Parsolex
PARTNER SOLUTIONS EXCELLENCE

Water Determination by Karl Fischer Titration

A drug component (e.g., excipient or active pharmaceutical ingredient) or a final drug product (e.g., tablet or capsule) may contain water within its contents, either bound as a hydrate within the crystalline structure or adsorbed onto the material surface. Further, water content may change throughout the shelf-life of the drug component (or drug product) and potentially affect the quality, efficacy, or stability of the material. Therefore, the ability to monitor and control the content of water within the drug component (or drug product) is important.

USP ⟨921⟩ *Water Determination* describes three different types of test methods that are common for the determination of water within pharmaceutical materials. These test methods include: **Method I** Karl Fischer ("KF") titration, **Method II** azeotropic distillation with toluene, and **Method III** gravimetric analysis (*i.e.*, loss on drying). Karl Fischer titration is the most widely used of these techniques for the determination of water within pharmaceutical materials. The methodology is highly specific for water, sample size requirements are often small (milligrams), and detection limits are low (down to 1 ppm). By comparison, loss on drying, typically requires a 1–2 g sample size and detects any volatile component present in the sample, not only water.

The German scientist Karl Fischer originally discovered that iodine consumes water in the presence of sulfur dioxide and an organic base, as described by the following reactions:

$$ROH + SO_2 + R'N \rightarrow [R'NH]SO_3R$$

$$[R'NH]SO_3R + H_2O + I_2 + 2R'N \rightarrow 2[R'NH]I + [R'NH]SO_4R$$

In practice, a small sample of the pharmaceutical material is dissolved (or extracted) into an appropriate solvent (*e.g.*, anhydrous methanol) while protected from atmospheric moisture by the titration apparatus. The titrant typically contains iodine, sulfur dioxide, an appropriate base (*e.g.*, imidazole), and an appropriate solvent (*e.g.*, diethylene glycol monoethyl ether). The titrant is volumetrically added to the sample solution until the titration endpoint is reached. The titration endpoint is determined by the presence and sustainability of free iodine and may be observed visually by a color change of the sample solution from yellow to amber. More commonly and more accurately, the endpoint is determined potentiometrically as the presence of iodine causes conduction at a double-pin platinum electrode submerged in the sample solution.

Pharmaceutical Testing

Parsolex performs water determination by Karl Fischer titration to support its clients' needs throughout the drug product lifecycle, which includes support of the following activities:

- Formulation development
- Process development
- Process scale-up
- Product stability testing
- CGMP release testing for pharmaceutical excipients and active ingredients

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WATER DETERMINATION

- CGMP release testing for commercial (or clinical stage) drug products

Parsolex utilizes two primary approaches for water determination by Karl Fischer titration, which include:

- Volumetric KF Titration by Direct Addition
- Volumetric KF Titration by Oven Extraction

Both approaches utilize the volumetric addition of a KF titrant to the titration vessel. The former approach requires the direct addition of the test sample to an appropriate solvent, whereas the latter approach uses an oven to extract the water from the sample and transfer the water to the titration vessel. Though the latter method often requires more sample material, sample interferences to the KF titration are often avoided leading to more accurate and reproducible water determination results.

Method Development and Validation

Method development and validation are required for the implementation of Karl Fischer titration for water determination for each sample type. Each sample type possesses unique characteristics that can affect the conditions required for the accurate implementation of the Karl Fischer titration, which include the solubility, thermal stability, and chemical interferences associated with the sample.

Parsolex has significant experience performing the development and validation of KF titration methods per guidance provided by the FDA[1] and the International Conference on Harmonisation[2].

Method performance characteristics, which include specificity, accuracy, repeatability, intermediate precision, linearity, range, and limit of quantitation, are evaluated throughout the method development and validation process. Parsolex performs method validation through application and execution of phase-appropriate method validation protocols.

Why Choose Parsolex?

Parsolex offers analytical services to our clients to support water determination testing by Karl Fischer titration. Parsolex is committed to fully understanding our clients' requirements and to delivering each project on agreed upon timelines with high-quality deliverables. Parsolex possesses in-depth experience with the successful execution of water determination testing by Karl Fischer titration per current regulatory guidance.

[1] *Analytical Procedures and Methods Validation for Drugs and Biologics: Guidance for Industry*, FDA, July 2015

[2] Q2(R1) *Validation of Analytical Procedures: Text and Methodology*, ICH Harmonised Tripartite Guideline, November 2005

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