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Titrimetric Assay of Salbutamol Sulfate Using Permanganate

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KEYWORDS

Assay

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Stoichiometry

ABSTRACT:

Introduction: Salbutamol, RS-[4-[2-(tert-butylamino)-1-hydroxyethyl]-2(hydroxymethyl) phenol] is a short acting β2-adrenergic receptor agonist used for the relief of Broncho-spasm in conditions such as asthma and chronic obstructive pulmonary disease [1-3]. Salbutamol is still commonly delivered as a racemic mixture (+,-). Salbutamol, even though S-Salbutamol is known to have a detrimental effect on asthma sufferers (in fact the exact opposite effect of the R Isomer) [4].

Objectives:A simple cost-effective, accurate and precise direct titrimetric method for the determination of Salbutamol sulfate (SBS) in pharmaceutical dosage forms has been developed and validated.

Methods:The method is based on the titration of SBS with acidified 0.01M potassium permanganate solution. The method is applicable over the range of 3.0-10.0mg SBS.

Results:The validation of the method yielded good results that included precision (RSD < 3.15% for intra- and inter-day precision, accuracy (relative error < 3.12%).It was also found that the additives present in the commercial tablets did not interfere with the assay and the results were comparable with the existing method.

Conclusions:The proposed method is free from rigid experimental conditions such as rigid pH control, liquid-liquid extraction, etc., and is characterized by simplicity and high sensitivity. This method employ inexpensive and easily available chemicals and hence cost-effective when compared to the existing methods. In addition, the method has a high tolerance limit for common excipients found in drug formulations. The proposed method is accurate and precise as indicated by good recoveries of the drugs and low RSD values. The proposed method can be applied for routine analysis and in quality control laboratories for quantitative determination of the drug both in the pure and dosage forms.

1. Introduction

Salbutamol sulphate (SBS) whose structure is given in figure 1 is a selective β-2-agonist antiasthmatic. Its primary action is to stimulate adenylcyclase which catalyzes the formation of cyclic adenosin monophosphate.

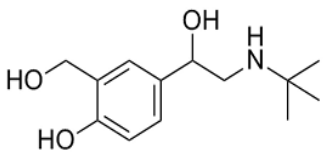

FIGURE 1. Chemical structure of salbutamol (SBS)

The drug is official in European Pharmacopoeia [5], which describes a potentiometric titration in non-aqueous medium, British Pharmacopoeia [6] and Indian Pharmacopoeia [7]. Some different methods of analysis have been reported for the determination of SBS, including HPLC [8-10] and UV-spectrophotometry [11,12], but most of the technique require extensive sample preparation prior to the measurement step, some are less sensitive and some other are relatively complicated in terms of assay procedure or equipment required for analysis.

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SBS in pharmaceuticals has been assayed by visible spectrophotometric methods based on reactions such as redox [13, 14], reduction followed by chelation [15], oxidative coupling [16, 17], diazotization and coupling [18-19], nitrosation [20], nitration [21], nitration followed by Meisenheiner complex formation [22] and charge-transfer complex formation [23]. However, many of these procedures suffer from some disadvantage, such as poor sensitivity, heating or extraction step, critical working conditions or the use of organic solvents, and are hence unsatisfactory for routine analysis. The visual titrimetric method [24] reported employs NBS as the oxidimetric titrant in the presence of potassium bromide and using methyl red as indicator. However, the method is applicable over a macro scale. Issaet al. [25] has reported a conductometric titration method using phosphotungstic and phosphomolybdic acids as titrants. Even these procedures are time consuming and less sensitive.

Different methods for the estimation of SBS in tablets, capsules and syrups employ N-bromosuccinimide [24, 26, 27], bromate–bromide solution [28] as an oxidizing agents, rhodamine-B and methylene blue dyes [26, 28] as reagents for spectrophotometric analysis. Diazotised o-nitroaniline [29] and diazotised paranitroaniline [30]for colour formation, continuous and stop flow methods [31] and spectroflourometric estimations [32].

Potassium permanganate ($KMnO_4$) is a strong oxidizing agent and it was first introduced into titrimetric analysis by F. Margueritteforthe titration of iron(II) [33]. The salt is also known as permanganate of potash and in this salt, manganese is in the +7 oxidation state. The innate intense purple color solution of permanganate absorbs in the vicinity of 550 nm. As a strong oxidant it does not generate toxic byproducts. The Mn-containing products from redox reactions depend on the pH. In acid solutions, permanganate is reduced to the faintly pink Mn^{2+} as represented by the following equation:

$$MnO_4^- + 8\ H^+ + 5e \rightarrow Mn^{2+} + 4\ H_2O$$

The standard potential in acid solution, E, has been calculated to be 1.51 volts, hence the permanganate ion in acid solution is a strong oxidizing agent [33]. Sulphuric acid is the most suitable acid, as it has no action upon permanganate in dilute solution. With hydrochloric acid, there is the likelihood of the reaction:

$$2\ MnO_4^- + 10\ Cl^- + 16\ H^+ \rightarrow 2\ Mn^{2+} + 5\ Cl_2 + 8\ H_2O$$

taking place, and some permanganate may be consumed in the formation of chlorine [33-35].

Potassium permanganate also finds some application in strongly alkaline solutions. $KMnO_4$ spontaneously reduced to green K_2MnO_4, wherein manganese is in +6 oxidation state.

$$MnO_4^- + e \rightarrow MnO_4^{2-}$$

The resulting green colormanganese(VI) shows maximum absorbance at 610 nm. In neutral solutions permanganate is only reduced by 3 e- to give manganese dioxide where Mn is in a +4 oxidation state. MnO_2 is brown in color. The half-cell reaction is:

$$MnO_4^- + 2\ H_2O + 3e \rightarrow MnO_2 + 4\ OH^-$$

and the standard potential E is 0.59 volt [33-35].

Exploiting the different colors of permanganate at different pH media, it has been used for the assay of etamsylate [36], reloxifene [37], pantaprazole sodium [38], famotidine [39], albendazole [40] and olanzapine [41].

2. Objectives

Reagents

All the reagents were of analytical-reagent grade and distilled water was used throughout the investigation. Pharmaceutical grade SBS (99.84 per cent pure) was received as a gift from Cipla India, Ltd., Mumbai, and used as received.

Potassium permanganate (0.01M): An approximately 0.01M solution was prepared by dissolving 395 mg of $KMnO_4$ (Merck, Mumbai, India) in water and diluting to 250 mL in a calibrated flask, and standardized using H.A Bright's procedure [42].

Sulphuric acid (2M): Concentrated acid (S.D. Fine Chem, Mumbai, India, sp. gr. 1.84) was appropriately diluted with water to get the required concentration.

Standard SBS solution: A stock standard solution equivalent to 1.0 mg mL^{-1} SBS was prepared by dissolving 100 mg of pure drug with water in a 100 mL calibrated flask.

Tablets: Asthalin-2.0 (Cipla India, Ltd., Mumbai, India) and Asmanil-2.0 (Inga Laboratories Pvt. Ltd., Mumbai, India) tablets were purchased from local commercial sources.

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3. Methods

Assay procedure

Procedure for pure SBS

A 10.0 ml aliquot of standard solution containing 3.0-10.0 mg of SBS was measured accurately and transferred into a 100 ml titration flask, 5 ml of 2 M H_2SO_4 was added and after 5 min, the content was titrated against 0.01M $KMnO_4$ to a first appearance of pink color.

The amount of SBS in the aliquot was computed from the following formula:

$$Amount\ (mg) = \frac{V_r \times M_r \times S}{n}$$

Where, M_r = relative molecular mass of drug
S = strength of $KMnO_4$, M.
V_r = ml of titrant reacted
n = number of moles of $KMnO_4$ reacting with per mole of SBS = 8.

Procedure for the analysis of tablet

Fifty tablets were weighed and finely powdered. An accurately weighed quantity of the tablet powder equivalent to 100 mg SBS was transferred into a 100 mL calibrated flask, and about 60 mL water was added. The content of the flask was shaken for 20 min; finally the volume was completed to the mark with water. The content was mixed well, and filtered through a Whatman No. 42 filter paper. First 10 mL portion of the filtrate was discarded, and a suitable aliquot of the filtrate (1 mg mL^{-1} SBS) was then subjected to analysis as in the procedure described for pure SBS.

4. Results

One mole of SBS for oxidation, consumed eight moles of KMnO4. This could be due to the presence of vulnerable oxidisable groups present in SBS. The reaction between SBS and $KMnO_4$ was found to occur in 1:8 (drug:oxidant) stoichiometric ratio and all the calculations are based on this stoichiometric ratio. Using 0.01M $KMnO_4$,3-10 mg of SBS was conveniently determined.

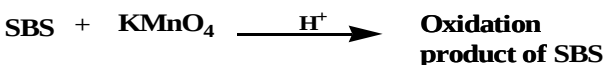

FIGURE 2. Reaction scheme for SBS

The various experimental parameters were optimized and used throughout the experiment.

5. Discussion

Optimization of reaction variables

In order to achieve the optimum conditions for the quantitative assay of SBS, fixed amount of the drug was treated with $KMnO_4$ under varying acidic conditions.

The reaction was found to be quantitative and stoichiometric in H_2SO_4 medium. A constant reaction stoichiometry of 1:8 [SBS:$KMnO_4$] was obtained in the range 3-10 mg. Reproducible and stoichiometric results were obtained when (2-10 mL) 5M H_2SO_4 was maintained. Hence 5 mL of 2M H_2SO_4 solution in a total volume was maintained found to be optimum. The reaction time was studied by titrating the drug with $KMnO_4$ at different time intervals. It was found that the reaction yielded a constant stoichiometry in the time range from 1 to 10 min, and at the standing time of 5 min and greater than 5 min, there was a constant and definite reaction stoichiometry. Hence, a standing time of 5 min was followed throughout.

Method validation

The proposed method has been validated for range and reaction stoichiometry, precision, accuracy, and recovery.

Range of determination

Under the experimental conditions, 3-10 mg could be determined with acceptable degree of accuracy and precision. Below the lower limit higher recoveries and above the upper limit lower recoveries were obtained. Over the range investigated (3-10 mg), a fixed stoichiometry of 1:8 [SBS:$KMnO_4$] was obtained in titrimetry which served as the basis for calculations.

Reaction stoichiometry

When different amounts of SBS (within working limits) were reacted with permanganate under the optimum conditions, giving a molar ratio of 1:8 [SBS:$KMnO_4$].

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Accuracy and precision of the method

In order to study the precision and accuracy of the proposed method, three concentrations of pure SBS within the linearity range were analyzed, each determination being repeated seven times (intra-day precision) on the same day and one time each for five days (inter-day precision). The percentage relative standard deviation (% RSD) was ≤ 2.74 % (intra-day) and ≤ 3.15 % (inter-day). In addition, the accuracy of the proposed method was measured by calculating the percentage relative error (% RE), which varied between 3.12 % and 2.25 %. The results of this study compiled in Table 1 indicate the high accuracy and precision of the proposed methods.

Table 1. Evaluation of Intra-day and inter-day accuracy and precision

SBS taken (mg mL^{-1})	Intra-day accuracy and precision (n=7)			Inter-day accuracy and precision (n=5)		
	SBS found[a] (mg mL^{-1})	RSD[b] %	RE[c] %	SBS found (mg mL^{-1})	RSD[b] %	RE[c] %
4.0	3.94	2.74	1.50	4.09	3.15	2.25
6.0	6.07	0.83	1.17	6.03	1.58	0.92
8.0	7.75	2.25	3.12	8.14	2.86	1.75

[a]Mean value of 7 determinations; [b]Relative standard deviation (%);[c]Relative error (%).

Robustness and ruggedness

To evaluate the robustness of the methods, two important experimental variables, viz., the amount of acid and reaction time, were slightly varied, and the capacity of the methods was found to remain unaffected by small deliberate variations. The results of this study are presented in Table 2 and indicate that the proposed methods are robust. Method ruggedness is expressed as %RSD of the same procedure applied by three analysts and using three different spectrophotometers by the same analyst. The inter-analysts' and inter-instruments' RSD values were ≤ 2.72 % indicating ruggedness of the proposed methods. The results of this study are presented in Table 2.

Table 2. Results of robustness and ruggedness expressed as intermediate precision (%RSD)

Robustness			Ruggedness	
Nominal amount, mg	Reaction times* (n=3)	Volume of acid[$]	Inter-analysts (n=3)	Inter-instruments[#] (n=3)
4.0	1.29	1.15	1.73	1.19
6.0	2.21	0.98	1.62	2.15
8.0	1.94	2.72	1.04	1.56

* Reaction time was 5 ± 1 min, [$] Volume of H_2SO_4, 5 ± 0.25 mL

Application to tablets

The results presented in Table 3 showed that there was a close agreement between the results obtained by the proposed method and the label claim. The results were also compared with those of the reference method [25] statistically by a Student's t- test for accuracy and variance ratio F- test for precision at 95% confidence level. The calculated t- and F-values indicate that there is no significant difference between the proposed methods and the reference method with respect to accuracy and precision.

Table 3. Results of analysis of tablets by the proposed method

Tablets analyzed	Label claim, mg/tablet	Found*(Percent label claim ± SD)	
		Reference method	Proposed method
Asmanil-2.0	2.0	98.29 ± 0.63	99.69 ± 1.02 t= 2.6 F= 2.62
Asthanil-2.0	2.0	101.9 ± 1.24	102.6 ± 1.39 t = 0.84 F = 1.26

Mean value of five determinations.
Tabulated t-value at the 95% confidence level is 2.78.
Tabulated F-value at the 95% confidence level is 6.39

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Recovery study

To further assess the accuracy of the methods, recovery experiments were performed by applying the standard-addition technique. The recovery was assessed by determining the agreement between the measured standard concentration and added known concentration to the sample. The test was done by spiking the pre-analyzed tablet powder with pure SBS at three different levels (50, 100 and 150%) of the content present in the tablet powder (taken) and the total was found by the proposed methods. Each test was repeated three times. In all the cases, the recovery percentage values ranged between 99.1 and 102.4 with relative standard deviation in the range 0.54-1.92 %. Closeness of the results to 100 % showed the fairly good accuracy of the methods (Table 4).

Table 4. Results of recovery study via standard addition method with tablet

Tablets studied	SBS in tablet µg mL^{-1}	Pure SBS added µg mL^{-1}	Total found µg mL^{-1}	Pure SBS recovered* Percent ±SD
Asmanil-2.0	2.99	1.5	4.46	99.4 ±0.72
	2.99	3	6.04	100.9 ±0.94
	2.99	4.5	7.59	101.3 ± 0.54
Asthanil-2.0	3.08	1.5	4.54	99.1 ± 0.57
	3.08	3	6.19	101.9 ± 0.87
	3.08	4.5	13.67	98.6 ± 0.67

*Mean value of three determinations.

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