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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR CONTROL OF PH AND ELECTRICAL CONDUCTIVITY IN SALBUTAMOL SOLUTIONS

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Abstract

Analytical method development and validation play an important role in the discovery, development, and manufacturing of pharmaceuticals. The process validation is of utmost importance while manufacturing a quality product. Salbutamol sulfate (SBS) is a very potent bronchodilator and is used extensively for treating different respiratory problems such as bronchial congestion, asthma and Chronic Obstructive Pulmonary Disease (COPD), etc. In this study, a method of need was developed for prospects to be used for better advances in solution stability and preservation by controlling pH and electrical conductivity. This method was developed using a pH/conductivity meter of accuracy ±0.02 and all procedures were done by maintaining the temperature of the solution at 25°C. The de-ionized water was used as a solvent to minimize any contaminant ions activity. During method development, the development, measurement and validation of the pH and electrical conductivity were performed. For developing a method for control the pH value of the solution was maintained at 5.00 so that the results show that the method developed is precise and accurate. Different validation parameters were studied such as linearity, accuracy, precision and robustness. The method was validated according to standard guidelines. The routine calibration of the pH/conductivity meter was done to obtain accurate readings and to avoid any mishandling of any step throughout the process. The results were precise and showed that the method developed is accurate. The method developed is suitable for the control of pH and electrical conductivity for the different solutions as these characteristics are necessary for their stability, quality and efficacy. The method developed is precise, stable and also enhances the action of salbutamol sulfate. It can serve as a new window for researchers to analyze and control the pH and conductivity of different formulations.

Keywords: Method Development, Validation, control of in salbutamol solutions, control of electrical conductivity in salbutamol solutions

1. Introduction

Measurements of pH and electrical conductivity are considered as most important for the control of almost all pharmaceutical preparations. Both of these are important while considering any type of chemical reaction in solutions and it has always been important factor for the stability of formulations throughout the shelf life or even during use by patients (1-3).

The pH scale arrays normally 0 to 14. At 25°C, a hydrated sample having a pH of below 7 is acidic, and a fluid arrangement having a pH of more than 7 is said to be alkaline. pH 7.0 is characterized as "neutral" at 25°C because the H_3O + fixation is equivalent to the OH- focus in the sanitized water (1, 4, 5). The pH of the International Association of Pure and Applied Chemistry is slightly different, based on physiochemical measures enumerated in IUPAC green book (1, 6). In the biochemical lab, pH is normally estimated utilizing an electronic pH meter, where the pH of hydrated samples might be resolved to about 0.01 pH unit if fitting consideration is taken (7-11).

Presently two methods are used to measure pH i.e. electrometric and chemical indicator methods. For the pH to be measured accurately, a calibrated glass electrode and pH meter (electrometric method) is used as a primary standard that shows even minute changes in the pH of the sample. pH meters are used instead of strips or litmus paper because of their high-resolution power even up to 0.001units, and they are highly precise and continuous in pH measurement (12).

When two solutions comprise the different amount of H+ ions are isolated by a glass layer; a potential difference is generated over the film over a detecting electrode while at the same time a voltage potential is generated on the reference electrode. The pH meter quantifies the voltage potential discrepancy (mV) between the detecting terminal and the outside (reference terminal) and through a calculation shows a pH reading. In acidic or basic arrangements, the voltage on the external layer surface changes relative to changes in [H+] (13).

1.1. pH electrodes

Along with defining pH, Sorensen also set forth an electrometric technique for assessment of this amount depending on the estimation of the potential, of the platinum-based or palladium-based hydrogen gas terminal that was created by Le Blancand was responsive to hydrogen ions (14-16). pH electrodes are described under the class of ion-selective electrodes (ISE). The glass electrodes which are used for measuring pH are very precise, choosy and most significant of ISEs (17-20). The measurements of all electrode potentials were done with relation to the reference electrode, at the same time on contact with the solution the potential created should be steady, free from temperature variations, be autonomous from the solution's pH, and stay steady for a significant period(19). The most frequently utilized reference electrodes are calomel and Ag/AgCl (21).

1.2 pH meter

A commonly used pH meter is an electronic voltmeter with greater resistance which gives the readings usually in digital values. To use the pH meter, the sample is placed in a container and the glass probe is placed in the sample (20, 22). A continuous signal of temperature is received in pH meters and controllers which make it dependent on the temperature of the sample solution while in manual temperature compensation (MTC) the temperature is to be added by the person working on pH. Automatic temperature compensation (ATC) is regarded as progressively feasible for most pH applications (23).

1.3 pH control (Buffers)

pH control is of prime importance whenever medicinal products are considered. pH is mainly controlled by the use of buffer solutions in all pharmaceutical products. Buffers' action in actuality is related to buffers capacity which is the concentration of an acid or base which is added to affect

the pH of the medium (24-26). There is a balance between materials having the capacity of expelling or discharging particles in buffered solutions (27-29).

1.4 Electrical conductivity

Conductivity is utilized wherever there is a need to know or measure ionic characteristics of solutions and also to quantify, screen, or control compound apportioning, transparency of mixtures, ionic strength of different liquids (30-33). Conductivity can also be used to estimate the purity of absolute organic liquids which are weak conductors and if there is increased conductance it shows that the sample liquid has added impurity i.e. salts or water (13, 34-39).

2. Development of the method

New analytical methods are developed on the foundation of previously developed methods found in present literature by using the previous or almost similar to previous tools (4, 40, 41). The development of innovative or upgraded methods typically modifies prevailing methodologies and instrumentation. Development considers all factors that may affect the process and these generally involve the selection of requirements and instruments to be utilized for developing the method (42-44).

3. Validation of the method

The scientific (analytical) method describes the technique by which different investigations are to be done and it also depicts all aspects which are required for analytical investigations (45). The most important elements involved for validation analysis are to study of the function of standardization, the limit of quantification and detection, accuracy, dependability, and uncertainty of measurements (46-49).

Analytical methods are validated on basis of the certain distinguishing feature as discussed in USP i.e. accuracy, precision, specificity, the limit of detection, the limit of quantization, linearity, range, robustness (50, 51).

3.1. Linearity

It is a measure of the difference between proportioning and this provides a direct relationship between two different measured parameters (45, 50, 51).

3.2. Accuracy

It is the narrowness between values found in measurement to reference standard value (45, 50, 51).

3.3. Precision

It is the closeness of values to reference between measurements obtained from multiple sampling of the same sample preparation under defined conditions (45, 50, 51).

3.4. Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in procedural parameters listed in the procedure documentation and indicates its suitability during normal usage (45, 50, 51).

Validation of procedure must consider the features as discussed in strategies of the international conference on harmonization related to diagnostic procedures. Any external procedure other than ICH guidelines must be authenticated (51, 52).

4. Instrument qualification (IQ)

A huge assortment of research center gear, instruments, and mechanized systematic frameworks, extending from basic nitrogen evaporators to complex numerous capacity advancements are utilized

in the pharmaceutical business to gain information to help guarantee that items are appropriate for their planned use (53, 54).

Design qualification is the recorded assortment of exercises that characterize the utilitarian and operational details of the instrument and criteria for the choice of the seller, because of the planned reason for the instrument. After an effective IQ, the instrument is prepared for OQ testing. Operational qualification (OQ) is the reported assortment of exercises important to show that an instrument will work as indicated by its operational particular in the indicated condition (55-57).

Testing exercises in the OQ stage may comprise of these test parameters. Performance qualification is the archived assortment of exercises important to exhibit that an instrument reliably performs as indicated by the determinations characterized by the client, and is proper for the planned use. After IQ and OQ have been played out, the instrument's proceeded with appropriateness for its expected use is shown through execution capability and performance is up to the mark (53).

5. Salbutamol Sulphate

5.1. IUPAC Name

4- [2-(tert-butylamino) -1- hydroxyethyl] -2 (hydroxymethyl) phenol; sulfate

5.2. Molar weight

576.7 g/mol

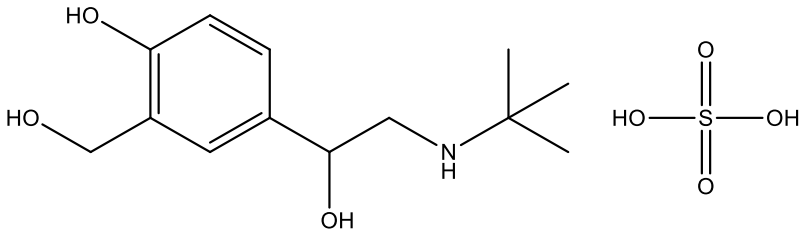

Figure 1: Chemical structure of salbutamol

5.3. Synonyms

Albuterol Sulphate

5.4. Description of Salbutamol

Sir David Jaack and coworkers in 1968 detected and established a sympathomimetic agent i.e. Salbutamol which is a short-acting β2-agonist (58, 59). Salbutamol sulfate is a white or practically white crystalline powder. Spontaneously solvable in water, for all intents and purposes insoluble or marginally dissolvable in ethanol (96 percent) furthermore, in Methylene Chloride (60, 61). This appears as a tertiary butyl group is replaced at nitrogen and a 3-hydroxy cluster is substituted by a hydroxymethyl group (62).

Salbutamol is not a catecholamine chemically so it is not affected by catechol-o-methyl transferase (COMT) and it stimulates beta2 receptors specifically and does not produce tachycardia in humans whenever an efficient quantity of salbutamol is administered as bronchodilator either orally or as an aerosol (63). Salbutamol (albuterol) is a β2-selective adrenoceptor agonist that represents its articulated bronchodilatory, heart, uterine and metabolic impacts. In many patients breathed in salbutamol is a first-line treatment, since it offers quick bronchodilation, usually relieving bronchospasm within minutes (64-67).

As indicated by the existing hypothesis the action of beta-receptor is brought about by the creation of cAMP (an intracellular molecule) as a second messenger (68, 69). The stimulant agents combine with β-receptors reversibly. Generally, bronchodilation mediated by β-agonists is by their direct effect on exterior receptors of mast cells, smooth muscle cells of airways, instead of on presynaptic receptors (70-72).

6. Method Development

In the study of pH and electrical conductivity of the different solution of active pharmaceutical ingredients and validation of controlling methods play a significant role, as these are used to determine the stability and performance of the drug. Method development is a critical step because this determines the outcomes of the study. Steps involved in method development are;

- pH development
- Development of electrical conductivity
- Measurement of pH and electrical conductivity
- Validation of pH and electrical conductivity

Generally, the all procedures during the development process were performed in Class-A (Borosilicate) glassware which is cleaned and flushed thoroughly with demineralized water and then dried before use in a hot air oven.

6.1. pH development

It includes different steps i.e. selection of particular pH value i.e. 5.0, in this case, was developed because of stability of the salbutamol solution on this pH value at different readings and also on different days of study. pH development at value pH=5.0 was done in such a way that a solution of concentration 0.5mg/ml of salbutamol sulfate was prepared with de-mineralized water as a solvent. pH of this solution was developed to the required value by using 0.1N H_2SO_4 solution, 0.01N NaOH solution and normal saline (0.9% NaCl solution) in minute quantities. For maintaining the developed pH sodium sulfate was used as a buffer.

6.2. Development of electrical conductivity

It was developed and maintained in correlation with pH value and its development, the solution of the same concentration was used and with the same acid, base and buffer solution conductivity were adjusted and maintained.

6.3. Measurement of pH

pH measurement is done repeatedly for every sample solution and for obtaining accurate pH readings the calibration of the pH meter was done.

6.4. Calibration

Before making a valid pH measurement the electrode must be calibrated with standard buffer solutions. When the meter gets the mV signal from the electrode and displays the correct pH reading then this is known as calibration. Calibration of pH meter can be done by different methods i.e. one-point calibration, two-point calibration and sometimes three-point calibration is also done. Before measuring or taking readings, the pH and conductivity meter is calibrated as per the following procedure.

- When the pH meter is in pH measuring mode the place the electrode in calibration buffer solution 1 i.e. buffer of pH 7.00 and mix for 5 seconds and take 30 seconds.
- Then press Cal Slope "Cal 1" shows on the left base of the screen and "Cal" is flickering. What's more, show up on the highest point of the screen, is flickering during adjustment. The meter arrives at the endpoint naturally as indicated by the preselected auto-endpoint mode, the adjustment point pH value (for example 7.00) with the temperature shown on the screen.
- Wash the pH terminal with unadulterated water and wipe it off with a tissue.
- Place the cathode in the succeeding buffer solution i.e. buffer of pH 4.00, mix and pause, at that point press Cal/slope, "Cal 2" shows on the base left of the screen and "Cal " is flickering. On the highest point of the screen, what's more, show up, is flickering during alignment. The meter arrives at the endpoint as per the endpoint mode, the alignment point pH value (for example 4.01) with the temperature shown on the screen.

- Press read/enter to store the 2-point calibration and leave the balance and slope are appeared on the presentation for 3 seconds at that point come back to the estimation screen.
- Now the pH meter is ready for pH measurement of the sample.

6.5. Measuring pH

Now as the instrument is ready *for measuring pH* this is done as;

- The buffer solution of pH=7 is used to check the pH and this reading must be somewhere in the range of 6.98 and 7.02 of the unit of pH.
- Then the electrode is placed in the sample solution, mix and hold for 30 seconds.
- Press read/enter in auto mode for measuring pH a sign blinks on the screen and it will stop flickering as it comesto an endpoint and shows the exact pH of the sample on the screen along with the temperature of the solution.
- There is a push-button i.e. pH/mV by using this we can switch between pH measuring mode to electrical conductivity measuring mode.
- Note the temperature posted on the screen of the pH-meter just like the pH of the sample after steadiness of reading on screen.
- To wash the electrode with purified water after taking every reading and by the same method also measure the pH of the different sample preparations.
- The pH meter and electrode are used to measure the pH as well as the electrical conductivity of the sample by switching between two values from the button.
- Electrical conductivity was measured against the pH of the sample while the temperature of the sample was maintained at 25^{o} Cby using MTC.
- After measurement of sample preparations, each day the electrode was stored in a storage solution of 3M potassium chloride (KCl) solution prepared freshly on daily basis.

6.5. Validation

After developing a new method validation is performed so that exactness of the process should be determined. Validation of the method was done by considering different parameters i.e. linearity, accuracy, precision and robustness.

6.6. Linearity

Solutions of different pH and their respective conductivity prepared so that the calibration curve can be plotted. Minimum five readings of each sample solution were taken and were plotted as pH against electrical conductivity. The slope should not be expressively away from zero.

6.7. Accuracy

Accuracy was checked in the following way that a sample solution of Salbutamol sulfate was prepared with a concentration of 0.5mg/ml with sterile deionized water as a diluent to minimize the encounter of contaminant ions. As we are developing the pH validation method so that the sample solution was divided into 3 different containers A, B, C and the pH of these A,B,C was established to 4.0,5.0 and 6.0 respectively. The required pH is 5.0 which is 100% and 80% of the required pH is 4.0 and 120% of the required pH is 6.0. After this we measured the relative standard deviations of three different samples at each pH i.e. 4.0, 5.0 and 6.0.

6.8. Precision

Precision was determined employing repeatability. For repeatability, five duplicate sample solutions were prepared and studied on three different days and their Relative standard deviation will be calculated. The generated %RSD values should not be more than 2.0%.

6.9. Robustness

The robustness of the process was concluded to evaluate the consequences of minor but cautious variations of different solution conditions on determinations of pH of Salbutamol Sulfate. This was determined during the validation procedure by changing the concentration of API, changing pH, changing temperature and changing buffer concentration and their relative standard deviations were calculated which should not be greater than 2.0 %.

7. Results and discussions

7.1 Selection of pH

Selection of pH is important in method validation as remaining values are compared to the selected standard value. pH was 5.0.

7.2 Selection of buffer

The selection of buffer is the critical factor as dealing with pH control and the only buffers are compound which helps to maintain the pH of the solution. As API is salbutamol sulphate so the sodium sulphate was used as buffer having a common ion effect it gives the maximum buffering property and maintained the required pH even up to more than three days of investigations.

7.3 Selection of pH/conductometer

Ohaus starter pH/conductometer was selected because of its easy handling, having both functions of measuring pH and electrical conductivity just by switching to the desired mode and also having a single probe having three functions of detecting pH, mV and temperature.

7.4 Selection of solvent

The solvent selection is an important step. A solvent should be carefully selected so that API is freely soluble and also solvent does not affect the results. For controlling pH and electrical conductivity sterile demineralized water was used as a solvent for preparing sample solutions because Salbutamol sulphate is freely soluble in water but as it is demineralized water having almost no or little effect on pH and especially the conductivity of the solution.

7.5 Selection of temperature

The selection of temperature is an important factor while dealing with pH and conductivity because the temperature has a great impact on both parameters. The most conveniently achievable and suitable temperature, the room temperature 25°C was selected and maintained for all sample preparations by using a water bath.

7.6 Reference solution

Commercially prepared sterile Salbutamol Sulfate (Ventolin® I/V) solution was used with concentration 0.5mg/ml as standard and was compared to our sample preparations.

7.7 Preparation of sample solution

The sample solutions were prepared in the selected solvent following requirements of analytical processing by using the API's powder in required concentrations for preparing sample solutions.

7.8 Calibration of pH/conductometer

Calibration is also important to ensure the correct measurements and calibration was performed on daily basis by using two-point calibration by using two different standard buffer solutions and after that daily base estimations were made.

7.9 Method validation

Validation of the analytical method was done by evaluating and measuring different validation characteristics including linearity, accuracy, precision and robustness. It is established that method is accurate and completely validated for control of pH and electrical conductivity of Salbutamol Sulphate solution by observations and results.

7.9.1 Linearity

Tables 1 and 2 describe the linearity, represented by calibration curve (fig.1) in which conductivity is plotted against the pH in the form of the regression equation and coefficient of correlation at different 12 values of pH of SBS solution controlled by use of a buffer.

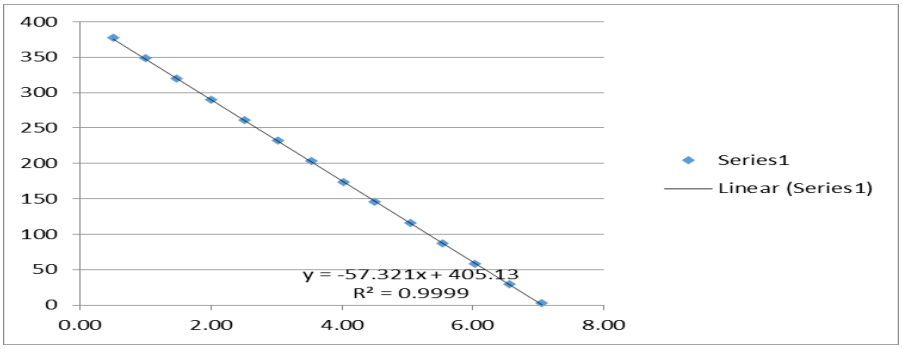

Figure 2: Calibration curve for pH against electrical conductivity

Table 1: Linearity study of salbutamol sulphate solution for pH

pH	Different readings of PH			AVERAGE	STDEV	RSD%
	1	2	3			
0.5	0.52	0.51	0.51	0.51	0.004714	0.91832
1	0.99	1	0.99	0.99	0.004714	0.474568
1.5	1.46	1.48	1.48	1.47	0.009428	0.639916
2	2	1.99	1.99	1.99	0.004714	0.236491
2.5	2.51	2.52	2.52	2.52	0.004714	0.187313
3	3.01	3.05	3.02	3.03	0.016997	0.561566
3.5	3.53	3.5	3.55	3.53	0.020548	0.582648
4	4.01	4.02	4.03	4.02	0.008165	0.203109
4.5	4.51	4.5	4.51	4.51	0.004714	0.104602
5	5.05	5.04	5.07	5.05	0.012472	0.246811
5.5	5.51	5.55	5.57	5.54	0.024944	0.449989
6	6.02	6.03	6.05	6.03	0.012472	0.206721

Table 2: Linearity study of salbutamol sulphate solution for electrical conductivity

pH	Conductivity at reference pH			Average	STDEV	RSD%
	1	2	3			
0.5	377	378	377	377.3333	0.471405	0.124
1	348	349	348	348.3333	0.471405	0.135
1.5	319	318	321	319.3333	1.247219	0.390
2	288	290	293	290.3333	2.054805	0.707
2.5	260	262	262	261.3333	0.942809	0.360
3	232	234	231	232.3333	1.247219	0.536
3.5	203	202	204	203	0.816497	0.402
4	175	174	173	174	0.816497	0.469
4.5	146	145	146	145.6667	0.471405	0.323
5	115	116	116	115.6667	0.471405	0.407
5.5	88	89	84	87	2.160247	2.483
6	57	59	58	58	0.816497	1.407

7.9.2 Accuracy

A sample of 0.5mg/ml concentration was prepared and accuracy was studied using pH and conductivity values 4.0,5.0, 6.0, for conductivity 174, 115 and 58 and their respective percentage i.e. 80%, 100% and 120%. The RSD was studied using three samples of each as shown in the following tables (Tables 3 and 4).

Table 3: Accuracy analysis of salbutamol sulphate solution for pH

Proposed Percentage	Controlled pH of sample solutions	pH	Average	STDEV	RSD%
80%	4.00	4.01 4.02 4.03	4.02	0.008165	0.203
100%	5.00	5.05 5.04 5.07	5.05	0.012472	0.246
120%	6.00	6.02 6.03 6.05	6.03	0.012472	0.206

Table 4: Accuracy analysis of salbutamol sulphate solution for electrical conductivity

Proposed Percentage	Controlled pH of sample solutions	Conductivity at controlled pH	Average	STDEV	RSD%
80%	4.00	174 173 175	174	0.816497	0.469
100%	5.00	115 116 115	115.6667	0.471405	0.407
120%	6.00	59 57 58	58	0.816497	1.407

7.9.3 Precision

Table (5, 6) explains the results of repeatability and intermediate precision is expressed in relative standard deviation. For repeatability 5 samples solutions of the same pH were prepared and repeatability was tested.

Table 5: Repeatability study of salbutamol sulphate solution for pH

Sr. #	Controlled pH	pH measured	Average	RSD%
1	5.00	5.02 5.05 5.03	5.03333333	0.303
2	5.00	5.01 5.04 5.03	5.02666667	0.303
3	5.00	5.04 5.01 5.02	5.02333333	0.304
4	5.00	5.05 5.03 5.01	5.03	0.397
5	5.00	5.04 5.01 5.05	5.03333333	0.413

Table 6: Repeatability study of salbutamol sulphate solution for electrical conductivity

Sr. #	Controlled pH	Conductivity measured at controlled pH	Average	RSD%
1	5.00	117 116 117	116.666667	0.494
2	5.00	117 116 116	116.333333	0.496
3	5.00	116 118 117	117	0.854
4	5.00	115 116 116	115.666667	0.499
5	5.00	115 117 116	116	0.862

7.9.4 Robustness

Robustness was analyzed by using different API concentration, buffer concentration, temperature as illustrated in table 7.

Table 7: Robustness analysis of salbutamol sulphate solution for pH

Parameter	Selected values	Different readings of pH	Average	RSD%
Concentration of API	0.1 mg/ml at pH 5.0	5.00 5.04 5.02	5.02	0.398
	1.5 mg/ml at pH 5.0	5.03 4.99 5.01	5.01	0.399
	2.0 mg/ml at pH 5.0	5.04 5.03 5.02	5.03	0.198
Concentration of buffer (Na_2SO_4) at standard API conc. i.e. 0.5mg/ml	0.048 gm at pH 5.0	4.99 5.06 5.03	5.02666667	0.698
	0.096 gm at pH 5.0	5.01 5.o4 5.02	5.015	0.140
Temperature	5.0 pH at 26°C	5.02 5.04 5.05	5.03666667	0.303
	5.0 pH at 28°C	5.04 5.02 5.01	5.02333333	0.304
	5.0 pH at 30°C	5..03 5.02 5.06	5.04	0.561

Table 8: Robustness analysis of salbutamol sulphate solution for electrical conductivity

Parameter	Selected values	Different readings of electrical conductivity	Average	RSD%
Concentration of API	0.1 mg/ml at pH 5.0	120 118 117	118.333333	1.290
	1.5 mg/ml at pH 5.0	118 121 120	119.666667	1.276
	2.0 mg/ml at pH 5.0	118 118 117	117.666667	0.490
Concentration of buffer (Na_2SO_4) at standard API conc. i.e. 0.5mg/ml	0.048 gm at pH 5.0	121 116 118	118.333333	2.126
	0.096 gm at pH 5.0	120 118 119	119	0.840
Temperature	5.0 pH at 26°C	118 117 116	117	0.854
	5.0 pH at 28°C	118 119 120	119	0.840
	5.0 pH at 30°C	118 119 116	117.666667	1.298

8. Conclusion

Salbutamol sulfate is an effective drug for respiratory diseases and is available on market in different dosage forms. Its stability is key to its therapeutic performance. In this study, the salbutamol solution was stabilized at specific pH andthe electrical conductivity of the solution was studied concerning pH. The control of pH and electrical conductivity was done based on repeated experimentation and analysis of many parameters such as suitable solvent, the temperature of the solution, suitable buffer and its concentration. In comparison to previous methods, this method is simple and cost-effective.

This analytical method may also be used for future studies during further investigations of the different dosage forms of salbutamol sulfate and may even be used for other pharmaceutical preparations. The method is validated based on linearity, precision, accuracy and robustness. The developed and validated method is new, precise, compliant and also is time-effective. This method could serve as a new window for researchers to analyze the different formulations and it provides an easy way to control the pH and conductivity of solutions.

As pH and conductivity are important parameters for stability and a stable product are good at their therapeutic performance, so this is the method that is directly linked with the efficacy of products and hence this would be very helpful for studying different products and making them efficacious. This method can be used easily and is effective too. The proposed method is not only appropriate for routine stability analysis but will also be suitable for understanding various parameters involved in the control of pH and electrical conductivity.

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