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USP Monograph Modernization Initiative: Chemical Medicines Assay by Potentiometric Titration

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PURPOSE

Many of the chemical medicine assay procedures are done by manual titration as per USP monographs. The manual titration procedure lacks data integrity and adds another layer of complexity. Pharmaceutical QA/QC needs an analytical technique with data integrity for FDA audits and reliable product release.

As science advances, the USP reviews monographs to assess if they should be changed to reflect recent innovations and technology updates making laboratory analysis more efficient, cost-effective, and safe. Autotitration combined with suitable equivalence point detection not only improves specificity, but fulfills data integrity. As part of USP monograph modernization, a new assay method for potassium bicarbonate and potassium carbonate is developed and validated using autotitration.

METHOD

Technology Selection: pKb values of potassium carbonate, a diacidic base, are ~8.3 and 3.69, corresponding to the addition of successive protons to the base. Separation techniques like Ion Chromatography (IC) cannot separate due to species conversion under chromatographic conditions. Potentiometric titration using a combined glass electrode distinguishes carbonate and bicarbonate easily, with two distinctive equivalence points when titrated against HCl.

Instrument: Dynamic Equivalence Point (DET) mode was used in autotitration – which controls the titrant addition based on the titration curve slope change and combines all the simple functions like “dosing”, stirring, titrating, calculating and stopping titration in a sequence. Figure 4 shows an autotitrator as used in this study.

Sample Preparation: 1 g of sample was weighed to 0.0001 g on an analytical balance, dissolved in 150 mL of carbonate free water and titrated immediately with 1N HCl. Methods are validated according to USP General Chapter <1225> VALIDATION OF COMPENDIAL METHODS.

RESULT

The method validation elements of specificity, system suitability, linearity, accuracy and precision, intermediate precision, and sample analysis were investigated for potassium carbonate and potassium bicarbonate, and the results met the validation criteria. The validation results are summarized in Table 1 below.

Specificity was checked by spiking a known quantity of potassium carbonate to potassium bicarbonate and vice versa. The appearance of the first inflection point due to carbonate is recorded (Fig.1). An increase in the second equivalence point due to excess bicarbonate is recorded with a potassium bicarbonate spike into potassium carbonate (Fig.2).

Linearity was checked with 5 samples covering 50% to 150% of the recommended sample weight (1.0 g), correlation coefficient (R) = 0.9999 was obtained (Fig 3).

Potassium Carbonate (K_2CO_3) and Potassium Bicarbonate ($KHCO_3$) – Assay by Potentiometric Titration

Analytical Performance Characteristics	Procedure	Acceptance Criteria	Results	Results
System Suitability	6 replicates using Sigma-Aldrich, Trizma base	RSD ≤ 0.5%	s(abs) = 0.0016, s(rel) = 0.16%	PASS
Specificity	Addition of 0.5 g of K2CO3 results in a additional inflection before the KHCO3 inflection; Addition of 0.125 g of KHCO3 results in increase in second inflection volume	not applicable	Both replicates show a second inflection before the KHCO3 inflection corresponding to pKb values. Both replicates show an increase in second inflection point due to excess KHCO3	PASS
Linearity	Five Linearity Solutions from 50-150% 0.5 g, 0.75 g, 1.0 g, 1.25 g & 1.5 g standard to 150 mL DI water; Duplicate analysis per sample weight. 5 linearity samples, duplicate determination	Correlation Coefficient (R) NLT 0.999	KHCO3: R2 = 0.9999 Equation: 10.054x + 0.1222 K2CO3: R2 = 0.99999 Equation: 14.325x + 0.0017	PASS
Accuracy & Precision	80%, 100% and 120% level of standard weight (1.0 g) in triplicate.	The average assay result at each level should be 100±2.0% of manufacturer’s CoA value. The RSD of the nine assay results should be NMT 1.0%.	Spectrum KHCO3 & K2CO3 used, 9 determinations RSD of 9 assays KHCO3 = 0.43%; RSD of 9 assays K2CO3 = 0.15% Assay within 100 ± 2.0% of manufacturer’s CoA value	PASS
Intermediate Accuracy & Precision	9 accuracy/precision solutions analyzed against a standardized titrant using a different electrode on a different day by a different user.	The average assay result at each level should be 100±2.0% of manufacturer’s CoA value. The %RSD of the nine assay results should be NMT 1.0%. The two average results for the first and second scientist differ by NMT 2.0%. Report the %RSD of the 18 assay results.	Spectrum KHCO3 & K2CO3 used; KHCO3 9 determinations RSD = 0.43%; RSD of all 18 accuracy & precision samples = 0.42% K2CO3: 9 determinations RSD = 0.05%; RSD of all 18 accuracy & precision samples = 0.41% Assay within 100 ± 2.0% of manufacturer’s CoA value	PASS
Sample Analysis	Two other sources of drug substance using standard sample weight and analyzed in duplicate, compare to manufacturer’s CoA values.	Report the average result and compare it with monograph specification of 99.5-100.5% and CoA of the manufacturer.	KHCO3: 2 replicates of: Chem Cruz, Lot K0415 MP Biomedicals, Lot Q5019 Chem Cruz Certified: 99.8%; Found: 100.03% MP Biomedicals: Certified: 100.39%; Found: 100.34% K2CO3: 2 replicates of: Chem Cruz, Lot H1919 Sigma Aldrich, Lot SLBS5238 Chem Cruz Certified: 99.1%; Found: 99.42% Sigma Aldrich: Certified: 99.8%; Found: 99.81%	PASS

Table 1: Validation Summary

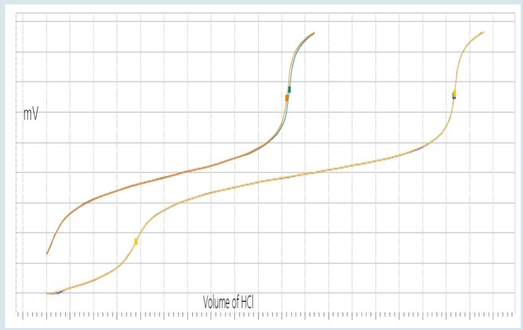

Fig 1: Specificity: Sodium Carbonate spiked with Sodium Bicarbonate

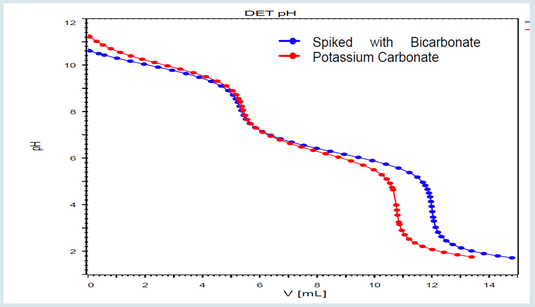

Fig 2: Specificity: Sodium Bicarbonate spiked with Sodium Carbonate

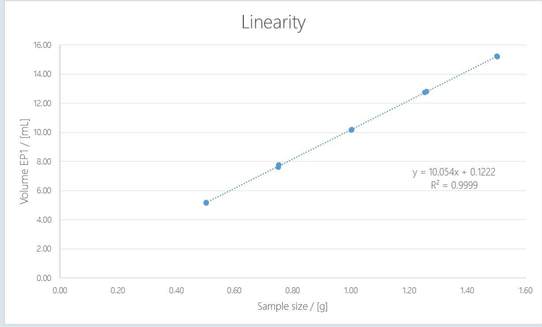

Fig 3: Linearity for Potassium Bicarbonate

Fig 4: Autotitrator and electrode used for chemical medicine assay

CONCLUSION

The new potentiometric titration assay method for potassium bicarbonate and potassium carbonate assay offers selectivity and fulfills all USP method validation requirements as per USP General Chapter < 1225>. Potentiometric titration based assay determination is faster and easy to use compared to the chromatographic techniques and can be easily automated to fulfill high throughput needs. Autotitration combined with appropriate equivalence point detection methods not only eliminates manual errors, but fulfills data integrity and 21 CFR Part 11 requirements, which makes the pharmaceutical QA/QC workflow easier.

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