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DETERMINATION OF PHARMACEUTICAL COMPOUNDS VIA N-BROMOSUCCINIMIDE AND RHODAMINE-B COUPLED SPECTROPHOTOMETRY

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Abstract
Simple, sensitive and selective methods are developed for the spectrophotometric determination of drugs, viz., Montelukast sodium, Prasugrel, Ondensetron, Rosuvastatin calcium, Amlodepine besylate based on their reactivity towards N- bromosuccinimide (NBS). The method involves the addition of excess NBS of known concentration in the presence of 1M HCl, reactants are allowed to react and the unreacted NBS is estimated by the measurement in the decrease in the absorbance of the Rhodamine-B dye (λ_{max} 557nm). This method has been applied for the determination of drugs in their pure form as well as in tablet formulations.

Keywords: Drugs, Quantification, NBS, Rhodamine-B, spectrophotometry, Validation

I. Introduction

1.1. Montelukast sodium

Montelukast sodium (MTK) is chemically (R-(E))- -(((1-(3-(2-(7-chloro-2-quinolinyl) ethenyl)phenyl)-3(2-(1-hydroxymethylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid, monosodium salt. [Fig. (a)]. Montelukast sodium primarily used for the treatment of asthma in children and adults. It is a potent selective inhibitor of leukotriene D4 (LTD4) at the cysteinyl leukotriene receptor cysLT1. Only a few methods viz, HPLC [1,2] and spectrofluorimetry[3],electrophoresis[4], UV-visiblespectrophotometry [5,6] LCMSI-MS[7] and spectrophotometry [8,9] appeared in the literature for the determination of MTK in bulk and pharmaceutical formulations.

Arnlodipine besylate (ADB) is a calcium channel blocking agent with vasodilators activity similar to that of nifedipine. It is mainly used for its antiarrhythmic, antianginal and antihypertensive activity (Heynen,). It is chemically known as 2-[(2-aminoethoxy) methyl]-4-(2-chloroprienyl)-1,4-dihydro-6-methyl3,5pyridinedicarboxylicacid,3ethyl,5methylesterbesylate. B.P describes a reversed phase high performance liquid chromatographic (RP-HPLC) [23] method for the determination of ADB in bulk and pharmaceutical formulations [Fig. 1(e)]. The literature survey reveals numbers of methods are reported for the quantitative determination of ADB alone or in combination with other anti-hypertensive drugs including spectroscopic and chromatographic methods [24, 25, and 26]. Therefore an attempt was made

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to develop a simple spectrophotometric method for the estimation of above mentioned drugs in pharmaceutical formulations.

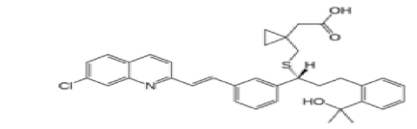

Figure-1(a) Montelukast sodium

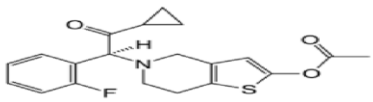

Figure-1(b) Prasugrel

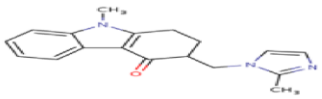

Figure-1 (c) Ondansetron

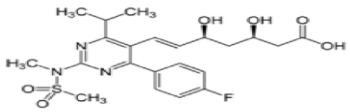

Figure-1 (d) Rosuvastatin Calcium

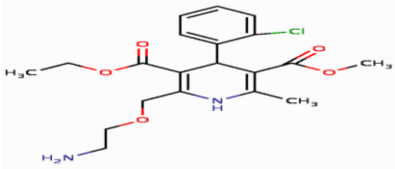

Figure-1 (e) Amlodepine besylate

II. Experimental

2.1. Reagents and Standards

The pharmaceutical grade drugs were supplied by Arabindo pharmaceuticals and Hetero drugs Pvt Ltd Hyderabad. Rhodamine-B, NBS, and HCl were purchased from S.D.Fine chem Pvt. Ltd., Mumbai, India. Whatman filter paper no.42 was used for filtration purpose. All the reagents used were of AR grade and double distilled water was used throughout the investigation. Tablets were purchased from the local market.

2.2. Instrumentation and Optical Characteristics

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 length. A high precision Analytical balance was used for weighing the reagents.

2.3. Preparation of standard stock solution

NBS (0.0099M) stock solution was prepared by dissolving 0.1779gm of sample in 100ml standard flask with double distilled water. Rhodamine-B (0.001M) solution was prepared by dissolving 50mg in 100ml standard flask with double distilled water. Stock solutions of both NBS and Rhodamine-B were further diluted to the concentrations of 70 $\mu g\ mL^{-1}$ and 50 $\mu g\ mL^{-1}$ respectively. Standard stock solutions of drugs were prepared by dissolving accurately weighed 40 mg drug to separate 100ml volumetric flasks. The stock solutions of MTK, PRL, OND, ROC and ADB were further diluted with the same solvent to obtain working concentrations. Concentrated HCl was diluted appropriately with double distilled water to get 1M acid solution.

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2.4. Assay procedure

Aliquots of pure drug solution (1 to 7 mL) were transferred into a series of 10 mL calibrated flask. To each flask, 1 mL of 1 m L^{-1} hydrochloric acid was added, followed by 1 mL of NBS solution (70 µg mL^{-1}). The contents were mixed and the flasks were set aside for 10 min under occasional shaking. Finally, 1 mL of Rhodamine- B solution (50 µg mL^{-1}) was added to each flask, diluted to the mark with water and the absorbance of solution was measured at 557 nm against a reagent blank after 10 min. The calibration curve was plotted by taking concentration (µg mL^{-1}) of the drugs in X-axis and absorbance in Y-axis.

2.5. Tablet analysis

Tablets of respective drug (MTK, PRL, OND, ROC, and ADB) were weighed and powdered. The average weight was calculated. The powder equivalent to 10mg were weighed accurately and made solution to 100ml with double distilled water to produce 100 µg mL^{-1} of each drug solution. The solutions were sonicated for 15min and filtered through whatmann filter paper No.42. The filtrate was further diluted to get working concentrations and absorbance was measured at 557 nm. The calibration curve was used to calculate the drug from tablets.

III. Validation

Validation is a process of establishing documented evidence, which provides a high degree of assurance that a specific activity will consistently produce a desired result or product meeting its predetermined specifications and quality characteristics. The method was validated for different parameters like Linearity, Accuracy and Precision.

3.1. Analytical characteristics

3.1.1. Linearity

The linearity of an analytical method is its ability to elicit test results that are directly or by a welldefined mathematical transformation proportional to the concentration of analyte in samples within a given range. The range of analytical method can be obtained from the linearity, precision and accuracy data. Results should be expressed in terms of correlation co-efficient.

3.1.2. Accuracy (%recovery)

Accuracy of an analysis is determined by systemic error involved. It is defined as closeness of agreement between the actual (true) value and analytical value and obtained by applying test method for a number of times. Accuracy may often be expressed as %Recovery by the assay of added amount of analyte. It is measure of the exactness of the analytical method.

3.1.3. Precision

The reproducibility of the proposed method was determined by performing tablet assay at different time intervals on same (intra-day precision) and on three different days (inter-day precision). Results of intraday precision are expressed in % RSD (Table-3).

3.2. Results and discussions

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The calibration curves for MTK, PRL, OND, ROC and ADB over a concentration range of 1.2-8.4µg mL^{-1}, 0.6-4.2µg mL^{-1}, 0.4-2.8µg mL^{-1}, 0.2-1.4µg mL^{-1} and 0.1-0.7µg mL^{-1} were plotted and molar absorptivity for drugs were calculated at the wavelength of 557nm. The regression characteristics are reported in Table-1. The result of assay is reported in Table-2. The percent recovery from commercial formulation was shown in table-3. The accuracy of the proposed method was evaluated by percentage recovery studies of the drugs. The %RSD was also less than 2%, for intra-day determinations 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 above mentioned drugs indicates that method is novel, 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 solvent used for the method are inexpensive and simple to prepare, and could be used in a quality control laboratory for routine drug analysis.

TABLE **1** Analytical and regression parameters of spectrophotometric method

Parameter	MTK	PRL	OND	ROC	ADB
λ max (nm)	557	557	557	557	557
Beer's Law Limits (µg mL^{-1})	1.2-8.4	0.6-4.2	0.4-2.8	0.2-1.4	0.1-0.7
Molar absorptivity, (L mol-1 cm-1)	$0.072x10^6$	$0.131x10^6$	$0.151x10^6$	$0.052x10^7$	$0.068x10^7$
Sandell sensitivity* (µg cm^{-2})	0.0059	0.0072	0.0062	0.0042	0.0069
LOD (µg mL^{-1})	0.836	1.714	1.294	0.386	0.747
LOQ (µg mL^{-1})	2.534	5.194	3.922	1.171	2.263
Regression Equation, Y**=a+bX					
Intercept, (A)	0.0804	0.1631	0.0949	0.1419	0.1487
Slope, (B)	0.1689	0.1386	0.1591	0.1187	0.144
Correlation Coefficient, (R)	0.9807	0.9227	0.9852	0.9931	0.9149

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Standard Deviation Of Intercept (Sa)	0.0428	0.0720	0.0624	0.0139	0.0326
Standard Deviation Of Slope (Sb)	0.011	0.0106	0.0145	0.0051	0.0073

*Limit of determination as the weight in µg / 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 mL^{-1}

TABLE 2 Determination of accuracy and precision of the methods on pure drug samples

Drug	Taken (µg mL^{-1})	Found (µg mL^{-1})	er (%)	Recovery (%)	RSD (%)	Proposed Method Mean ± SD
MTK	2.5 3.0 3.5	2.48 3.01 3.52	0.8 0.33 0.57	99.2 100.3 100.5	0.680	100 ± 0.680
PRL	1.0 3.0 4.0	1.0 2.98 3.98	0.00 0.66 0.5	100 99.33 99.5	0.349	99.61 ±0.348
OND	2.0 4.5 7.0	2.03 4.47 6.92	1.5 0.66 1.14	101.5 99.33 98.85	1.412	99.89 ±1.412
ROC	3.0 3.5 5.5	2.99 3.54 5.42	0.33 2.00 1.45	99.66 101.1 98.54	1.286	99.76 ±1.283
ADB	3.5 4.0 5.0	3.5 4.09 5.09	0.00 2.25 1.8	100 102.2 101.8	1.155	101.3 ±1.171

Table-3 Results of assay of tablets by proposed method and statistical evaluation

Tablets	Taken (µg mL^{-1})	Found (µg mL^{-1})	er (%)	Recovery (%)	RSD (%)	Reference method Mean ± SD	Proposed method mean ± SD	Student's t-test	F-test

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MTK (L-MONTUS)	2.5 3.0 3.5	2.52 3.06 3.46	0.8 2.0 1.14	99.2 102 98.8	1.743	4.98 ±0.62	100 ± 0.680	0.1296 (0.906)	1.202 (5.28)
PRL (PRASITA)	1.0 3.0 4.0	1.0 2.95 4.02	0.00 1.66 0.5	100 98.33 100.5	1.140	100.04 ±0.69	99.61 ±1.13	0.743 (1.476)	2.68 (4.107)
OND (ONDEM)	2.0 4.5 7.0	2.01 4.46 6.94	1.5 0.88 0.85	100.5 99.11 99.14	0.796	100.18 ±0.671	99.58 ±0.79	0.434 (1.943)	1.386 (3.05)
ROC (ROSUVAS)	3.0 3.5 5.5	3.01 3.44 5.45	0.33 1.71 0.90	100.3 98.28 99.09	1.024	99.75 ±1.057	99.22 ±1.01	1.112 (2.353)	1.095 (3.28)
ADB (STAMLO)	3.5 4.0 4.5	3.52 4.02 4.5	0.57 0.5 0.00	100.5 100.5 100	0.287	100.04 ±0.43	100.3 ±0.28	0.359 (0.978)	2.358 (5.39)

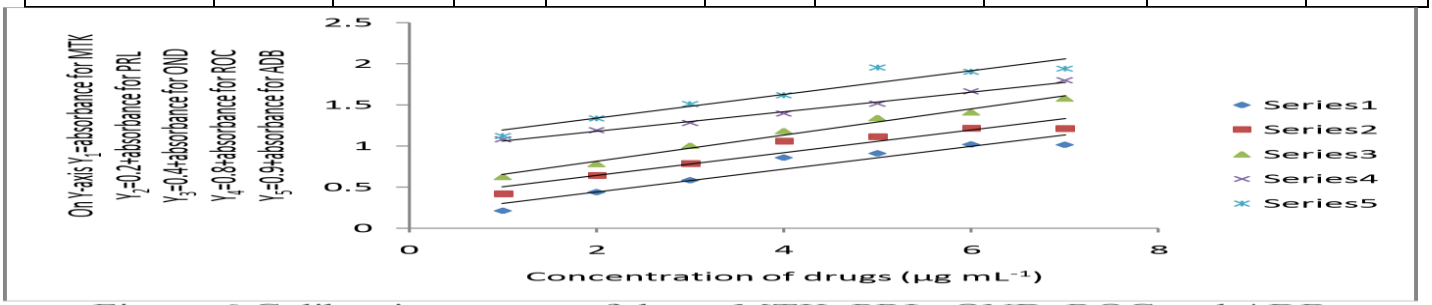

Figure-6 Calibration curves of drugs MTK, PRL, OND, ROC and ADB

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