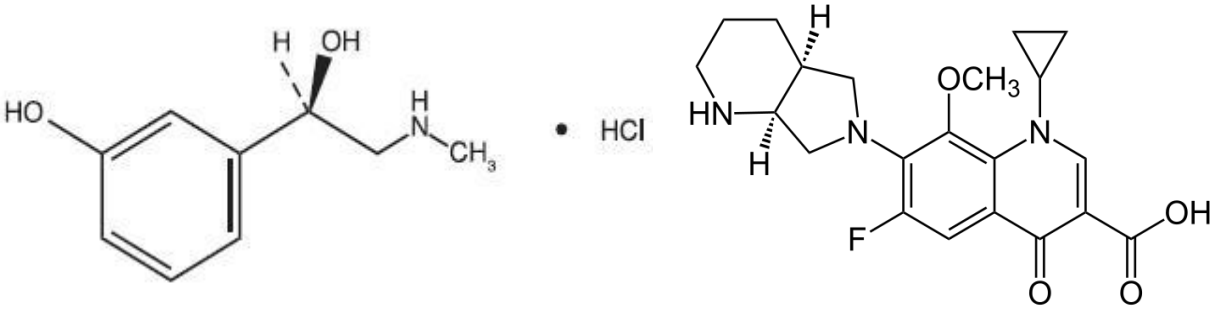
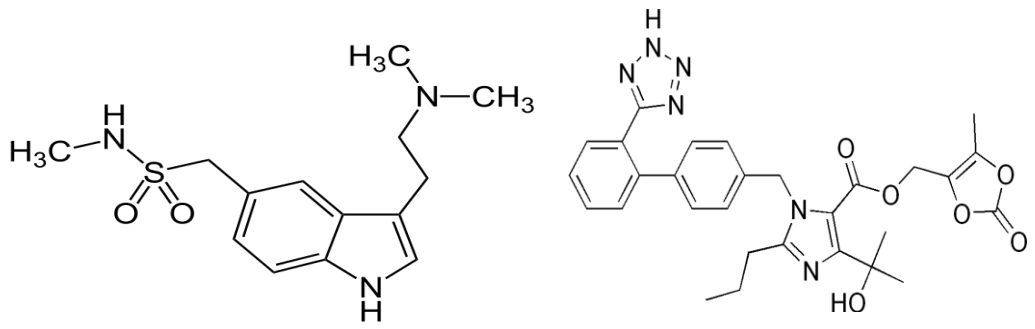
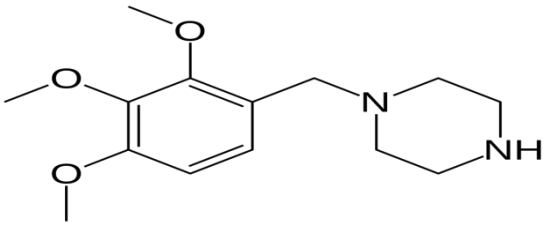
Fig. 1:Structures of drugs



Gemifloxacin (GEM),(Fig.1a): **Moxifloxacin (MOX),(Fig.1b)**



Olmesartan medoxomil (OLM),[Fig. 1c]: **Sumatriptan succinate (SUM), [Fig.1d]:**



Trimetazidine di hydrochloride(TMZ)),[Fig.1e]:

Fig2:Calibration curves:

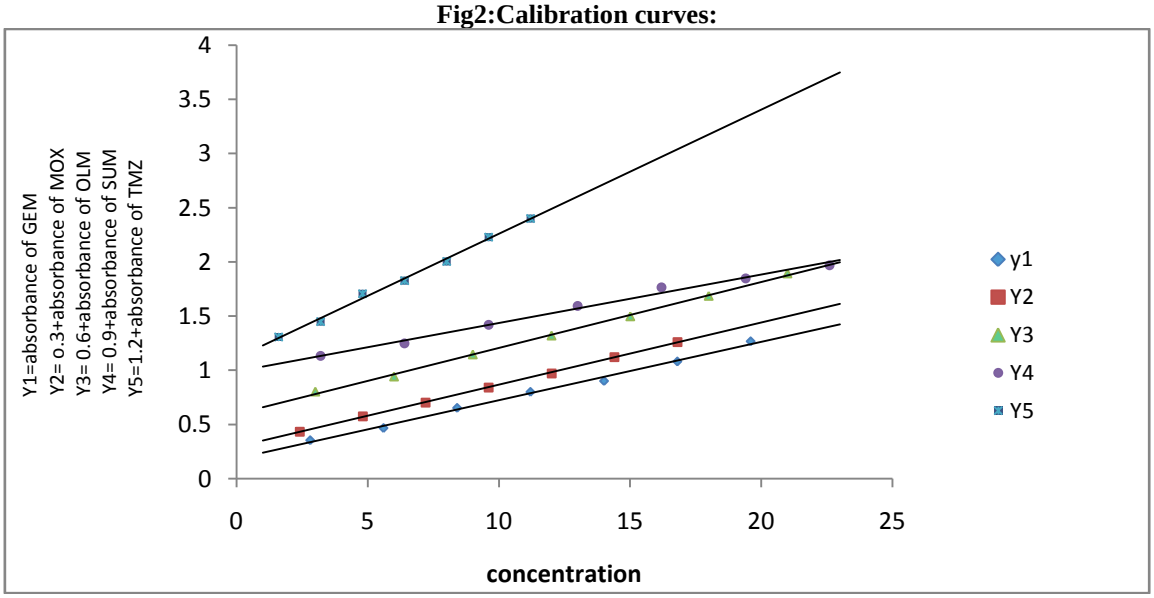


Table-1:Comparision of various techniques.

Drug	Method	Sensitivity	Recovery
GEM	1)UV-Spectrophotometry 2)LC-DAD method 3)Spectrofluorimetric method 4)Potentiometry	1.5-11.25 µg mL^{-1} 0.25-20 µg mL^{-1} 10-1000 ng mL^{-1} 10^{-7}-10^{-2} ML^{-1}	99.2% 99.9 % 97.6% 99.4%
MOX	1) UV-Spectrophotometry 2)HPLC	1.5-11.25 µg mL^{-1} 20-80 µg mL^{-1}	98.66% 100.7%
OLM	1)UV-spectrophotometry 2)RP-HPLC 3)Capillary zone electrophoresis 4)HPLC	5-50 µg mL^{-1} 32-160 µg mL^{-1} 2.0-50 µg mL^{-1} 80-320 µg mL^{-1}	99.75-100.43% 99.42% 99.09%
SUM	1)HPLC 2)HPTLC 3)UV spectrophotometry 4)Ion association method 5)Visible spectrophotometry	10-100 µg/ml 100-1000 µg/ml 0.5-3.5 µg/ml 2-10 µg/ml 4-20 µg/ml	99.79% 99.94-100.3% 99.30% 99.304%
TMZ	1)Spectrophotometry 2)Spectrofluoimetry	0.4-2.56 µg mL^{-1} 4-20 µg mL^{-1}	98-99.2% 99.7%

Table-2: Analytical and regression parameters of spectrophotometric methods.

Parameters	**GEM**	**MOX**	**OLM**	**SUM**	**TMZ**
λmax nm	520	520	520	520	520
Beer's law limit(µg mL^{-1})	3.0-21.0	2.4-16.8	3.0-21.0	3.2-22.4	1.6-11.2
Sandell sensivity*(µg/cm^2)	0.0188	0.0175	0.016	0.022	0.0069
Limit of detection(µg mL^{-1})	1.369	1.53	1.99	0.05	0.068
Limit of quantification(µg mL^{-1})	4.15	4.66	6.05	0.15	0.20
Regression equation**					
Intercept(a)	-0.187	-0.003	-0.002	0.09	-0.086

Slope(b)	0.053	0.057	0.060	0.044	0.144
Correlation coefficient(r)	0.994	0.999	0.998	0.991	0.995
Standard deviation of intercept(S_a)	0.022	0.0266	0.0363	0.0007	0.003
Variance(S_a^2)	$4.84x10^{-4}$	$6.76x10^{-4}$	$10.496x10^{-4}$	$0.49x10^{-6}$	$0.09x10^{-4}$
Standard deviation of slope(S_b)	0.00141	0.0005	0.0648	0.00141	0.002

*Limit of determination as the weight in µg per mL of solution, which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and path length of 1 cm. Y** = a+bX, where Y is the absorbance and X concentration of drugs in µg per ml.
mL

Table 3: Determination of accuracy and precision of the methods on pure drug sample.

Drug	Taken(µg mL^{-1})	Found(µg mL^{-1})	% error	%Recovery	%RSD	Proposed method mean±S.D
GEM	1.5 4.0 5.5	1.51 4.02 5.49	0.66 0.5 0.18	100.66 100.5 99.8	0.448	100.32±0.457
MOX	1.5 3.0 4.5	1.49 3.01 4.49	0.66 0.33 0.22	99.33 99.99 99.99	0.380	99.77±0.381
OLM	2.0 4.0 6.0	2.01 4.04 5.9	0.5 1.0 1.6	100.5 101 98.3	1.439	99.93±1.436
SUM	3.0 5.0 6.5	3.01 4.9 6.6	0.33 2.0 1.53	100.3 98 101.5	1.778	99.93±1.778
TMZ	1.0 4.0 7.0	1.02 3.98 7.01	2.0 0.5 0.14	102 99.5 101	1.248	100.83±1.25

Table-4 :Results of assay of tablets by the proposed methods and statistical evaluation and recovery experiments by standard addition method.

Tablet	Drug taken (µg mL^{-1})	Drug found (µg mL^{-1})	Error (%)	Recovery (%)	RSD (%)	Reference Method mean±SD	Proposed Method mean±SD	t-test	F-test
Gemistar (GEM)	4.5 7.5 10.5	4.49 7.49 10.48	0.222 0.133 0.190	99.77% 99.86% 99.80%	0.080	99.49±0.43	99.78±0.080	1.9	0.034
Moxif (MOX)	3.6 8.4 10.8	3.59 8.39 10.81	0.277 0.119 0.092	99.72% 99.88% 100.09%	0.185	98.86±0.2	99.89±0.185	0.006	0.85
Benicar (OLM)	4.5 7.5 10.5	4.52 7.49 10.49	0.444 0.133 0.095	100.4% 99.86% 99.90%	0.299	100.1±0.19	100.05±0.300	0.785	2.49
Sumitrex (SUM)	4.8 7.0 10.2	4.79 7.01 10.18	0.208 0.142 0.196	99.79% 100.1% 99.80%	0.176	99.3±0.314	99.89±0.176	1.97	0.316
Cardimax-SR(TMZ)	2.4 5.6 8.0	2.41 5.61 7.99	0.416 0.178 0.124	100.41% 100.17% 99.87%	0.264	97.2±1.4	100.14±0.265	0.630	0.003

*Average of six replicate determinations.

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