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Water determination in drugs containing thiols

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Abstract

A new rapid analytical method is applied for water determination in α-Mono-thioglycerol and Captopril tablets containing thiols, and therefore, not amenable for direct Karl Fischer titration. The method is based on the consecutive titration first of thiol by a novel reagent, and then of water by a conventional K. Fischer reagent in the same sample and cell with the electrometric 'dead-stop' location of the end point in both titrations. The new reagent consists of iodine, potassium iodide and sodium acetate in non-aqueous medium. Estimated repeatability and accuracy of both water and thiol determinations are satisfactory.

Keywords: Water determination; Thiol determination; Drugs in tablets; Karl Fischer titration; Validation

1. Introduction

The pharmaceutical industry produces a number of drugs containing thiol derivatives which are used as antidotes, expectorants, antirheumatic and other therapeutic remedies. The USP (1995) methods for water determination in such drugs (articles 731 and 921) are based on 'loss on drying' in a vacuum desiccator at 60°C with or without P_2O_5 or azeotropic toluene distillation. It should be noted that 'loss on drying' is labor-consuming method which does not guarantee complete dehydration of tablets containing, for example, gluing components, fillers and stabilizers (Sherman, 1983). The best method for water determination is still Karl Fischer reagent (KFR) titration, however, the KFR is not amenable for the analysis of thiols, because iodine (a component of KFR) react simultaneously both with water and thiol (Mitchell and Smith, 1980). The functional -SH group via oxidation by iodine forms sulfide derivatives in the presence of a base (Cheronis and Ma, 1964). The majority of primary thiols are oxidized up to disulfides and the stoichiometry of this reaction is $-SH:I_2 = 2:1$, while tertiary thiols react with iodine by the mole ratio $-SH:I_2 = 1:1$ and produce sulfinyl iodides. There are no general iodometric methods for the determination of all thiols, because the stoichiometry of the reaction between the functional-SH group and iodine depends on the thiol structure (Cheronis and Ma, 1964). The thiol

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determination according to the USP (1995) (pp. 263, 960, 2271) is carried out by HPLC, iodometry or UV spectrometry.

A novel reagent and rapid method were developed by us (Sherman et al., 1998) for the simultaneous determination of water and thiol in samples which are not amenable for direct KF titration. This method is based on the consecutive titration first of thiol by the novel reagent and then of water by a conventional KFR in the same cell and sample with double burette and electrometric 'dead-stop' location of the end-point in both titrations. The method can be used for the analysis of drugs containing fillers or other matrix components, e.g. lactose, starch, talc, stearin, cellulose, magnesium stearate, etc. which do not react with the novel reagent and the KFR. Carbonates, bicarbonates, oxides of metals, sulfites are the interferences. The novel method has the following advantages: rapidity, simplicity and the use a single test portion for two analytes determination without any blank and extra solvent. Evaluation of the validation parameters of the method was performed for three artificial samples of α-monothioglycerol (Sherman et al., 1996a). The artificial samples were prepared by the intimate mixing of purchased α-monothioglycerol with the known quantity of water. The evaluated parameters of the method such as accuracy, recovery, repeatability, reproducibility and the limit of quantitation satisfied requirements of the AOAC (1993). The method has been adopted as an AOAC Peer-Verified Method, number 1:1998.

In the present paper the new method is applied for water and thiol determination in Captopril tablets. The results of application are compared with the data (Sherman et al., 1996b) previously obtained for the artificial samples of α-monothiolglycerol.

2. Materials and methods

2.1. Reagents and apparatus

Composition, preparation and standardization of the novel reagent, the KFR and apparatus are described earlier (Sherman et al., 1996a). A titroprocessor with two dosimates or another apparatus for electrometric 'dead-stop' location of the end point titration can also be used. Thiol determinations in α-monothioglycerol and in Captopril tablets are carried out by 0.1 and 0.02 N solution of the reagent accordingly, depending on the thiol concentration in analyzed drug. The KFR titre is ca 0.5 mg water per ml. The reagents are stored in air-tight containers made of amber glass.

2.2. Analyzed drugs

Three artificial samples of α-monothioglycerol, containing $98 \div 92\%$ mass of thiol and $1 \div 5\%$ mass of water are prepared from purchased one (Sigma, USA). Three kinds of Captopril tablets (TEVA Pharm. Ind. Ltd, Israel) containing 12.5, 25, and 50 mg of 1-[(2s)-3-mercapto-2-methyl-1-oxopropyl]-L-proline and starch, cellulose, magnesium stearat, glucose and others indifferent fillers in each tablet accordingly.

2.3. Sample preparation

A solid or liquid test portion of the sample (20–120 mg) is weighed in a micro weighing bottle and together with this bottle is placed in a titration flask as it is described earlier for the determination of ascorbic acid in drugs (Sherman and Kuselman, 1999). Before being analyzed a solid test portion is slowly powdered in China mortar. The liquid test portion is taken by using a medical syringe or pasteur pippete without any pretreatment. The novel reagent 2.5–3 ml necessary for thiol titration is introduced into the titration flask before the test portion to ensure the solubility of the drug or a quantitative extraction of analytes from it.

3. Results and discussion

According to USP (1995) (p. 263 and 2271) the α-monothioglycerol and captopril determinations are carried out by the iodometric titration. Since α-monothioglycerol and captopril are primary thiols they are oxidized by iodine up to disulfides in both titrations by the novel reagent as well as the

Table 1
'True' values of water and thiol determination in α-monothioglycerol and Captopril tablets

Drug	Water		Thiol	
	X_{tr}, %	S_r, % rel.	X_{tr}, %	S_r, % rel.
α-Monothioglycerol	0.98	0.03	98.45	0.26
α-Monothioglycerol	2.45	0.03	96.65	0.30
α-Monothioglycerol	4.82	0.07	94.40	0.56
Captopril 12.5	4.09	2.08	24.96	0.56
Captopril 25	3.95	1.74	25.02	0.48
Captopril 50	4.16	2.39	25.00	0.42

KFR. The stoichiometry of these reactions is expressed as the mole ratio of $-SH:I_2 = 2:1$ (Cheronis and Ma, 1964; Mitchell and Smith, 1980).

The results of the analyses (average of ten replicates) by the USP (1995) (p. 2271) method were accepted as 'true' thiol contents in three kinds of α-monothioglycerol. By analogy the 'true' captopril concentrations in the tablets were obtained from the results of the iodometric titration in isopropanol as a solvent for the working medium (average of five replicates). Captopril is extracted in these conditions from the matrix (tablets) quickly and completely. Captopril disulfide produced during the titration is dissolved in the working medium without any problems.

'True' water contents for α-monothioglycerol (average of ten replicates) and Captopril tablets (average of five replicates) were calculated as a difference between the two titrations: the sum of the thiol and water determination by KFR and the thiol by the iodometric titration only. Such calculation of 'true' water content is accepted, because α-monothioglycerol and captopril are oxidized completely by iodine.

'True' values of analytes in analyzed samples X_{tr} and corresponding relative standard derivations S_r are presented in Table 1.

The titration of thiol by the novel reagent and then of water by KFR as well as the calculation of thiol and water contents are described in our c work (Sherman et al., 1996b). Total titration time is not more than 8–10 min. The results of water and thiol determination in α-monothioglycerol and Captopril tablets are presented in Table 2.

Table 2
Results of water and thiols determination in α-monothioglycerol and Captopril tablets by the new method

Drug	X_{av}, %	S_r, % rel	S_{rc}, % rel.	B, % rel	B_c, % rel.
Water					
α-Monothioglycerol	0.99	2.00	2.67	−1.01	7.82
α-Monotioglycerol	2.53	1.91	2.32	3.16	6.78
α-Monotioglycerol	4.81	1.77	2.11	−0.21	6.17
Catopril 12,5	4.03	2.47	2.11	−1.49	6.79
Captopril 25	3.97	2.94	2.17	0.51	6.34
Captopril 50	4.05	2	2.16	−2.56	6.32
Thiol					
α-Monorthioglycerol	99.93	0.34	1.34	1.49	4.22
α-Monothioglycerol	96.89	0.33	1.34	2.53	3.92
α-Monothioglycerol	94.14	0.46	1.35	0.28	3.95
Captopril 12.5	24.88	0.57	1.65	−0.32	4.82
Captopril 25	24.96	0.43	1.65	−0.24	4.82
Captopril 50	25.05	0.53	1.65	0.20	4.81

Precision is evaluated on the repeatability level and characterized by the relative standard deviation of replicates S_r. The values of S_r for α-monothioglycerol are calculated from the data obtained by the scheme: four replicates per day during 5 days. All the data are 'homogeneous' ones for different days and so they were averaged (Sherman et al., 1996a). Therefore for Captopril tablets S_r values are calculated from the shortened experiment consisting of five replicates obtained during 1 day. From Table 2 one can see that for water determination $S_r < 3\%$ rel. and for thiol determinations $S_r < 0.6\%$ rel. for all samples. These values satisfy the Horwitz' criterion (AOAC, 1993):

$$S_r < S_{rc} = 2^{(1 - 0.5 \log C)} \times 0.67, \quad (1)$$

where S_{rc} is the critical S_r value according to the Horwitz' criteria, C is the concentration of the analyte in decimal fractions.

Accuracy is characterized by the relative bias B of average results X_{av} obtained by the new method from the 'true' values X_{tr}:

$$B = (X_{av} - X_{tr}) \times 100/X_{av}, \ \%\text{rel.} \quad (2)$$

Its values satisfy the following criterion based on the normal distribution and the Horwitz' one:

$$B < B_c\{P\} = U\{P\} \times S_{Rc}, \quad (3)$$

where $U\{P\} = 1.96$ is the coefficient of the normal distribution at the level of confidence $P = 0.95$, and

$$S_{Rc} = 2^{(1 - 0.5 \log C)} \quad (4)$$

is the critical value of the standard deviation reproducibility S_R, according to the Horwitz' criterion.

So, the application of the method by these assessments is satisfactory also. Moreover, we are sure, the new method can be applied for the analysis of other drugs containing thiols and free of other components reacting with iodine.

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