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RESEARCH ARTICLE

QUANTIFICATION OF POTASSIUM CHLORIDE IN FINISHED DOSAGE FORMS USING HILIC WITH EVAPORATIVE LIGHT SCATTERING DETECTOR (ELSD)

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ABSTRACT

A simple and efficient reverse phase high performance liquid chromatography (HPLC) method was developed for assay and dissolution of Potassium chloride in Potassium chloride extended release tablets and capsules. The analyte was detected by Evaporative light scattering detector (ELSD) at a Nitrogen gas flow rate of 1.6 mL/min. Phenomenex Luna Hydrophilic interaction liquid chromatography (HILIC) column was used to separate both potassium (cation) and chloride (anion) in a single run. The proposed method was validated as per USP and ICH recommendations for Precision, Ruggedness, Accuracy, Linearity, Specificity, Filter interference and Robustness. The linearity of the method ranged from 125 µg/mL to 1500 µg/mL, accuracy results ranged from 99.7% to 101.6% and the overall Relative Standard Deviation (RSD) for Method precision and Intermediate precision was 1.2% to 1.4%. The method can be used successfully to analyze potassium chloride drug product for its potassium chloride content.

INTRODUCTION

Potassium chloride is a metal halide salt composed of potassium and chlorine. It is a white crystalline solid and odorless that is commonly used for the prevention and treatment of potassium depletion and/or hypokalemia. [1]. Potassium ions participate in a number of essential physiological processes, including the maintenance of intracellular tonicity, neurohumoral transmission, the contraction of cardiac, skeletal, and smooth muscle, and the maintenance of normal renal function. The intracellular concentration of potassium is approximately 150 to 160 mEq per liter. The normal adult plasma concentration is 3.5 to 5 mEq per liter. An active ion transport system maintains this gradient across the plasma membrane. Since potassium and chloride are one of the most important intracellular ions that regulate various physiological processes, these are often prescribed as dietary supplements in various diseased conditions as adjuncts or as main therapy. Potassium chloride is available as extended release Tablets and Capsules containing 600 and 750 mg, respectively, of potassium chloride, USP, equivalent to 8 and 10 mEq of potassium, respectively. In order to effectively monitor the quality of the dosage forms containing these supplements, a simple and efficient method of analysis is required that is rapid, sensitive, reproducible and cost effective. A variety of techniques are available to estimate the content of Potassium in different matrices like titrimetry, colorimetry, gravimetry, flame photometry, ion chromatography and atomic absorption spectroscopy. Conventional chemical methods involving titrimetry, gravimetry and colorimetry reported [2-8] for the estimation of potassium was reviewed with the intention of verifying the feasibility of the methods for the current formulated potassium chloride product. It was noted that the methods were lengthy and tedious with narrow working range with poor accuracy and applicability for formulated product.

Usage of specialized equipment for quantifying potassium is also reported, J K Dawborn et. al using technicon auto analyzer, but this method though yielded accurate results, required equipment that are not readily available at quality control laboratories of most of the pharmaceutical companies, thus making the method unfeasible in current settings [9]. The method reported by Xin Yu Jiang employing the use of Rayleigh light scattering technique [10] was also found to be unsatisfactory for the intended use as the working range for the method is very narrow i.e. 0.20 µg/mL to 1.60 µg/mL and it also requires specialized equipment that is not readily available at most of the quality control laboratories. The USP monograph method [11] for the estimation of potassium chloride from potassium chloride extended release tablets and Capsules was evaluated for the current application. The method employs atomic absorption spectrophotometer equipped with a potassium hollow-cathode lamp and an air–acetylene flame, the absorbance is measured using potassium emission line of 766.5 nm. The method involves tedious sample treatment, for example, samples to be diluted to about

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5000 fold for assay and about 270 fold for Dissolution. Practical difficulties were encountered during the sample analysis especially when the method was adapted for dissolution release profiling, where one would have to analyse at least 50 samples for mapping the time bound drug release profile. Due to the multiple dilutions involved, small variations in the absorbance are proportionally multiplied leading to erroneous results. Similarly flame photometry also could not be exploited for the reasons of sample treatment. Although other reported methods are available for the estimation of potassium, employing sophisticated instrumentation like atomic absorption spectroscopy, ion chromatography etc, practical difficulties are associated with these techniques, like complicated sample treatment, tedious procedure, high cost of analysis, and limitations related to repeatability, linearity and accuracy of the technique. A need was felt to develop a new robust method with greater linearity range, based on more commonly used technique that was cost effective and convenient in terms of greater accuracy and precision at quality control laboratory. To the best of our knowledge, there are no chromatographic methods in the literature for the analysis of potassium chloride in solid dosage forms. An attempt has been made to develop an efficient and selective method for the determination of potassium chloride contents in tablets/Capsules.

Method development

To begin with, various derivatization strategies were considered to enhance the analyte response but were later abandoned due to the lack of sensitivity and need of specialized chemicals. IC technique was not considered due its limited linearity range and need for the extensive sample dilution to get a linear response, its column and suppressor is most expensive and needs extensive care. To overcome the above limitations an attempt was made to use evaporative light scattering detector (ELSD) with Hydrophilic interaction liquid chromatography (HILIC) analytical column. ELSD is a universal detector with sensitivity to all the compounds. The principle of ELSD applies to all solutes having a lower volatility than the mobile phase used in their separation. In ELSD, the mobile phase containing solute is nebulized into tiny particles, the solvents in the droplet was evaporated and analyte particle enter into a detector chamber then it is scattered by light. The intensity of the light scattered from solid suspended particles depends on their particle size and proportional to analyte concentration. The advantages[12,13] of selecting ELSD is, all the non volatile compounds irrespective of it's chromophoric nature can be detected with high sensitivity and greater linearity range. It enables us to use the gradient elution method without any baseline drift and solvent peak thereby increasing the sensitivity and accuracy. HILIC chromatography is easy to use and works well where traditional reverse phase methodology fails; it allows for the increased retention of hydrophilic analytes using reverse phase solvents. In addition to increased retention for polar compounds, the elution order is typically the opposite of that for reversed phase with the most polar compounds eluting after the non-polar compounds, resulting in an alternative selectivity, called reverse of reverse phase chromatography.

The sensitivity and response was optimized by adjusting the nitrogen gas flow rate, detector drift tube temperature, gain and sample injection volume to get a linear response for potassium and chloride peak for the concentrations corresponding to undiluted sample which is about 800µg/mL for Dissolution and 750µg/mL for Assay analysis respectively. Finally the method was optimized with 100mM Ammonium acetate and Acetonitrile as mobile with a short run time of 5 minutes. Additionally, this method was extended for analyzing the drug from 0.1N Hydrochloric acid (pH 1.2), Sodium acetate buffer pH 4.5 and potassium phosphate buffer pH 6.8. For Sodium acetate buffer pH 4.5 and potassium phosphate buffer pH 6.8 dissolution medium, chloride peak was integrated for quantification due to the presence of potassium and sodium in the dissolution medium itself. The chloride peak displayed excellent linearity. The concentration and area counts were mathematically transformed into logarithmic form [14] and logarithms of the relevant peak responses versus logarithms of concentrations in mg/mL was plotted for each analyte from the Standard solutions and the regression line was determined using least-squares analysis. From the regression line the amount of dissolved potassium chloride was calculated using the equation $y = mx + c$. The obtained logarithmic concentration was converted to normal value by applying antilogarithms. The above developed analytical method was validated as per USP and ICH recommendations [15, 16] to ascertain its suitability for the intended use and subsequently used successfully for routine quality control and stability tests analysis.

MATERIALS AND METHODS

Chemicals, reagents and product

HPLC grade Ammonium acetate was purchased from Qualigens Fine Chemicals (Mumbai, India). Acetonitrile, Methanol and Acetone were purchased from Merck Specialties Private Limited (Mumbai, India). HPLC grade water from Milli-Q Water Purification system Millipore Inc, (USA) was used for all analytical work. Potassium chloride USP Drug substance was obtained from K+S Kali GmbH (Werk Werra, Standort WI), Potassium Chloride extended release tablets and capsules of 600 and 750 mg of each dosage form were provided by FDF R&D Center, Mylan Laboratories Limited, Hyderabad, India. Nitrogen gas cylinders with a purity of > 99.9% were procured from BOC Gases (Mumbai).

Instruments

Waters HPLC (Waters 2695 separation module, Waters Inc., USA) connected with Evaporative light scattering detector (Alltech 3300 ELSD, Grace Davison) was used. Data collection and analysis were performed using Empower II software (Waters Corporation, Milford, MA).

Chromatographic conditions

The chromatographic separation was achieved using Phenomenex Luna Hydrophilic interaction liquid chromatography (HILIC) Column (150 mm x 4.6 mm, 5µ). The column temperature was maintained at 30°C and the Injection volume was 5 µL. The analytes were eluted isocratically at a flow rate of 1.0 mL/min with 100mM Ammonium acetate and Acetonitrile in the ratio of 35 : 65 (v/v) with a run time of 5 minutes. The analytes were detected by Evaporative Light Scattering Detector at a nitrogen gas

flow rate of 1.6 L/min. Detector temperature was maintained at 60°C. The chloride and potassium peaks eluted at about 2 and 3 minutes respectively.

Preparation of standard solutions:

Preparation of standard solution for assay analysis

Potassium chloride standard stock solution was prepared by dissolving Potassium chloride in water (7500µg/mL). Five concentration levels of calibration standards were prepared by diluting potassium chloride standard stock solution with water to give a final concentration of 375µg/mL, 600µg/mL, 675µg/mL, 750µg/mL and 900µg/mL respectively.

Preparation of standard solution for dissolution analysis

Potassium chloride standard stock solution was prepared by dissolving Potassium chloride in water (8340µg/mL). Five concentration levels of calibration standards were prepared by diluting the potassium chloride standard stock solution with water to give a final concentration of 167µg/mL, 417µg/mL, 667µg/mL, 884µg/mL and 1000µg/mL respectively.

Preparation of sample solutions

Preparation of sample solution for assay analysis

Tablets were crushed to a fine powder. Powder equivalent to 3000 mg of potassium chloride was dissolved by sonication in 1000 mL of water. The sample solution was further diluted to obtain a concentration of 750 µg/mL, this was filtered through 0.45µm PVDF or Nylon syringe filter. Similarly, capsule sample having a final concentration of 750 µg/mL was also prepared and analysed.

Preparation of sample solution for dissolution analysis

Dissolution tests on six intact tablets/capsules were performed on USP Dissolution Apparatus II (paddle) with 900 mL of Purified water as the Dissolution medium, rotated at a speed of 50/100 rpm for two hours. Dissolution samples were withdrawn after specified time point and filtered through 0.45µm PVDF or Nylon syringe filter and injected into the chromatograph as such.

RESULTS AND DISCUSSION

Analytical method validation

Analytical method validation for the estimation of potassium chloride from finished dosage form was performed according to ICH Tripartite guideline on Validation of Analytical Procedures: Text and Methodology [15] and USP/NF current monograph recommendations [16].

System Suitability Evaluation

Relative standard deviation for area counts of six replicate injections of standard solution (750µg/mL for Assay and 833µg/mL for Dissolution) was not more than 2.0%. The correlation coefficient for the regression line obtained from calibration standards was not less than 0.995. The results obtained during the validation studies of Assay and Dissolution is tabulated in Table-1. The system suitability limits were proposed based upon commonly accepted limits for chromatographic analysis. All the system suitability limits obtained during the validation study were within the proposed limits.

Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present.The specificity of the method was evaluated by injecting placebo solution (Excipients) in the said chromatographic conditions. No interference was observed from the placebo. The resolution between the peaks due to chloride and potassium was found to be more than 5. Typical chromatograms of Placebo, Standard and Sample corresponding to Assay and Dissolution are presented in Figure 1 to 6.

Forced Degradation

Potassium chloride is very stable inorganic salt having the melting point about 773°C. Based on the proven stability, forced degradation studies in acid, alkali and peroxide medium was not performed. Drug product and placebo were exposed to heat (105°C for about 72 hours), humidity (25°C/90%RH for about 48 hours), light (for 1.2 million Lux hours) and UV light (for 200 W/m^2). No degradation was achieved in the above said conditions.

Precision

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Precision for Assay

This is done to establish the ruggedness of the method where environmental factors like instruments, analyst and day are considered. Six samples each were processed by two different analysts on two different days using two different lots of analytical column. The Assay and overall %RSD for twelve results were calculated and found to be well within the predefined acceptance criteria. The results are tabulated in Table-2.

Precision for Dissolution

Six units of tablets and capsules of each strength were processed by two different analysts on two different dissolution apparatus on different days using two different lots of analytical column. The dissolution and overall %RSD for twelve results were calculated and found to be well within the predefined acceptance criteria. The results are tabulated in Table-3. The dissolution results of potassium chloride extended release tablets from different dissolution medium are tabulated in Table-4.

Linearity

The linearity of an analytical procedure is its ability to obtain test results which are directly proportional to the concentration of analyte in the sample. Potassium chloride standard solutions were prepared from 40% to 200% (300µg/mL to 1500µg/mL)

Table1: System Suitability Data

System suitability parameters	Results for Assay	Results for Dissolution	Acceptance criteria
USP Tailing	1.3	1.2	The USP Tailing for Potassium peak should be not more than 2.0.
USP Plate Count	6163	6118	The USP Plate count for Potassium peak should be not less than 3000.
% RSD	0.4	1.8	RSD for area counts of Potassium peak from six replicate injections of standard solution should be not more than 2%.
Correlation coefficient	0.9999	0.9999	The correlation coefficient for the regression line is not less than 0.995.

Table 2: Precision data for Assay of Potassium chloride dosage form

Name	% Assay							
	KCl ER Tablets				KCl ER Capsules			
	600mg Strength		750mg Strength		600mg Strength		750mg Strength	
	MP	IP	MP	IP	MP	IP	MP	IP
Mean	98.6	97.3	98.4	96.7	101.2	100.2	99.2	100.7
% RSD	1.0	1.1	0.8	1.4	1.3	0.9	1.1	0.8
Overall Mean	97.9		97.5		100.7		99.9	
Overall % RSD	1.2		1.4		1.2		1.2	
Acceptance criteria	RSD for % assay results of both the analysts should be not more than 2.0%.							

Where ER : Extended Release; MP: Method precision and IP: Intermediate precision

Table 3: Precision data for Dissolution of Potassium chloride dosage form

Name	% Dissolution at 2Hrs							
	KCl ER Tablets				KCl ER Capsules			
	600mg Strength		750mg Strength		600mg Strength		750mg Strength	
	MP	IP	MP	IP	MP	IP	MP	IP
Mean(N=6)	35	37	35	36	35	35	36	35
Difference	2.0		1.0		0.0		1.0	
Acceptance criteria	1. Each unit is within the range Q(35%) ± 30% of the labeled amount of KCl is dissolved in 2 hours. 2. Difference between the mean dissolution results of Method precision and Intermediate precision should not exceed an absolute 10%.							

Where, MP: Method precision and IP: Intermediate precision

Table 4: Dissolution of Potassium chloride dosage form from different dissolution medium

Name	% Dissolution of KCl ER tablets at 24Hrs			
	Water medium	0.1N HCl medium	Acetate buffer pH 4.5 medium	Phosphate buffer pH 6.8 medium
Mean(N=6)	101	101	95	97
% RSD	0.7	1.1	3.1	1.6
Acceptance criteria	RSD for should not be more than 10%			

Table 5: Linearity data for Assay

Sr. No.	Linearity Level	Concentration (µg/mL)	Log Concentration (µg/mL)	Log area
1	40%	300.08	2.4772	6.15422
2	50%	375.10	2.5741	6.28078
3	80%	600.16	2.7783	6.53027
4	100%	750.20	2.8752	6.64922
5	120%	900.24	2.9544	6.76242
6	150%	1125.30	3.0513	6.86506
7	200%	1500.40	3.1762	7.00963
Correlation Coefficient				0.9997
Slope				1.2295
Y-Intercept				3.1145
Residual sum of square				0.00037938
Acceptance Criteria: The correlation coefficient should not be less than 0.995.				

Table 6: Linearity Data for Dissolution

Sr. No.	Linearity Level	Concentration (µg/mL)	Log Concentration (µg/mL)	Log area
1	15	125.09	2.0972	5.69546
2	20	166.78	2.2221	5.83473
3	50	416.95	2.6201	6.35841
4	80	667.12	2.8242	6.62117
5	100	833.90	2.9211	6.72360
6	120	1000.68	3.0003	6.81723
Correlation Coefficient				0.9997
Slope				1.2598
Y-Intercept				3.0484
Residual sum of square				0.0006473
Acceptance Criteria: The correlation coefficient should not be less than 0.995.				

Table 7: Accuracy data for Assay

Recovery level	Mean % Recovery	%RSD
10 %	99.7	0.7
50 %	99.8	0.8
80 %	101.2	0.3
100 %	101.6	0.4
120 %	101.4	0.6
150%	100.0	0.9

Acceptance Criteria:

a. The Individual recovery should be between 97.0% and 103.0%.
b. The average recovery of each level should be between 97.0% and 103.0%.
c. The RSD for each level should be not more than 2.0%.

Table 8: Accuracy data for Dissolution

Recovery level	Mean %Recovery	%RSD
15 %	101.9	1.1
20 %	98.8	1.0
50 %	100.7	1.7
80 %	102.1	2.1
100 %	101.6	1.7
120 %	99.1	2.2

Acceptance Criteria:

a. The Individual recovery should be between 95% and 105%.
b. The RSD for each level should be not more than 5%.

Table 9: Robustness data

System suitability parameter	Control	Flow rate		Column oven temperature		Mobile phase composition		Detector temperature		Nitrogen gas flow	
		0.9mL/min	1.1mL/min	25°C	35°C	Buffer: ACN (35:58)	Buffer: ACN (35:72)	58°C	62°C	1.4 L/min	1.8 L/min
Tailing factor	1.4	1.4	1.3	1.3	1.4	1.4	1.4	1.4	1.5	1.5	1.4
Theoretical plates	5557	6231	5077	6038	5031	5126	5471	4785	5179	4651	4957
% RSD	1.8	1.7	1.3	1.8	1.5	0.8	2.5	2.0	0.8	1.2	1.6
Correlation $_{coeffint}$	0.9997	0.9993	0.9996	0.9986	0.9995	0.9994	0.9993	0.9995	0.9995	0.9986	0.9985
Acceptance Criteria	The USP Tailing for Potassium peak should be not more than 2.0. The USP Plate count for Potassium peak should be not less than 3000. RSD for area counts of Potassium peak from six replicate injections of standard solution should be not more than 2%. The correlation coefficient for the regression line is not less than 0.995.										

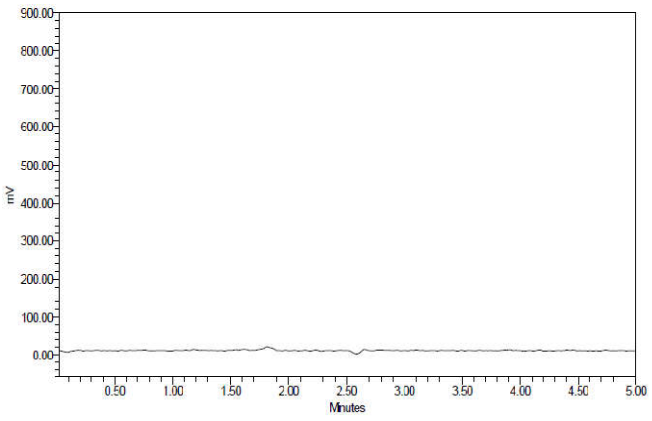

Figure 1 : Typical Placebo Chromatogram of Assay

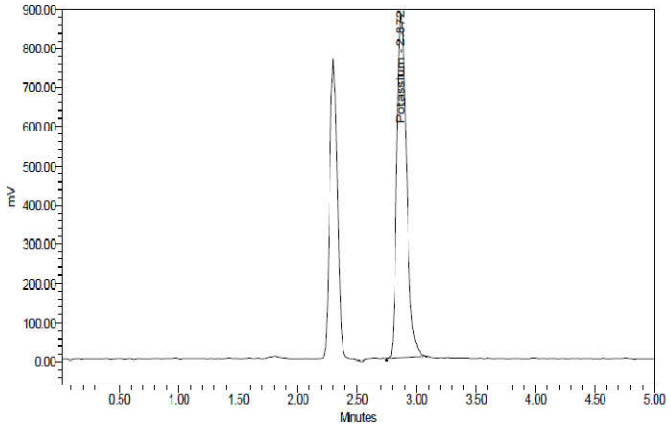

Figure 2 : Typical Standard Chromatogram of Assay

of sample concentration for assay and 15% to 120% (125µg/mL to 1000µg/mL) of sample concentration for dissolution. A graph was plotted between log area counts and log concentration. The correlation coefficient from the regression line was calculated by linear fit method and it is found to be 0.9997 indicating that the method is linear in the above said range. The results are tabulated in Table -5 to 6 and linearity graphs are shown as Figure-7 and Figure-8.

Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted

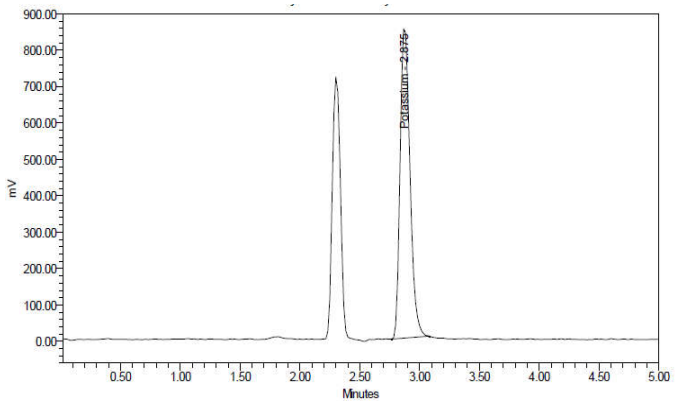

Figure 3 : Typical Sample Chromatogram of Assay

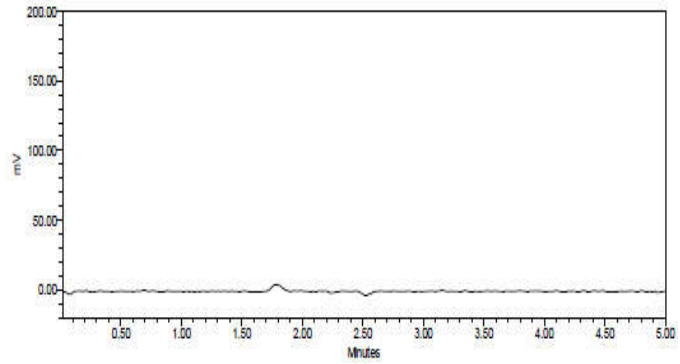

Figure 4 : Typical Placebo Chromatogram of Dissolution

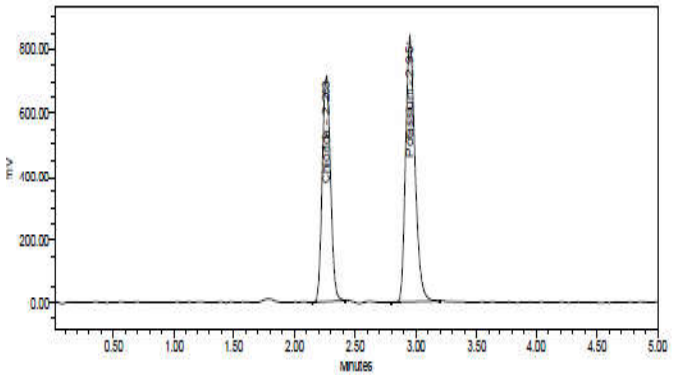

Figure 5 : Typical Standard Chromatogram of Dissolution

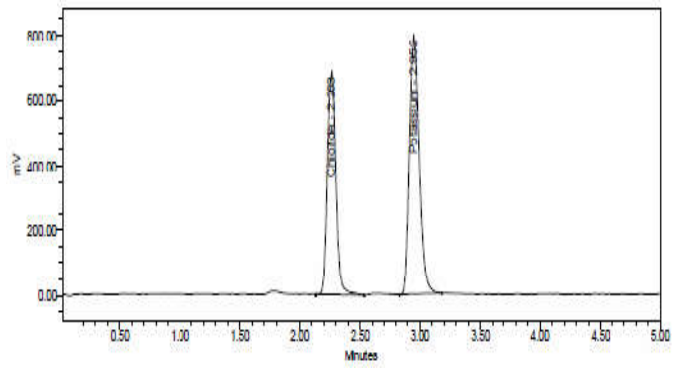

Figure 6 : Typical Sample Chromatogram of Dissolution

either as a conventional true value or an accepted reference value and the value found. This is sometimes termed trueness. Accuracy of the method was performed by addition of known

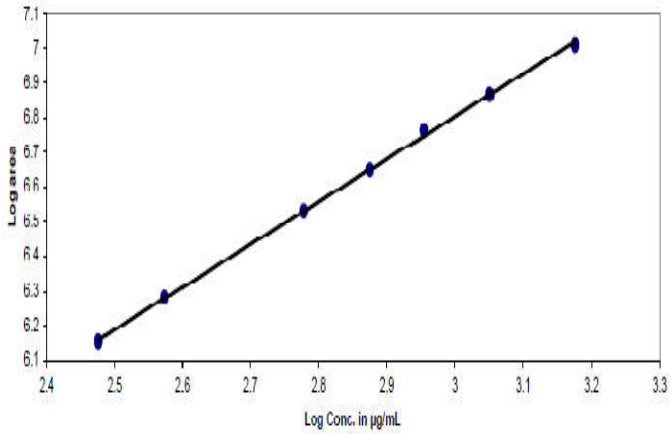

Figure 7: Linearity graph for Assay

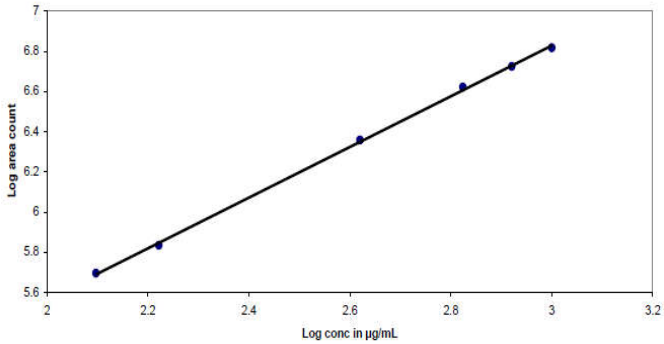

Figure 8: Linearity Graph for Dissolution

concentrations of Potassium chloride Active Pharmaceutical Ingredient (API) into placebo (only recipients) at 10% to 150% of sample initial concentration for assay and 15% to 120% for dissolution on higher strength, to establish recovery of the method. Each level was prepared in triplicate and analysed. The mean % recovery was found to be between 99.7 and 101.6% with the % RSD from 0.3 to 0.9% for assay and 98.8 and 102.1% with the %RSD from 1.0 to 2.2% for dissolution, indicating that the method has excellent accuracy. The results are tabulated in Table -7 and 8.

Filter interference

A study to ascertain the suitability of filters was conducted using two different construction materials of filters namely 0.45 µm PVDF filter and 0.45 µm Nylon filter respectively. The standard solution and sample solution was analysed and the results indicate that the both filters are compatible indicating any one of the filters can be used for routine purpose without loss of analyte.

Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate ariations in method parameters and provides an indication of its reliability during normal usage. The robustness of the method was evaluated by small but deliberate variation in the flow rate of mobile phase (± 10%), Column oven temperature (± 5°C), Mobile phase composition (Buffer : Acetonitrile 35:65 to 35:58 and 35:72), Detector drift tube temperature (± 2°C) and Nitrogen gas flow (± 12.5%). The system suitability

was evaluated by injecting the standard solution and calibration standard solutions as per the method. There is no significant variation was observed in the system suitability results. It is observed that the increase in the acetonitrile in the mobile phase composition produces increased retention of analyte and vice versa, thereby meets the column principle. The increase in the nitrogen gas flow rate produces the tiny droplet resulting in less peak response than the control and decrease is produces the big droplets resulting in more peak response. The variation in the detector drift tube temperature is not significantly affecting the response. It is evident from the data that the method is robust for minor variations in the above said method parameters and is suitable for its intended use. The results are tabulated in Table-9.

Conclusion

An efficient reverse phase HPLC method was developed and validated for the quantification of potassium chloride dosage forms like tablets and capsules for assay and dissolution tests. There was a need for a simple method to analyse inorganic ions without the usage of sophisticated instruments and sample treatment. The validated method shows high sensitivity and uses commonly available analytical instruments with minimum sample processing steps leading to high throughput, thereby fulfilling the need of pharmaceutical industry. The method is capable of analyzing the active drug from different matrix which has been proven from the recovery studies in both capsules and tablets formulation. Additionally the method was found to be robust which is seen from the wide pH range of about 1 to 7 used as dissolution medium. The developed method has been proved equivalent to the recommended USP monograph method for assay and dissolution method. This potentially can lead to cost benefit to the laboratory since current USP method prescribes detecting the analyte by atomic absorption spectroscopy with multiple sample processing steps.

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16. ICH Topic Q 2 (R1) Validation of Analytical Procedures:Text and Methodology, ICH Harmonised Tripartite Guideline.

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