Applying USP <921> to your Moisture Determination Lab and Karl Fischer Titrations

Introduction
Many pharmacopeia materials contain water as hydrates or in adsorbed form. The determination of the water content is important to maintaining compliance with the Pharmacopeia guidelines.

Why measure moisture?
The moisture content influences the physical and chemical properties of a substance such as:
- Purity
- Agglomeration in the case of powders
- Microbiological stability
- Flow properties
- Density
- Weight
- Viscosity
- Refractive index
- Stability

Navigating the USP Water Analysis Methods

The USP monographs offer several alternatives for moisture determination. When searching for guidance, go to the USP Monographs for individual items. Water determination if required will be listed under the heading Specific Tests and will refer to method followed by the allowed concentration range. In the case below Method 1 <921> is specified.

Sample Requirements
- Should not react with the KF reagent
- Sample must be soluble or the water will be yielded.
- For Biologics see the individual monograph.
- For Botanicals see Articles of Botanical Origin <561>.

Method I will be the focus of this poster, but first lets briefly look at the other two options.

Method I (a) Direct Titration – Test specimen is added to the titrator and moisture is directly titrated. Water is determined by Method I sub-heading (a), unless noted in the individual monographs.

Method I (b) Residual Titration – This is a back-titration, test specimen is added to an excess of KF reagent unconsumed reagent is titrated with a standard solution of water in solvent.

Method I (c) Coulometric Titration – Iodine is generated in solution.

Water result by a USP regulated method

The Karl Fischer Reaction

Sample Requirements
- Sample must be soluble or the water must be extracted out of the sample completely.
- Should not react with the KF reagent

KF Reaction Requirements
- Alcohol – Methanol, Ethanol, DEGEE, etc.
- Sulfur dioxide (SO2)
- Iodine
- Base – Imidazole

\\[ \text{R-OH} + \text{SO}_2 + \text{R'N} \rightarrow [\text{RN}][\text{SO}_2][\text{CH}_3] \]

Reaction 1 occurs when the reagents are made.

\\[ (2) \text{H}_2\text{O} + \text{I}_2 + [\text{RN}][\text{SO}_2][\text{CH}_3] + 2 \text{R'N} \rightarrow [\text{RN}][\text{SO}_2][\text{CH}_3] + 2 [\text{RNH}] \]

Reaction 2 occurs during the titration.

Water and iodine are consumed in equimolar amounts in the reaction. Polarimetric titration measures the change in electrical conductivity of the solution to determine end point.

If you know the amount of I2 consumed, you can calculate the amount of water that was present in the sample.

For Coulometric titrations, water is determined by the electrical charge used to generate iodine.

MilliporeSigma offers a complete line of Aquastar® Karl Fischer reagents and water standards.

Summary
Safe and accurate moisture analysis results.
USP guidance is quite simple to understand.
Although USP <921> discusses reagent formulation, commercially available Karl Fischer instrumentation and reagents are suitable to use.

Join our webinar:
USP <921>: Methods for Moisture Determination and Karl Fischer Titration
Date: Thursday December 7th, 2017
Time: 10:00 am CST
Register here: