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Research Article

DEVELOPMENT AND VALIDATION OF SPECTROPHOTOMETRIC METHODS FOR DETERMINATION OF LEUKOTRIENE RECEPTOR ANTAGONIST MONTELUKAST SODIUM IN BULK AND PHARMACEUTICAL FORMULATIONS

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ABSTRACT

Objective: Simple, sensitive, precise, reproducible, and validated visible spectrophotometric methods have been developed for the determination of leukotriene receptor antagonist drug, namely, montelukast (MNT) sodium in bulk and pharmaceutical preparations.

Methods: Three spectrophotometric methods are based on the formation of yellow-colored ion-pair complexes between MNT sodium and three dyes, bromocresol green, bromophenol blue, and methyl orange with absorption maxima at 420, 416, and 426 nm, respectively.

Results: The stoichiometric ratio of the formed ion-pair complexes was found to be 1:1 (drug:reagent) for all methods, as deduced by Job's method of continuous variation. Several parameters such as pH, buffer type and volume, reagent volume, sequence of addition, and effect of extracting solvent were optimized to achieve high sensitivity, stability, low blank reading, and reproducible results. Under the optimum conditions, linear relationships with good correlation coefficients (0.9993–0.9999) were found over the concentration ranges of 1.0–10, 1.0–12, and 1.0–16 µg/mL with a limit of detection of 0.30, 0.29, and 0.27 µg/mL for bromocresol green, bromophenol blue, and methyl orange methods, respectively.

Conclusion: The proposed methods were validated in accordance with ICH guidelines and successfully applied to the analysis of MNT sodium in pharmaceutical formulations. Statistical comparison of the results obtained by applying the proposed methods with those of the reference method revealed good agreement and proved that there was no significant difference in the accuracy and precision between the results.

Keywords: Montelukast sodium, Ion-pair complex, Spectrophotometry, Method validation, Pharmaceutical formulations.

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INTRODUCTION

Montelukast (MNT) sodium is chemically designated as [R-(E)]-1-[[[1-[3-[2-(7-chloro-2quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio] methyl]cyclopropane acetic acid, sodium salt (MNT) (Fig. 1) [1]. MNT is a leukotriene receptor antagonist used as an alternative to anti-inflammatory medications in the management and chronic treatment of asthma [2].

The literature survey revealed that few methods were described for the determination of MNT such as spectrophotometry [2-9], spectrofluorimetry [10], electrochemical [11], electrophoresis [12,13], and high-performance liquid chromatography [14-21]. Most of these reported methods are either not appropriately sensitive or tedious and utilized expensive instruments that are not available in most quality control laboratories.

Spectrophotometric methods represent the most convenient analytical technique in most pharmaceutical laboratories for industrial quality control due to it is easier, less expensive, less time consuming, and hence it is an important alternative to other analytical techniques with clear advantages in terms of cost of analysis. Extractive spectrophotometric procedures are popular for their sensitivity in the assay of drugs and, therefore, ion-pair extractive spectrophotometry has received considerable attention for the quantitative determination of many pharmaceutical compounds [22-24]. Table 1 described the reported spectrophotometric methods for the determination of MNT.

The aim of the present work is to develop simple, sensitive, accurate, precise, low-cost, and validated extractive spectrophotometric methods for the determination of MNT in bulk and pharmaceutical formulations. The proposed methods are based on the ability of MNT to form stable ion-pair complexes with bromocresol green (BCG), bromophenol blue (BPB), and methyl orange (MO). No interference was observed in the assay of MNT from common excipients in levels found in dosage forms. These methods are validated by statistical data.

METHODS

Instruments

All absorption spectra were made using Kontron Unikon 930 ultraviolet (-visible) spectrophotometer (German) with a scanning speed of 200 nm min-1 and a bandwidth of 2.0 nm, equipped with 10 mm matched quartz cells. An Adwa AD1000 pH-meter (Romania) equipped with a glass electrode was used for the measurement of pH-values.

Materials and reagents

All reagents, chemicals, and solvents used were of analytical or pharmaceutical grade and all solutions were prepared fresh daily.

Pure sample of MNT was kindly supplied by Delta Pharmaceutical Industries, Cairo, Egypt, with a purity of 99.70±0.52% by applying the reported method [2]. Montelair tablets, labeled to contain 5.0 mg MNT per tablet, product of Jedco Company, Cairo, Egypt, and Delmonkast tablets, labeled to contain 10 mg MNT per tablet, product of Delta Pharmaceutical Industries, Cairo, Egypt, were purchased from local pharmacies.

Table 1: Comparison between the reported spectrophotometric methods and the present method for the determination of montelukast

Method	Wavelength (nm)	Beer's law (μg/mL)	Molar absorptivity (L/mol/cm)	Reference
Bromothymol blue	410	5.0–25	5.72×10^3	[2]
Bromocresol purple	415	4.0–20	4.95×10^3	
$FeCl_3$/HCl	440	2.0–10	3.2841×10^4	[3]
Orcinol/Conc. HCl	420	4.0–20	2.8964×10^4	
Wool fast blue	585	50-250	1.9×10^3	[4]
Fe^{3+}/1, 10-phenanthroline	510	4.0–20	1.652×10^4	[5]
Fe^{3+}/MBTH	610	2.0–10	0.7176×10^4	
Fe^{3+}/2, 2'-Bipyridyl	430	4.0–20	1.672×10^4	
UV	344.30	5.0–25	-	[6]
Area under curve	342.93 nm-343.75 nm	5.0–25	-	
First-order derivative spectroscopy	347.91	5.0–25	-	
UV	283	3.0–45	-	[7]
UV	285	2.4–24	-	[8]
Bromocresol green	420	1.0–10	3.407×10^4	Proposed work
Bromophenol blue	416	1.0–12	4.95×10^4	
Methyl orange	426	1.0–16	2.90×10^4	

UV: Ultraviolet

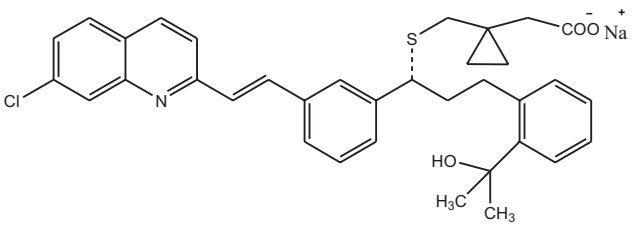


Fig. 1: The chemical structure of montelukast sodium

BCG, BPB, and MO (BDH Chemicals LTD, Poole, England) and used without further purification. Stock solutions (1.0×10^{-3} mol/L) of reagents were prepared by dissolving the appropriate weight of each dye in 5.0 mL of ethanol (96%, v/v) and diluted to 100 mL in a calibrated flask with bidistilled water. These solutions were kept in the refrigerator.

Series of buffer solutions of NaOAc–HCl (pH=1.99–4.92), NaOAc–AcOH (pH=3.4–5.6), and potassium hydrogen phthalate–HCl (pH=2.0–7.0) were prepared by following the standard methods [25]. The pH of each solution was adjusted to an appropriate value by the addition of 0.2 mol/l hydrochloric acid or sodium hydroxide with the help of the pH meter. Freshly prepared solutions were always employed. Chloroform, methylene chloride, and carbon tetrachloride were obtained from (BDH Chemicals Ltd., Poole, England) and anhydrous sodium sulfate was obtained from (Prolabo).

Preparation of stock standard solution

Stock standard solutions (100 μg/mL) and (1.0×10^{-3} mol/L) of MNT were prepared by dissolving 10 and 60.82 mg of pure MNT in bidistilled water and further diluted with bidistilled water to the mark in a 100 mL volumetric flask. The standard solutions were stable for at least 7.0 days when kept in the refrigerator. Serial dilution with the same solvent was performed to obtain the appropriate concentration range.

General recommended procedure

Accurately measured aliquots (0.1–1.6 mL) of MNT (100 μg/mL) were transferred into 10 mL measuring flasks. A volume of 2.0 mL of 1.0×10^{-3} mol/L BCG, BPB, or MO was added. Then, 3.0 mL NaOAc–HCl buffer at the optimum pH 3.0, 3.5, and 4.0 using (1.0×10^{-3} mol/L) BCG, BPB, and MO, respectively, and the volume was completed to 10 mL with distilled water. The ion-pairs were extracted with 10 mL of dichloromethane by shaking for 2.0 min, and then the combined dichloromethane extracts were dried over anhydrous sodium sulfate. The absorbance of the yellow-colored ion-pair complexes was measured at 420, 416, and 426 nm, using BCG, BPB, and MO, respectively, against the reagent blank similarly prepared in the same manner except an addition of drug. All measurements were made at room temperature (25 ±2°C). In the three proposed methods, a standard curve was prepared by plotting the absorbance values versus concentrations of MNT.

Procedure for tablets

Twenty tablets containing MNT were finely pulverized and weighed. A weighed quantity of the powdered tablets equivalent to 10 mg of MNT was transferred into a 100 mL volumetric flask, about 20 mL of ethanol was added and the flask was sonicated for 30 min. The volume was completed to the mark with bidistilled water, mixed well, and filtered through a Whatman No. 1 filter paper into 100 mL volumetric flask, discarding the first 10 mL, then the conical flask was washed with a few mL of bidistilled water. The wash was added to the same volumetric flask and then the flask was made up to volume with bidistilled water. Aliquots containing MNT in the final concentration ranges 1.0–10, 1.0–12, and 1.0–16 μg/mL for BCG, BPB, and MO methods, respectively, was analyzed as described under "General recommended procedure." The concentration of MNT was determined either from the calibration curve or using the corresponding regression equation. The method of standard addition was used for the accurate determination of MNT content.

Stoichiometric relationship

The stoichiometric ratios of the ion-pairs formed between MNT and the reagents were determined by applying the continuous variation [26] and the molar ratio [27] methods at the optimum wavelengths. In the continuous variation method, equimolar solutions were employed: A 1.0×10^{-3} mol/L standard solution of drug and 1.0×10^{-3} mol/L solution of dye was used. A series of solutions was prepared in which the total volume of the studied drugs and the dye was kept at 2.0 mL. The drug and reagent were mixed in various complementary proportions (0.2:1.8, 0.4:1.6, 0.6:1.4, 0.8:1.2, 1.0:1.0, 1.2:0.8, 1.4:0.6, 1.6:0.4, and 1.8:0.2) and completed to volume in a 10 ml calibrated flask with the appropriate solvent for extraction following the above-mentioned procedure. In the molar ratio method, the concentration of MNT was kept constant 1.0 ml of (1.0×10^{-3} mol/L) while that of dyes (1.0×10^{-3} mol/L) is regularly varied (0.2–2.4 mL). The absorbance of the prepared solutions measured at optimum condition and at the optimum wavelength for each complex.

RESULTS

Optimization of the reaction conditions

Effects of pH

It was observed that the effective extraction of the complex depends on the type of the buffer used and its pH. The effect of pH was studied by extracting the colored complexes in the presence of various buffers such as NaOAc–HCl (pH=1.99–4.92), NaOAc–AcOH (pH=3.4–5.6), and potassium hydrogen phthalate–HCl (pH=2.0–7.0). It is evident that

the maximum color intensity and maximum absorbance were found in NaOAc-HCl buffer. It is evident that the maximum absorbances of the ion pair complexes were obtained at pH 3.0, 3.5, and 4.0 for BCG, BPB, and MO methods, respectively (Fig. 2). Buffer volume was determined by applying the same experiment and variation the volume regularly (0.5–5.0 mL). The higher absorbance value and reproducible results were obtained by using 3.0 ml of NaOAc–HCl buffer solutions.

Effect of reagent concentration

The MNT concentration was kept constant, while the concentration of BCG, BPB, or MO was varied from 0.5–4.0 mL of 1.0×10^{-3} mol/L. The results showed that the absorbance of the extracted ion-pairs increased by increasing the BCG, BPB, or MO volume until 2.0 mL. After this volume, the absorbance remains constant by increasing the volume of the reagents (Fig. 3). Hence, an excess of reagents has no effect on the determination of the drug.

Choice of extracting solvent

Different organic solvents as dichloromethane, carbon tetrachloride, chloroform, and ether were tested as extractive solvents for the proposed methods. Dichloromethane was preferred to other solvents for its selective and obtained the highest absorbance with dichloromethane. It was also observed that only one extraction with total volume 10 mL dichloromethane was adequate to achieve a quantitative recovery of the complexes, maximum absorbance intensity, and considerably lower extraction ability for the reagent blank and the shortest time to reach the equilibrium between both phases.

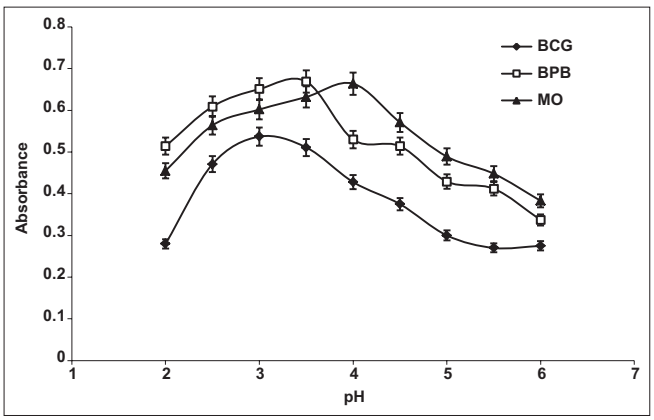


Fig. 2: Effect of pH of buffer solution on the ion-pair complex formation between (10, 12, and 15 µg/ml) MNT and (1.0×10^{-3} mol/l) bromocresol green, bromophenol blue, and methyl orange reagents, respectively (n=3.0)

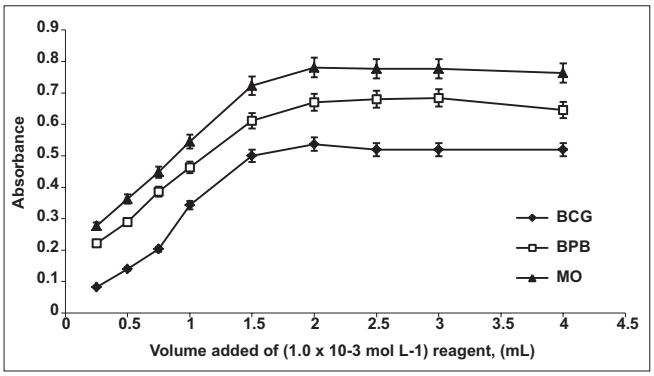


Fig. 3: Effect of volume of (1.0×10^{-3} mol/L) bromocresol green, bromophenol blue, and methyl orange reagent on the ion-pair complex formation with (10, 12, and 15 µg/mL) MNT, respectively (n=3.0)

Effect of shaking time and temperature

The optimum shaking time was investigated by shaking from 0.5 to 5.0 min. Maximum and constant absorbance value was obtained when extracted after 1.5 min shaking. Therefore, shaking time of 2.0 min was maintained throughout the experiment. The effect of temperature on colored complexes was studied by measuring the absorbance values over the temperature range 20–35°C. It was found that the absorbance of the colored ion-pair complex was constantly up to 30°C. At higher temperatures, the drug concentration was found to increase due to the volatile nature of the dichloromethane. Therefore, the temperature chosen was room temperature (25 ± 2°C) as the best temperature for the determination of MNT in bulk and pharmaceutical formulations. The absorbance of the complexes remains stable for at least 16 h at room temperature.

Composition of the ion-pair complexes

The molar ratio between MNT and BCG, BPB, or MO in the ion-pair complexes was determined by Job's method of continuous variation. Job's method of continuous variation of equimolar solutions was employed: A 1.0×10^{-3} mol/L standard solution of drug base and 1.0×10^{-3} mol/L solution of BCG, BPB, or MO was used. A series solution was prepared in which the total volume of drug and reagent was kept at 2.0 mL in the total volume of 10 mL of the aqueous layer. The absorbance of extracting an ion-pair in each instance was measured at the optimum wavelength and plotted against the mole fraction of the drug. The results indicate that the (1:1) (drug:dye) ion-pair complex was formed through the electrostatic attraction between the positive charged MNT^{+} ions and negatively charged dye, D^{-} ions (Fig. 4 and Scheme 1). The extraction equilibrium can be represented as follows:

$$MNT^{+}_{(aq)} + D^{-}_{(ag)} \leftrightarrow MNT^{+}D^{-}_{aq} \leftrightarrow MNT^{+}D^{-}_{(org)}$$

Where MNT^{+} and D^{-} represent the protonated drug and the anion of the dye (BCG^{-}, BPB^{-}, or MO^{-}), respectively, and the subscript (aq) and (org) refer to the aqueous and organic phases, respectively.

Method of validation

Linearity

At described experimental conditions for MNT determination, standard calibration curves with reagents were constructed by plotting absorbance vs. concentration of MNT. The statistical parameters were given in the regression equations calculated from the calibration graphs A = aC + b, where A is the absorbance and C is a concentration in µg/mL. The linearity of calibration graphs was proved by the high values of the correlation coefficient (*r*) and the small values of the *y*-intercepts of the regression equations. The apparent molar absorptivity of the resulting colored ion-pair complexes and relative standard deviation (RSD) of response factors for each proposed spectrophotometric method

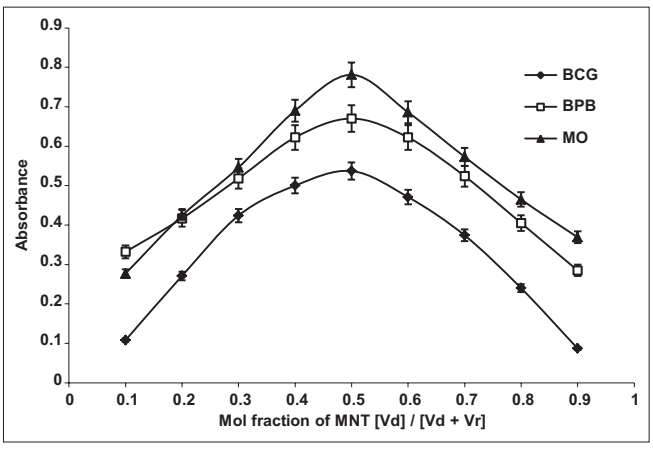


Fig. 4: Job's method of continuous variation graph for the reaction of montelukast with the studied dyes, [drug]=[dye]=(1.0×10^{-3} mol/L) (n=3.0)

was also calculated and recorded in Table 2. The molar absorptivity of each method was calculated, and its values showed that the molar absorptivity of BPB > BCG > MO ion-pair complexes.

Sensitivity

The limits of detection (LOD) and quantitation (LOQ) for the proposed methods were calculated using the following equation [28,29]:

$$LOD=3s/k \text{ and}$$

$$LOQ=10\ s/k$$

Where s is the standard deviation of ten replicate determinations values of the reagent blank and k is the sensitivity, namely the slope of the calibration graph. In accordance with the formula, the LOD was found to be 0.30, 0.29, and 0.27 µg/mL for BCG, BPB, and MO methods, respectively.

According to this equation, the limit of quantitation was found to be 1.0, 0.97, and 0.90 µg/ml for BCG, BPB, and MO methods, respectively.

Accuracy and precision

The specificity of ion-pair reaction and selective determination of MNT which was the basic nitrogenous compound with acid dyes could be possible. Percentage relative standard deviation (RSD%) as precision and percentage relative error (RE%) as the accuracy of the suggested methods were calculated. Precision was carried out by six determinations at three different concentrations in these spectrophotometric methods. The percentage relative error calculated using the following equation:

$$RE\ \%=[(\text{founded} - \text{added})/\text{added}] \times 100$$

The inter-day and intra-day precision and accuracy results are shown in (Table 3). These results of accuracy and precision show that the proposed methods have good repeatability and reproducibility.

Robustness and ruggedness

For the evaluation of the method robustness, some parameters were interchanged; pH, dye concentration, wavelength range, and shaking time. The capacity remains unaffected by small deliberate variations. Method ruggedness was expressed as RSD% of the same procedure applied by two analysts and in two different instruments on different days. The results showed no statistical differences between different analysts and instruments, suggesting that the developed methods were robust and rugged (Table 4).

Effects of interference

To assess the usefulness of the method, the effect of diluents, excipients, and additives which often accompany MNT in its pharmaceutical formulations was studied. The results indicated that there is no interference from excipients and additives, indicating a high selectivity for determining MNT in its pharmaceutical formulations.

Applications to pharmaceutical formulations

The proposed methods have been successfully applied to the determination of MNT in dosage forms (Montelair tablets and Delmonkast tablets). The results in Table 5 showed that the excipients in the dosage forms do not interfere. A statistical comparison of the results for the determination of MNT from the same batch of material by the proposed and reported methods [2] is shown in Table 5. The results agreed well with the label claim and agreed with the results obtained by the reported method. Statistical analysis of the results

Table 2: Statistical analysis of calibration graphs and analytical data in the determination of montelukast using the proposed methods

Parameters	Bromocresol green	Bromophenol blue	Methyl orange
Wavelengths λ_{max} (nm)	420	416	426
Beer's law limits (µg/mL)	1.0–10	1.0–12	1.0–16
Molar absorptivity ε, (L/mol/cm)×10^4	3.407	4.95	2.90
Sandell's sensitivity (ng cm^{-2})	17.85	12.29	20.98
Regression equation[a]			
Intercept (*a*)	0.0008	-0.007	-0.0008
Standard deviation of intercept (*Sa*)	0.0085	0.0047	0.0063
Slope (b)	0.0553	0.0838	0.0489
Standard deviation of slope (*Sb)*	0.0012	0.0019	0.0027
Correlation coefficient (r^2)	0.9999	0.9996	0.9993
LOD (µg/mL) [b]	0.30	0.29	0.27
LOQ (µg/mL) [b]	1.0	0.97	0.90
Mean±SD	99.78±0.64	99.86±0.48	99.65±0.73
RSD% (n=6)	0.64	0.48	0.73
RE%	0.67	0.50	0.77
t-test[c]	0.22	0.51	0.12
F-test[c]	1.51	1.17	1.97

[a]A=a + bC, where C is the concentration in µg/mL, A is the absorbance units. [b]LOD: Limit of detection, LOQ: Limit of quantification, ε: Molar absorptivity. [c]Theoretical values of t and F at *P*=0.05 are 2.571 and 5.05, respectively

Table 3: Intra-day and inter-day precision and accuracy data for montelukast obtained by the proposed methods

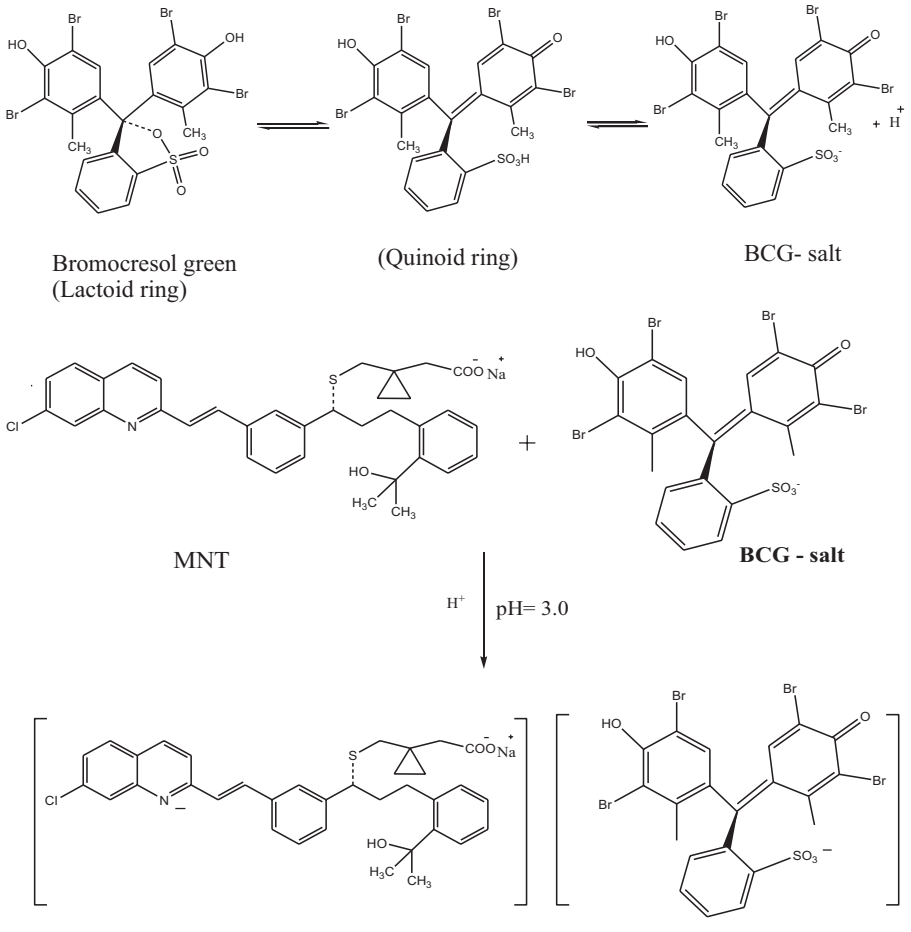
Method	Added (µg/ml)	Intra-day				Inter-day			
		Recovery %	Precision RSD %[a]	Accuracy RE %	Confidence limit[b]	Recovery %	Precision RSD%[a]	Accuracy RE %	Confidence limit[b]
Bromocresol green	3.0	99.20	0.57	−0.80	2.976±0.017	99.50	0.62	−0.50	2.985±0.019
	6.0	99.40	0.79	−0.60	5.964±0.047	98.80	0.98	−1.20	5.828±0.058
	9.0	100.80	1.20	0.80	9.072±0.109	99.70	1.17	−0.30	8.973±0.105
Bromophenol blue	4.0	99.00	0.60	−1.0	3.960±0.024	98.60	0.53	−1.40	3.944±0.021
	8.0	100.30	1.15	0.30	8.024±0.092	99.60	1.07	−0.40	7.968±0.085
	12	99.50	0.80	−0.50	11.940±0.096	100.80	1.20	0.80	12.096±0.145
Methyl orange	5.0	99.40	0.73	−0.60	4.970±0.036	99.70	0.42	−0.30	4.985±0.021
	10	101.0	0.96	1.0	10.100±0.097	99.30	0.86	−0.70	9.930±0.085
	15	99.20	1.42	−0.80	14.880±0.211	99.80	1.10	−0.20	14.97±0.165

[a]Mean of six determination, RSD%, percentage relative standard deviation; RE%, percentage relative error. [b]Confidence limit at 95% confidence level and five degrees of freedom (t=2.571)

Table 5: Application of the standard addition technique for the determination of montelukast in pharmaceutical formulations using the proposed methods

Sample	Taken (µg/mL)	BCG		BPB		MO		Reported method [2]
		Added (µg/mL)	Recovery[a] (%)	Added (µg/mL)	Recovery[a] (%)	Added (µg/mL)	Recovery[a] (%)	
Montelair tablets	2.0	-	99.20	-	99.60	-	99.30	
		2.0	100.40	2.0	99.10	3.0	99.0	
		4.0	99.70	4.0	99.00	6.0	100.30	
		6.0	98.80	6.0	99.80	9.0	99.50	
		8.0	99.30	8.0	99.10	12.0	98.90	
Mean±SD			99.48±0.61		99.32±0.36		99.40±0.56	99.63±0.59
RSD%			0.61		0.36		0.56	0.59
V			0.37		0.16		0.31	0.35
S.E			0.27		0.13		0.25	0.26
t-value[b]			0.35		0.90		0.57	
F-value[b]			1.06		2.19		1.13	
Delmonkast tablets	2.0	-	99.00	-	100.40	-	99.60	
		2.0	99.50	2.0	99.30	3.0	101.20	
		4.0	100.90	4.0	99.00	6.0	99.40	
		6.0	100.20	6.0	98.50	9.0	99.80	
		8.0	98.70	8.0	99.70	12.0	99.00	
Mean±SD			99.66±0.90		99.38±0.72		99.80±0.84	99.50±0.68
R.S.D%			0.90		0.72		0.84	0.68
V			0.81		0.52		0.70	0.46
S.E			0.40		0.32		0.37	0.30
t-value[b]			0.28		0.50		0.56	
F-value[b]			1.76		1.13		1.52	

[a]Average of six determinations. [b]Theoretical values of t and F are 2.776 and 6.39, respectively at confidence limit at 95% confidence level and five degrees of freedom (p=0.05). BCG: Bromocresol green, RSD: Relative standard deviation, BPB: Bromophenol blue, MO: Methyl orange



Scheme 1: Proposed reaction mechanism for the ion-pair complex formation between MNT and bromocresol green

using Student's t-test for accuracy and F-test for precision revealed no significant difference between the proposed and reported methods at the 95% confidence level with respect to accuracy and precision [26] (Table 5).

To ascertain the accuracy and validity of the proposed methods, a recovery experiment was performed through the standard addition technique. With a fixed and known amount of MNT in dosage form (pre-analyzed), pure drug was added at different concentrations and the total was found by the proposed methods. The results of this study presented in Table 5 indicated that the commonly added excipients did not interfere with the assay.

DISCUSSION

The nitrogenous drug (MNT) is present in positively charged protonated forms and anionic dyes present mainly in the anionic form at a pH ≥3.0. Hence, when treated with an acid dye at pH range (2.5–5.5) of acidic buffer solutions, a yellow ion-pair complex which is extracted with methylene chloride solvent is formed. The absorption spectra of the yellow ion-pair complexes formed between MNT and BCG, BPB, or MO reagents were measured in the range 350–550 nm against the blank solution and show maximum absorbance's at 420, 416, and 426 nm, respectively.

CONCLUSION

This paper describes the application of extractive ion-pair complexation reaction with dyes for the quantification of MNT in bulk and pharmaceutical formulations. Compared with the existing spectrophotometric methods, the proposed methods have the advantages of relatively simple, rapid, cost-effective, and more sensitive for determining MNT in bulk and pharmaceutical formulations. Moreover, the proposed methods are free from tedious experimental steps such as heating, unlike the previously reported spectrophotometric methods cited earlier. The most attractive feature of these methods is its relative freedom from interference by the usual diluents and excipients in amounts far in excess of their normal occurrence in pharmaceutical formulations. The statistical parameters and the recovery data reveal high precision and accuracy of the proposed methods besides being robust and rugged. Therefore, the validated method could be useful for routine quality control assay of MNT in bulk and pharmaceutical formulations.

AUTHORS' CONTRIBUTIONS

Prof. Dr. Ragaa El Sheikh has generated the research idea and interpreted the data and helped to draft the manuscript. Prof. Dr. Wafaa El Sayed Hassan has suggested the research idea and participated in the design of the study. Miss. Marwa Mohammed El-Gabry was prepared the solutions, carried out the experiments, interpreted the data, and helped to draft the manuscript. Prof. Dr. Saleh S. Idris has suggested the research idea and participated in the design of the study. Dr. Osama Mohammed Salem has participated in the design of the study and carried out the experiments. Dr. Ibrahim Shouab Ali has participated in the design of the study and carried out the experiments. Prof. Dr. Ayman A. Gouda helped in check spelling, reducing plagiarism, interpreting the data, reviewed the manuscript, and submits the manuscript for publication.

CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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