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Research Article

METHOD VALIDATION FOR THE DETERMINATION OF WATER CONTENT OF METERED DOSE INHALER BY KARL FISCHER COULOMETER

Momin Mohammad Abdul Motalib[1], Afrose Afrina[1], Khan Mohammad Salahuddin[1], Mashud S.M. [2], Anisuzzaman Sharif Md.[1]*
[1]Department of Pharmacy, Jahangirnagar University, Savar, Dhaka, Bangladesh
[2]Sir Salimullah Medical College, Dhaka, Bangladesh

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*E-mail: shamim729@yahoo.com

ABSTRACT
This study aimed to validation of water content determination method of inhaler by Karl Fischer Coulometer to outline a simple procedure. The system suitability test was performed by injecting standard solution (0.1% water standard).The average % recovery was found 99% which is within the acceptance limit of 95% to 105%. From the specificity study, it was observed that there was no response in case of blank (without sample or standard) measurement, and the spike sample (with 0.1%water standard) showed positive response. In the linearity study the squared correlation coefficient was found to be 0.999, which indicated that the method was linear. It was observed that %RSD of system precision, repeatability, and intermediate precision were 3%, 6% and 7% respectively which was within the acceptance limit (5% for system precision and 10% for repeatability and intermediate precision).The result of accuracy in terms of average % recovery of water was 99% with average %RSD 1% and 95% confidence interval was 97.58 to 99.98. The method was found to be robust for changing titrant source, titrant volume and rotation of stirrer. The titrant was found to be stable up to 24 hours. So, it can be a good alternative to existing methods for water content determination.

KEYWORDS: Inhaler, Karl Fischer coulometer, water content, validation.

INTRODUCTION

Method validation is the process of testing a measurement procedure to assess its performance and to make certain that performance is acceptable. Validation or revalidation of method is essential before their introduction into routine use.[1] The International Conference on Harmonization (ICH) has developed a text on the validation of analytical procedures.[2] Guidelines on submitting samples and analytical data for methods validation also proposed by the United States Food and Drug Administration.[3-5] The United States Pharmacopoeia (USP) has published specific guidelines for method validation for compound evaluation.[6]

Metered-dose inhaler (MDI) delivers a specific amount of medication (bronchodilator, corticosteroid or a combination of both) to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used drug delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases.[7] In pressurized metered-dose asthma inhalers Chlorofluorocarbons (CFCs) have historically served as the propellants of choice, but concern has been raised in recent decades regarding their damaging effect on the ozone layer. Among the alternative propellants being considered is Hydrofluoro alkane (HFA) in asthma inhalers.[8] According to Guidance for Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) drug products, ethanol is added to HFAs to increase the solubility of excipients such as surfactants - oleic acid. While water is quite insoluble in pure HFAs, the presence of ethanol allows greater solubility. The MDI formulation composition will have a direct effect on the degree or extent of agglomeration or suspendibility of the drug substance particles. Preferential interaction of the suspended drug substance with the various internal container and closure system components (e.g., adherence of the drug substance to the walls of the container or valve components) may also contribute to a non-homogeneous distribution of drug substance. The above mentioned phenomena may be exacerbated with time, can contribute to inconsistent medication dose delivery and particle size distribution. Study showed that the drug-free MDIs produced lower electrostatic charges than the commercial medicated ones .The charges of both HFAs shifted towards neutrality or positive polarity as the water content increased. The spiked water would increase the electrical conductivity and/or decreased the electro negativity of the liquid propellant surface. The mean number of elementary charges per droplet decreased with decreasing droplet size.[9]

According to Karl Fischer-application bulletin 137/3 the reagent and solvent should be in the same liquid during coulometric water determination. The reagent is released by the induction of an electrical current. The amount of current required convert the water is the determinant of the amount of moisture. Coulometric water determination is primarily used for the determination of small amounts of water.. The objective of present study is to outline a simple procedure for the water content determination method for commercially available salbutamol sulfate metered dose inhaler.

MATERIALS AND METHODS

Chemicals, Reagents & Standards

Hydranal and methanol solution for Karl Fischer coulometer were from Sigma Aldrich, Germany and Merck KGaA, Germany respectively. 0.1% water standard from Merck KGaA, Germany was used. Inhaler samples were collected from the local market of Bangladesh.

Instruments, Equipments & Apparatus

A Karl Fischer Coulometer from Metrohm Ltd., Switzerland, analytical four digit balance from Mettler, Switzerland, and syringe with needle from JMI Bangla Co. Ltd, Bangladesh were used.

Methods

System Suitability

Water standard vial was broken to open. Approximately 1 ml of standard solution was filled in the syringe using the needle. Syringe was rinsed by turning it round and holding the needle point up to expel the entire contents (air and standard solution). This moistens the whole inner surface of the syringe. The syringe was filled with the entire remaining contents of the vial, with no aspiration or air. The needles were wiped and weight of the syringe was tarred on the balance. After starting the KF coulometer approximately 0.5 ml of the standard solution with one stroke was injected directly under the surface of the KF solution. The syringe was removed from the KF solution and re-weighed. The total water content given by the KF (C) was recorded. Above steps were repeated by injecting approximately 2.0 ml. and 3.5 ml. Percent recovery for the three determinations were calculated

Sample analysis

The pMDI unit was shaken and the stem was attached to the adaptor in the titration cell. After performing all actuations weight of the inhaler was entered in the KF. pMDI unit was disconnected from the needle adaptor. The unit was reweighed to record weight difference. Water content determined automatically by the KF (C) was recorded. Above steps were repeated 3 times per unit.

Validation

The coulometric method was validated by determining its system suitability, specificity, linearity, precision, accuracy, robustness and stability study. The system was deemed suitable if the % recovery was 95-105%. Specificity demonstrated that for blank there will be no response but for spike sample it should have positive response. For the method to be linear the R^2 value should be close to 1.In case of system precision the %RSD should be not more than 5% and method precision and intermediate precision should be within 10%.In accuracy study the recovery obtained did not differ from the real value in more than ± 5%. The method should be robust through the change of titrant (different source), titrant volume and rotation of stirrer.

RESULTS AND DISCUSSION

System suitability testing

System suitability testing is an integral part of analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operation and samples to be analyzed constitute an integral system that can be evaluated as such. Table-1 shows the system suitability data. For system suitability three different concentrations (0.5g, 2.0g and 3.5g) of 0.1% water standard was used and % recovery was evaluated.

Table 1 represents that the % recovery for three different determinations is within 95-105%. So the system was suitable for further analysis.

Specificity

Specificity of an analytical method is its ability to assess unequivocally the analyte in the Presence of components that may be expected to be present. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical Procedures.[6] Table-2 shows the specificity data.

From this study it was observed that, in case of blank there is no response but for standard measurement it shows positive response. So the method is very specific for determination of water.

Linearity

The linearity of an analytical method is its ability to elicit test results directly proportional to the concentration of the analyte in samples within given range. [11]

Linearity was determined by injecting a range of known amount of water standard (0.2g, 0.5g, 2.0g, 3.5g, and 5.0g) and evaluating the change of response of water found in microgram.Figure-1 shows the linearity data.

Figure -1 indicates that with the concentration the amount of water (mcg) increased and correlation co-efficient (R^2) value was 0.9997 that reveals the method is linear[12]

Precision

The precision of an analytical method is the degree of repeatability of the results in a series of experiments run during a single session by single operator with identical reagents and equipments.[12]

System precision:

Sample repeatability was assessed by performing replicate determinations (n=6) of the 0.1% water standard (2.0g) and % recovery of the results were calculated. The results showed that % relative standard deviation of system precision is 3% which is within the acceptance limit of 5%.

Method precision:

Method Precision will be assessed by six replicate determinations of 1g of Sample (required actuations) from a single canister. The results show that % Relative Standard Deviation of sample repeatability was 6% which is well within the acceptance limit of 10%.

Intermediate precision:

Intermediate precision or ruggedness study of an analytical method is the degree of reproducibility of the test results obtained by the analysis of the same samples under a variety of normal test conditions i.e. different instrument, analysts, days etc.[2, 10] Sample for Intermediate precision was assessed by six replicate determinations of 1g of sample (required actuations) from a single canister and % Recovery of the results was calculated. RSD of two analysts (n=12) was within the limit (limit 10%). So the water content method for inhaler can be considered to be rugged enough.

Accuracy

The accuracy of an analytical method is the closeness of test results obtained by that method to the true value.[11] Accuracy may often be expressed as percent recovery by the assay of known, added amount of analyte.

Accuracy shall be carried out by spiking of 0.1% water standard over a range 50%, 100% and 150% of test concentration, analyzing each sample three times; with three replicates of each concentration .[12] The recovery obtained did not differ from the real value in more than ± 5%. Table-4 represents the accuracy data.

The results of accuracy in terms of % recovery was within the acceptance limit of 95% to 105% and the %RSD was below 5%.

Robustness

The robustness of an analytical method is a measure of its capacity to remain unaffected by small but deliberate variation in method parameters and provides an indication of its reliability during normal usage. [11] The robustness was evaluated by checking the effect of change of titrant (different source), effect of change of titrant volume and effect of change of rotation of stirrer.

It was observed that there is no significant change in the system suitability parameters and %RSD By changing titrant

source, titrant volume change and rotation change of stirrer it was within the acceptance limit.

Stability study

The titrant stability experiment was performed under room temperature at intervals of Initial, 3, 6, 12, 18, 24 hours. The Titrant was found to be stable for 24 hours, and %RSD and % Difference from Initial of %Recovery was within the acceptance limit for both conditions.

CONCLUSION

The water content method adopted for the metered dose inhaler by Karl Fischer Coulometer is precise, linear, accurate, rugged and robust enough. The titrant solution was found to be stable up to 24 hours. Hence this method can be considered for its intended purpose to establish the quality of the product during stability study and routine analysis with consistent and reproducible results.[2] this approach demonstrated significant time savings over conventional validation approaches while providing assurances of acceptable method specificity, accuracy, precision, linearity, and Robustness.

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TABLE – 1: SYSTEM SUITABILITY STUDY

Determinations	0.1% water Standard(g)	Result (ppm)	% Recovery
1	0.5048	1013.5	99
2	2.0106	980.2	96
3	3.6124	1051.0	103
Mean			99
SD			3.5
%RSD			3.5

TABLE–2: SPECIFICITY STUDY

Sample ID	Sample Size (g)	Result (ppm)
Blank measurement		No Response
Standard measurement	2.0015	1007.6

TABLE- 3: INTERMEDIATE PRECISION OR RUGGEDNESS STUDY

Analyst Name		Analyst-1	Analyst-2	
Date of analysis		25.04.2011	26.04.2011	
Sl. No.	Sample(g)	Result (ppm)	Sample (g)	Result (ppm)
01	1.0009	298	1.0102	275
02	1.0032	292	0.9812	286
03	0.9987	274	0.9866	302
04	0.9998	294	0.9926	244
05	0.9771	255	0.9987	299
06	1.0092	298	0.9895	257
Mean(n=6)		285	Mean (n=6)	277
Standard deviation		17.26	Standard deviation	23.16
Relative standard deviation		6	Relative standard deviation	8

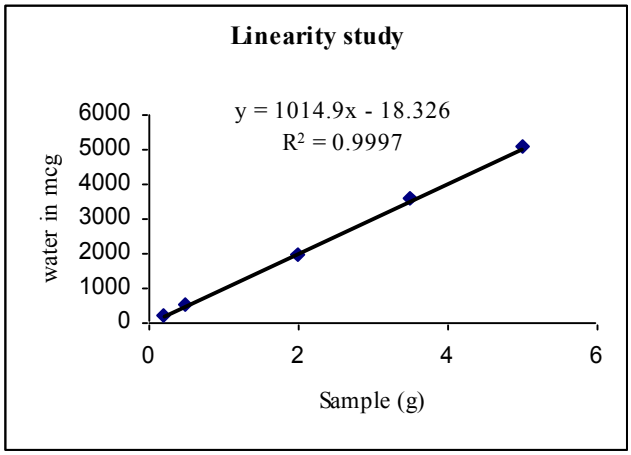
Combined Results of both analysts (n=12):
Mean : 281
Standard Deviation : 20.21
Relative Standard Deviation : 7

TABLE- 4: ACCURACY STUDY

Sample ID	Sample (g)	Result (µg)	%RSD	% Recovery	%RSD
Sample -0.25g (50%)	0.2510	259.5	2	101	1
	0.2549	262.5		101	
	0.2501	253.3		99	
Sample -0.50g (100%)	0.5012	505.7	2	99	2
	0.4948	486.7		96	
	0.4997	500.2		98	
Sample -0.75g (150%)	0.7515	750.4	1	98	1
	0.7519	763.0		99	
	0.7501	749.2		98	

Sample ID	50%	100%	150%	%RSD	50%	100%	150%	%RSD
Minimum	253	487	749	1	99	96	98	1
Maximum	263	506	763	2	101	99	99	2
Average	258	498	754	2	100	98	98	1
95% Confidence Interval : 97.28 – 99.98								

FIGURE 1: LINEARITY STUDY



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