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

Biljana Atanasovska[1*]; Jelena Acevska[1]; Natalija Nakov[1].
Faculty of Pharmacy, University "Ss. Cyril and Methodius", 1000 Skopje, Republic of North Macedonia

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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 and drug products.

❖ **Role of the components in the KF reaction**

➢ **Solvent** - must be able to dissolve the sample. 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.

➢ **Concentration of the titrant** - depends on the amount of water present in the sample.

➢ **Organic base** - functions solely as a pH buffer; in most cases the type of the base has no influence on the KF reaction rate but the amine bases also have important electron-donor properties that may be of importance.

➢ **The right choice of the solvent / titrant system is crucial for obtaining accurate and reproducible results**

- Sometimes it is very difficult to identify slightly incorrect results because the problem is not so evident.
- In cases where the KF method is applied to a sample with an uncertain composition; if 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.
- 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

- KFT was performed on Karl Fischer Titrator DL38, Mettler Tolledo (Figure 1).
- 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.

Figure 1: Karl Fischer Titrator

Results and discussion

- It is necessary before use of the KF apparatus to perform a standardization of the titrant concentration and performance verification (according to the OMCL Qualification of equipment guideline).
  - The repeatability of the titrant concentration was 0.36%, mean recovery (n=3) of the water content of Water Standard 1% was found to be 99.0 %.
    - The acceptance criteria for repeatability and recovery were met (Table 1).
- 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.
- 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 5 mg initial water content (M) for the sample.

	Concentration of titrant (mg/mL)	Recovery (%)
1	5.0518	99.0
2	5.0886	99.0
3	5.0592	99.0
Mean	5.0692	99.0
RSD	0.36	/

Table 1: The titrant standardization and the instrument check

- Six sequential additions of known amount of Water Standard 1% (in range from 0.17g to 0.33 g, 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%) (Table 2).

	Mass (g)	% found	W2 (mg H_2O found)	W1 (mg H_2O added)	Recovery (%)	X cum (H_2O added)	Y cum (H_2O found)
	0.1495	3.30					
1	0.1717	0.97	1.665	1.717	97.00	1.717	6.599
2	0.1977	1.00	1.977	1.977	100.00	3.694	8.576
3	0.2260	0.98	2.215	2.260	98.00	5.954	10.791
4	0.2537	0.99	2.512	2.537	99.00	8.491	13.302
5	0.28	0.99	2.768	2.796	99.00	11.287	16.070
6	0.332	0.99	3.287	3.320	99.00	14.607	19.357
			Mean recovery (%)		98.7		

Table 2: The mean recovery of the water content

- 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 (Figure 2).
  - Slope (b): 0.989; *y*-axis intercept (a): 4.908; R^2:1.0
    - The values 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), was calculated as a ration between a and b.
  - d value: 4.96; e_1 value: -0.5; e_2 value: 0.6
    - **The chosen solvent / titrant system was found suitable**

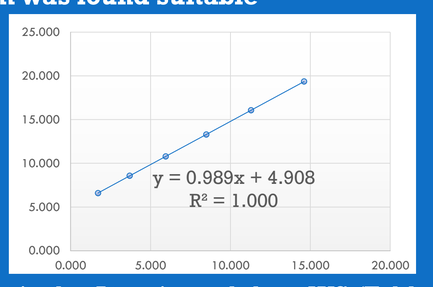

Figure 2: Cumulative amount of water (g) added *vs.* sum of the cumulative amount of water (g) found after each addition

- KF method was applied for determination of the water content in the Atropine sulphate WS (Table 3).
- 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 was 5 mg; 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.**

Sample	Weight (g)	Amount of water (%)	Total amount of water (mg)
1	0.1495	3.30	5
2	0.1426	3.31	5
3	0.1535	3.31	5
	Mean	3.3	5
	RSD	0.2	/

Table 3: KF method applied for determination of the water content in the Atropine sulphate WS

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.
The shown step-by-step approach for the implementation of the Ph. Eur. suitability test can serve as an example of its proper application.

Reference

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