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Short communication

Implementation of the Ph. Eur. suitability test for semi-micro determination of water

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Introduction

Karl Fischer titration (KFT) is a widely used quantitative method for semi-micro determination of water in active pharmaceutical ingredient (API) and drug products. The water content determination is significant to ensure drug product quality. For example, water could induce degradation of API, undesired crystalline transitions and promotes microbiological activity in the drug product (Connors, 1988; MacLeod, 1991; Yoshioka & Stella, 2002). Therefore, the water content is a part of the specification of the API and drug product (ICH Q6A, 2000).

The KFT is based on stoichiometric reaction of water with iodine in a suitable solvent (alcohol), in presence of an amine base. The sulfur dioxide reacts with the alcohol to form an ester which is neutralized by the base. The anion of the alkyl sulfurous acid is the reactive component and is already present in the KF reagent. The titration of water constitutes the oxidation of the akyl-sulfite anion to alkyl sulfate by the iodine. This reaction consumes water. The endpoint of the titration is reached when all the water is consumed (Scholz, 1984).

Each of the mentioned components of the KF reaction has a specific role. The solvent must be able to dissolve the sample, the reagent components, as well as the KF reaction products. The type of solvent is chosen with respect to the stability, reaction rate, conductivity, side reactions and solvation of the sample in the reagent solution. The concentration of the titrant used for the KF titration depends on the amount of water present in the sample. Titrant 5 entraps 5 mg of H_20 per mL titrant and it is used for larger amounts of water. The organic base functions solely as a pH buffer. Although in most cases the type of the base has no influence on the KF reaction rate, the amine bases also have important electron-donor properties that may be of importance (Larson, 2008). Therefore, the right choice of the solvent / titrant system is crucial for obtaining accurate and reproducible results.

In some cases, it is easy to identify that the chosen solvent / titrant system is inappropriate because the endpoint of the titration could not be reached in a reasonable time or the reproducibility is low. But sometimes it is very difficult to identify slightly incorrect results because the problem is not so evident. Therefore, in cases where the KF method is applied to a sample with an uncertain composition; there are no available information about the method validation or other solvent / titrant system is used instead of those prescribed by the validated method, it is necessary to verify the suitability of the chosen solvent / titrant system.

The aim of this paper is to implement the suitability test, given in the general chapter of the Ph. Eur., in order to verify the accuracy of the determination of the water content in atropine sulphate working standard with the chosen solvent / titrant system.

Materials and methods

Chemicals and Reagents

CombiTitrant 5 (Merck) containing iodine, imidazole and 2-Methylimidazole was used as a one-component reagent for KF titration and CombiMethanol (Merck) was used as a solvent. The suitability of the method was verified using Water Standard 1% (10 mg H_2O/1 g) (Merck). Atropine sulphate working standard (WS) was used as a sample.

Karl Fisher Titration method

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KFT was performed on Karl Fischer Titrator DL38, Mettler Tolledo. The evaluation of the suitability of the selected solvent / titrant system was performed according the procedure given in Ph. Eur. 2.5.12 (Ph. Eur. 10.0). The amount of the sample introduced in the titration vessel was 0.15 g (accurate weight), the stirring time before titration was 30 s and the water content was determined in triplicate.

Results and discussion

To ensure the accuracy and the precision of the water content determination, it is necessary before use of the KF apparatus to perform a standardization of the titrant concentration and performance verification. The titrant standardization and the instrument check was conducted in accordance to the OMCL Qualification of equipment guideline (GEON, 2022). The repeatability of the titrant concentration was 0.36%, whereas the mean recovery of the water content determined after three independent additions of Water Standard 1% was found to be 99.0%; thus the acceptance criteria for repeatability and recovery were met.

The monographs for atropine sulphate described in Ph. Eur. and USP doesn't provide information about the solvent / titrant system used for the water content determination. In order to evaluate the suitability of the chosen solvent / titrant system (methanol / Titrant 5, respectively), the water content in atropine sulphate WS was determined in the first place. The water content was found to be 3.3%, which corresponds to 4.93 mg initial water content (M) for the sample. Thereafter, six sequential additions of known amount of Water Standard 1% (in range from 0.17g to 0.33g, corresponding to 50-100% of the amount of water found in the sample) were added in the same titration vessel and the water content was determined after each addition. The mean recovery of the water content (98.7%) was found to be within the acceptable limits (97.5 – 102.5%).

Afterwards, six points calibration curve was constructed from the cumulative amount of water (g) added *vs.* the sum of the cumulative amount of water (g) found after each addition and M. The slope (b) of the regression line was 0.989, whereas the *y*-axis intercept (a) was found to be 4.908. The correlation coefficient of the regression line was found to be 1.0. The value of the b also met the given criteria in Ph. Eur 2.5.12.

The *x*-axis intercept (d), needed for the calculation of the percentage errors (e_1 and e_2) related to the water content determined, was calculated as a ration between a and b. The value of d was found to be 4.96. The calculated values for e_1 and e_2 were -0.5 and 0.6, respectively; thus the acceptance criteria were met.

Since the chosen solvent / titrant system was found suitable, the KF method was applied for determination of the water content in the Atropine sulphate WS. The mean amount of water (n=3) found in the atropine sulphate WS was 3.31%, with relative standard deviation (RSD) of 0.2%. The repeatability acceptance criteria depend on the titrant strength and the absolute amount of water found in the sample. The absolute amount of water found the atropine sulphate WS was 5 mg. Generally, the maximal permitted RSD (n = 3) for Titrant 5, when the absolute amount of water is in range between 2 mg – 5 mg, is 5 %. Considering the obtained low value for RSD (0.2%), the method's repeatability acceptance criteria were met.

Conclusion

The implementation of the Ph. Eur. suitability test proved that methanol and Titrant 5 are suitable as solvent and titrant, respectively, for determination of the water content in Atropine sulphate WS. The described KF method generate accurate and reproducible results and could be applied in pharmaceutical quality control laboratories.

References

Connors, K.A., 1988. The Karl Fischer Titration of water. Drug Dev. Ind. Pharm. 14, 1891-1903. https://doi.org/10.3109/03639048809151996

European Pharmacopoeia (Ph. Eur.) 10th Edition. 2019. EDQM Council of Europe, Strasbourg, France

General European OMCL Network (GEON), Quality Management Document, PA/PH/OMCL (07) 108 R11. 2022. Qualification of equipment Annex 5: Qualification of automatic titrators.

ICH Q6A: Specifications: Test procedures and acceptance criteria for new drug substances and new drug products; chemical substances. 2000

Larsson, W., 2008. New Approaches to Moisture Determination in Complex Matrices based on the Karl Fischer Reaction in Methanolic and Non-Alcoholic Media. VMC, KBC, Umeå University, Umeå. ISBN: 978-91-7264-687-2.

MacLeod, S.K., 1991. Moisture Determination usinf Karl Fischer titrations. Anal. Chem. 63(10), 557-566. https://doi.org/10.1021/ac00010a001

Scholz, E., 1984. Karl Fischer. In: Karl Fischer Titration. Chemical Laboratory Practice. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-69989-4_1

Yoshioka, S., Stella, V.J., 2002. Stability of Drugs and Dosage forms. Kluwer Academic Publishers, eBook ISBN 0-306-46829-8.

The United States Pharmacopeia 44. The National Formulary - 39. 2021. Rockville, Md. United States Pharmacopeial Convention, Inc.