TITRATION APPLICATION NOTE T-210

Assay of potassium carbonate and potassium bicarbonate

Fully automated, reliable, and selective potentiometric titration assay method according to USP<1225>

Potassium carbonate and potassium bicarbonate are important raw materials for the pharmaceutical industry. As active pharmaceutical ingredients (APIs), both can be used in effervescent tablets and powders as dietary supplements to help patients with low or high blood potassium levels and corresponding health problems like high blood pressure or kidney disease. The potassium level is important for the metabolic panel and electrolyte balance which can be life-threatening if imbalanced.

For both materials, the other species is the most important impurity. A selective method is therefore required for the assay. Separation of the two species by ion chromatography is not possible because the eluent (mobile phase) changes the ratio of carbonate to bicarbonate, falsifying the test result.

The pK_b values of potassium carbonate, a diacidic base, are approximately 8.3 and 3.69, respectively. These values correspond to the addition of

successive protons to the base. Potentiometric titration with a combined glass electrode easily distinguishes between carbonate and bicarbonate when titrating against hydrochloric acid with two distinct equivalence points – even in high potassium concentrations. Therefore, titration is the method of choice for pharmacopeias such as USP and Ph.Eur.

This Application Note describes a potentiometric titration method, without any special preparation, for a potassium bicarbonate ($KHCO_3$) and potassium carbonate (K_2CO_3) assay that provides selectivity and meets all USP method validation requirements under USP General Chapter <1225>.

SAMPLE AND SAMPLE PREPARATION

This application is demonstrated on potassium carbonate (K_2CO_3) and potassium bicarbonate ($KHCO_3$) from the following suppliers: Spectrum, Sigma Aldrich, Chem Cruz, and MP Biomedicals.

No sample preparation is required.

EXPERIMENTAL

The determinations are carried out on an automated system consisting of an OMNIS Sample Robot S equipped with Dis-cover, OMNIS Dosing Module, and an OMNIS Professional Titrator equipped with a dEcotrode Plus (**Figure 1**).

Carbonate-free, deionized water is automatically added to a reasonable amount of sample, and then the solution is stirred to dissolve the sample. Afterwards, the sample is titrated with standardized hydrochloric acid (HCl) until after the equivalence point is reached.

The different requirements for the validation according to USP<1225> are listed in **Table 1.**

Figure 1. OMNIS Sample Robot S with Dis-Cover functionality, Dosing module, and OMNIS Advanced Titrator equipped with dEcotrode Plus for the determination of potassium carbonate and potassium bicarbonate.

Table 1. Procedures for the different analytical performance characteristics for the validation of potassium carbonate and potassium bicarbonate.

Performance Characteristics	Potassium carbonate	Potassium bicarbonate
System Suitability	Six replicates using Sigma-Aldrich, Trizma base	
Specificity	Addition of 0.5 g of K_2CO_3 results in an additional inflection before the $KHCO_3$ inflection	Addition of 0.125 g of $KHCO_3$ results in increase in second inflection volume
Linearity	Five linearity samples from 50–150%. Duplicate analysis per sample weight.	
Accuracy & Precision	80%, 100%, and 120% level of standard weight (1.0 g) in triplicate	
Intermediate Accuracy & Precision	Nine accuracy/precision solutions analyzed against a standardized titrant using a different electrode on a different day by a different user	
Sample Analysis	Two other sources of drug substance using standard sample weight and analyzed in duplicate, compare to manufacturer's CoA values	

RESULTS

The method validation elements of **Table 1** which include specificity, system suitability, linearity, accuracy and precision, intermediate precision as well as accuracy, and sample analysis were examined for potassium carbonate and potassium bicarbonate and the results met the validation criteria. The validation results are summarized in **Table 2**. The assay determination according to USP<1225> for K_2CO_3 and $KHCO_3$ is shown separately in **Table 3**.

Table 2. Results for the potassium carbonate assay and potassium bicarbonate assay determination according to USP<1225> for K_2CO_3 and $KHCO_3$.

Sample (n = 9)	Assay in %	SD(rel) in %
Potassium carbonate	99.58	0.15
Potassium bicarbonate	100.40	0.43

Specificity was checked by spiking potassium bicarbonate with a known amount of potassium carbonate and vice versa. The determination of potassium bicarbonate with a resulting equivalence point is shown in **Figure 2**.

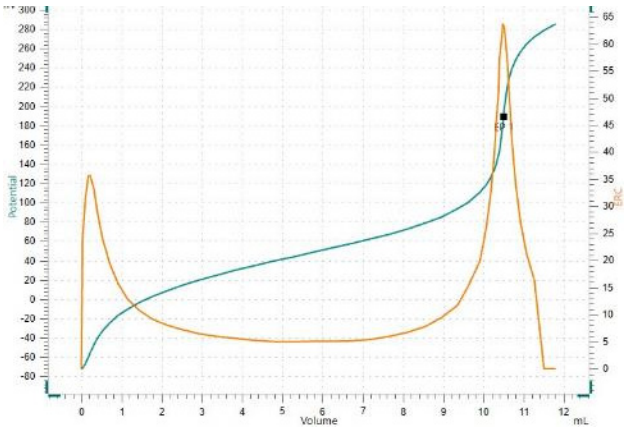

Figure 2. Titration curve of the assay determination of potassium bicarbonate. EP1 corresponds to potassium bicarbonate.

A spiked sample (i.e., potassium bicarbonate spiked with a known amount of potassium carbonate) is shown in **Figure 3**. If the titration curves of potassium bicarbonate and a spiked sample are overlaid, the shift of the second equivalence point is clearly seen (**Figure 4**).

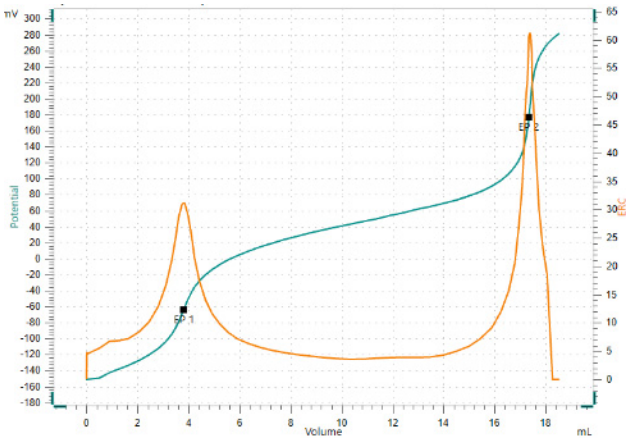

Figure 3. Titration curve of the assay determination of potassium bicarbonate spiked with potassium carbonate. EP1 corresponds to potassium carbonate and EP2 to potassium bicarbonate.

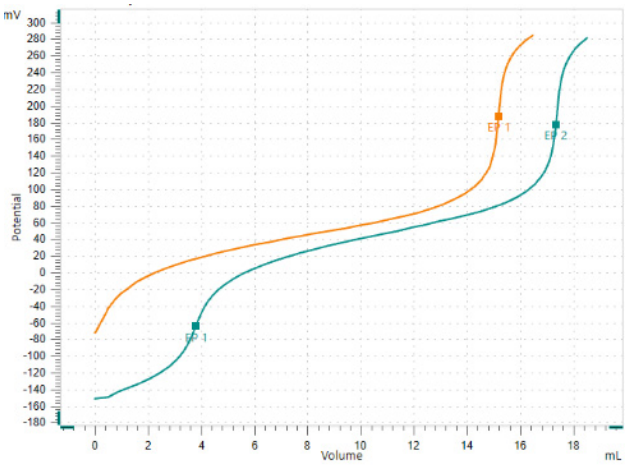

Figure 4. Curve overlay of the assay determination. Only potassium bicarbonate spiked with potassium carbonate shows two EPs.

Linearity was checked with five samples ranging from 50% to 150% of the recommended sample weight (1.0 g), and a correlation coefficient (R^2) of 0.9999 was obtained (**Figure 5**).

Overall, this method demonstrates acceptable results and well-defined titration curves for the determination of $KHCO_3$ and K_2CO_3.

Table 3. Acceptance criteria and results for the validation of potassium carbonate and potassium bicarbonate.

Performance Characteristics	Acceptance Criteria	Results
System suitability	RSD ≤0.5%	SD(abs) = 0.0016 SD(rel) = 0.16%
Specificity	Not applicable	Both replicates show a second inflection before the $KHCO_3$ inflection corresponding to pK_b values. Both replicates show an increase in second inflection point due to excess $KHCO_3$
Linearity	Correlation coefficient (R^2) ≥0.999	$KHCO_3$: R^2 = 0.9999 K_2CO_3: R^2 = 0.99999
Accuracy & Precision	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 ≤1.0%	$KHCO_3$: RSD (n = 9) = 0.43% K_2CO_3: RSD (n = 9) = 0.15% Assay within 100 ± 2.0% of manufacturer's CoA value
Intermediate Accuracy & Precision	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 ≤1.0%. The two average results for the first and second scientist differ by ≤2.0%. Report the %RSD of the 18 assay results.	$KHCO_3$: RSD (n = 9) = 0.43%; RSD (n = 18) = 0.42% K_2CO_3: RSD (n = 9) = 0.05%; RSD (n = 18) = 0.41% Assay within 100 ± 2.0% of manufacturer's CoA value
Sample Analysis	Report the average result and compare it with monograph specification of 99.5–100.5% and CoA of the manufacturer	$KHCO_3$: Chem Cruz Certified: 99.8%; Found: 100.03% MP Biomedicals Certified: 100.39%; Found: 100.34% K_2CO_3: Chem Cruz Certified: 99.1%; Found: 99.42% Sigma Aldrich Certified: 99.8%; Found: 99.81%

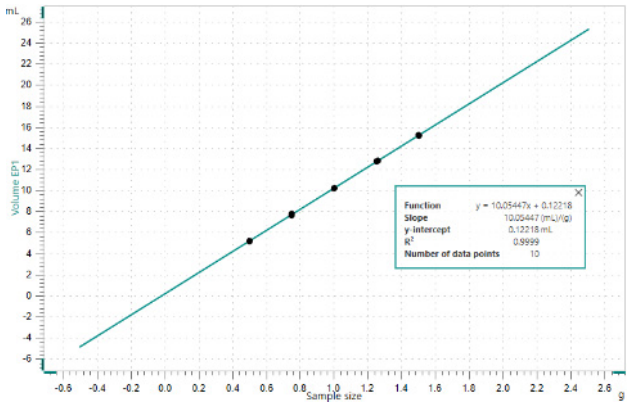

Figure 5. Linearity of the assay determination of potassium bicarbonate. Potentiometric titration in duplicate with 0.5 g, 0.75 g, 1.00 g, 1.25 g, and 1.50 g sample size.

CONCLUSION

Potentiometric titration-based potassium assay determination is faster and easier to use compared to chromatographic techniques and can be easily automated to fulfill high throughput needs.

The use of fully automated potentiometric titration instead of manual titration increases the accuracy and reliability of the results. Fully automated titration combined with appropriate equivalence point detection methods not only eliminates manual errors, but fulfills data integrity and 21 CFR 11 requirements, which makes the pharmaceutical QA/QC workflow easier.

Using an OMNIS Sample Robot with Dis-Cover functionality allows the fully automated determination of up to four samples in parallel, freeing up valuable time of the operator and thus increasing the productivity in the lab. In addition, it ensures that key requirements of regulatory compliance guidelines, such as data integrity, are met. The OMNIS system offers the opportunity to customize the system according to your needs and expand it for other required titration applications on pharmaceuticals.

Analytes:	**Active pharmaceutical ingredients (APIs)**
Matrix:	**Pharmaceutical drugs; Tablets, capsules, pharmaceutical powders**
Method:	**Titration**
Industry:	**Chemical; Pharmaceuticals**
Standards:	**USP<1225>**