

Latest Developments of Karl Fischer Reagents More Convenience and less Toxicity

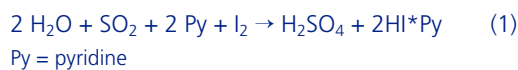
Karl Fischer Titration

The Karl Fischer titration is a widely used titrimetric method for water determination in various substances. The determination of water is important to check the product quality and to assure even chemical and physical properties of the product. In the pharmaceutical industry for example a stable water content is important for intermediate powders which are formed to tablets. When the powder is too dry, the tablets crumble, when it is too wet, the tablets will stick to the blister foil.

The loss-on-drying often used is not suitable for a variety of samples since it determines all volatile material and not only the water content.

Karl Fischer's Original Reagents

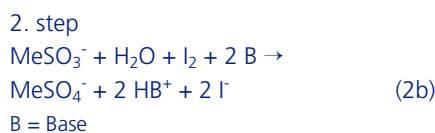
In 1935 the German chemist Karl Fischer (figure 2) needed a method for moisture determination in sulphur dioxide. He mixed a reagent containing pyridine, sulphur dioxide and iodine according to the Bunsen equation without the excess of water. He formulated [1]:



He validated the reagent by adding known amounts of water but never attempted to modify his formulation. In the next 40 years the Karl Fischer titration was slightly modified, but there was no significant progress. The KF titration was disliked by the laboratory technicians since it was difficult to determine the end-point, the reagent contained pyridine and was malodorous.

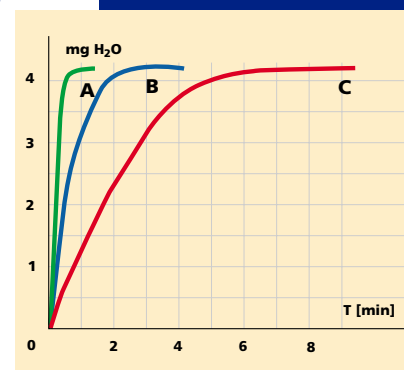
First Generation of Pyridine-free Karl Fischer Reagents

In the beginning of the 80s Eugen Scholz at Riedel-de Haën in Germany started investigations on KF reagents. The objective was to develop a reagent without the pyridine odour. After a few months he formulated the following reaction equation [2]:



He discovered that the methanol takes part in the reaction forming the methyl sulphite, one active species in the KF titration. As Anders Cedergren noticed some years before the pyridine was just a buffering agent and not a reactive part [3]. According to the results it was possible to replace the unpleasant pyridine with the odourless imidazole. The second advantage

Figure 1:
Titration curves
A= 2 component reagent, pyridine-free
B= 1 component reagent, pyridine-free
C= 1 component reagent, containing pyridine



Contents:

- Theory of Karl Fischer titration
- Reagents for general use
- Reagent for special applications
- Non-toxic Karl Fischer reagents

of the imidazole is its higher basicity which leads to a faster reaction speed and more stable end-points (figure 1). Within a short period of time, various reagents for general use in one-component titration, two-component titration and coulometric titration had been formulated.

Second Generation of Pyridine-free Karl Fischer Reagents: Specialities

Water determination in a variety of different products had been possible at that point. But there were still a large group of samples which underwent side reactions with the ingredients of the KF reagents. Acids and bases change the pH which supports side reactions [4], and fats and oils do not dissolve. A very typical side reaction is the generation of ketals

from ketones and methanol. During this reaction water is formed and causes false results and fading end-points (figures 3 + 4).

Typical acetal formation (3)

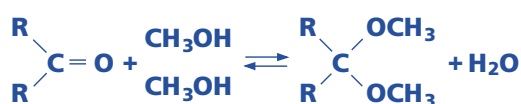


Figure 3:
Titration of acetone in methanol, no end-point found

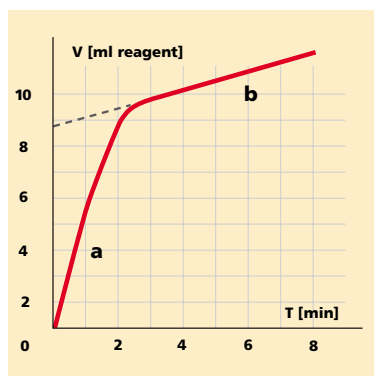
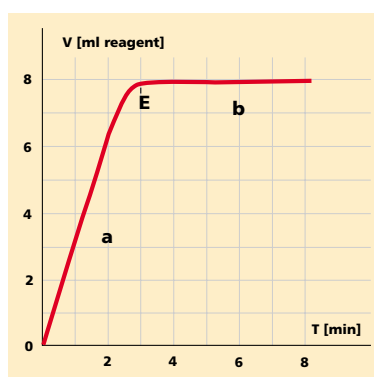


Figure 4:
Titration of acetone in HYDRANAL®-Working Medium K, stable end-point found



Therefore, it was necessary to develop reagents which did not undergo side reactions while keeping their reactivity. Systematic investigations of various organic solvents showed that halogenated alcohols react according to equation (2a) and do not form by-products with carbonyl compounds as (3), [2].

Chloroform also has a positive effect on the KF titration and in addition it dissolves a variety of compounds which are insoluble in methanol.

In coulometric determination, the conductivity of such compounds generates problems. Chloroform has a very low dielectric constant, thereby making it impossible to form a coulometric reagent based on pure chloroform. On the other hand, a suitable alcohol is necessary to keep the exact stoichiometry of the Karl Fischer reaction. A conductivity of at least 10 mS/cm is also required in the reagent. Trifluoroethanol is the solution: it improves the conductivity and does not undergo side reactions.

Third Generation of Karl Fischer Reagents: environmentally friendly

In the late 80s health and environment became important points in public discussion. Carbon-tetrachloride, which was part of all commercial coulometric catholytes for KF titration, was forbidden in the USA because of its cancerogenicity. Halogenated hydrocarbons became more expensive to dispose. Therefore attempts were made to remove these solvents from KF reagents. Unfortunately, we found that they were needed as reaction partners, not only as solvents. Carbontetrachloride and chloroform were reduced in the cathodic KF reaction [5].



These reductions form electrochemical inert products (chloride, chloroform and methylene chloride) which could not be oxidised at the anode. In a catholyte without halogenated hydrocarbons, methyl sulphite is reduced. The reduction products diffuse into the anode compartment of the coulometric cell where they act as water.

We found that ammonium salts can be used as a reactive agent in KF catholytes. In this case, hydrogen ions are reduced to hydrogen which evaporates out of the cell and does not disturb the anodic reaction.

For analysis of ketones the halogenated alcohols can be replaced by glycol ethers and long chain alcohols.

Forth Generation of Karl Fischer

Reagents: non-hazardous

Environmentally friendly is not automatically also friendly for mankind. A lot of KF reagents have still been based on methanol. Methanol is considered toxic and displays the skull and crossbone on the label. Our next goal was to make a reagent line which protects the people in the lab as good as possible from the danger of hazardous chemicals.

For the **HYDRANAL**[®]-Composite products, the one-component reagents for the volumetric titration this has already been done in the late 80s. These reagents contain a long-chain ether as solvent, the diethylenglycol monoethyl ether which is non-toxic and not easy flammable. Since the base imidazole buffers the acid sulphur dioxide, the reagent is not irritant for skin or eyes. Particular studies have been made under GMP conditions to prove these properties.

The remaining reagents were the two-component reagents for volumetric titration and the coulometric reagents which all contained methanol as main ingredient.

Methanol has a close-related «brother» in chemical understanding, the ethanol. Ethanol has not been used in the past for Karl Fischer reagents for two reasons. First, the reaction rate of the Karl Fischer reaction in pure ethanol is very slow. Secondly, the electrochemical behaviour varies from the methanol, the conductivity is lower, that hinders the suitability in a coulometric reagent.

The first problem could be dissolved by «speeding-up» the ethanol. Special salts are added to the solvent which increase the reaction speed in ethanol and do not disturb the Karl Fischer titration. Based on this technique the two component reagents **HYDRANAL**[®]-Solvent E and **HYDRANAL**[®]-Titrant E as well as the working medium **HYDRANAL**[®]-CompoSolver could be developed [6] (see also figure 5).

The conductivity for a coulometric reagent mainly consisting of ethanol could be adjusted to the a/m requirements by using special additives. This knowledge led to **HYDRANAL**[®]-Coulomat E. As additional benefit this reagent can be used as anolyte and as catholyte as well for the cell with diaphragm. A special catholyte reagent is no longer necessary.

Plenty of formulations and mixtures are created around the described reagents in order to make the Karl Fischer titration as convenient as possible.

All these investigations caused a better understanding of the complicated mechanisms of Karl Fischer reactions and led to Karl Fischer reagents which were more stable, had better accuracy and less safety risks than the «obscure mixture» Karl Fischer had published in 1935.

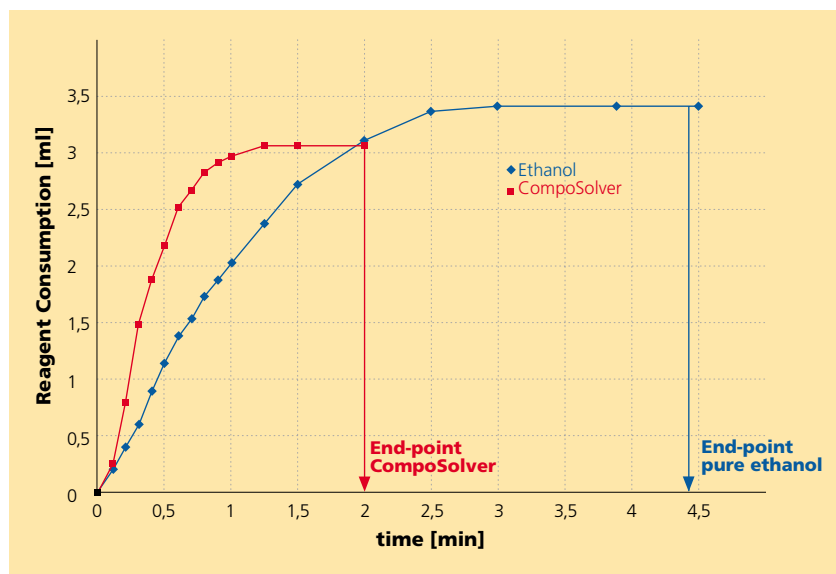


Figure 5:
Titration curve pure ethanol,
delayed titration
Titration curve **HYDRANAL**[®]-
CompoSolver; rapid titration

References

- [1] Fischer, K.; «Neues Verfahren zur mass-analytischen Bestimmung des Wassergehaltes von Flüssigkeiten und festen Körpern», *Angew. Chemie*, 48, 394, 1935
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- [5] Scholz, E.; «Karl Fischer Coulometry - the Cathode Reaction», *Fresenius J. Anal. Chem.*, 348, 269, 1994
- [6] Hoffmann, H.; «Karl-Fischer-Reagenz enthaltend Ethanol als alkoholische Komponente», *European Patent Application 98121169.1*; 1998.

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