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Green potentiometric method for determination of sildenafil citrate in pharmaceutical dosage forms

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Abstract:
Background: The main challenge of the pharmaceutical industry in the last years is to implement eco-friendly methods in quality control of medicines based on the principles of green analytical chemistry. In this study, green analytical method for potentiometric titration of sildenafil citrate (SC) in film-coated tablets was optimized and validated.
Materials and Methods: The quantitative determination of sildenafil citrate in film-coated tablets, dissolved in 50 mL 1% (v/v) Polysorbate 80 solution, was performed using potentiometric titration with 0.1 M sodium hydroxide. Validation of the method included linear regression analysis based on eleven different quantities of the sildenafil citrate, active substance and determination of specificity, precision and accuracy in accordance with ICH guideline.
Results: The use of polysorbate 80 as a solubilization agent enabled elimination of the toxic organic solvents needed for non-aqueous potentiometric titration of active pharmaceutical ingredients with low solubility. The obtained results from method validation study confirm the linearity of the method. Statistical evaluation of the data obtained from regression analysis confirm that the method is acceptable for determination of the content of SC in API. The recovery values (98.0 % - 102.0 %), the obtained results for the relative standard deviation (below 0.5%) and F test confirm the accuracy and precision of the method. The results obtained from the method validation study comply to the defined acceptance criteria, confirming the applicability of the proposed method.
Conclusion: The proposed method is applicable for determination of the content of SC in raw material, as well as in finished product (tablets). The method implements the principles of green analytical chemistry, providing one possible approach for overcoming the challenges of the pharmaceutical industry for transfer of non-green methods used in quality control into green and environment friendly methods.
Key Word: Sildenafil citrate; film-coated tablets; potentiometric titration; surfactants

I. Introduction

Development of methodologies that comply with the concept of green analytical chemistry (GAC) is becoming a global trend in recent years. The use of these methodologies includes the pharmaceutical industry as well. The GAC concept from the aspect of analytical method development is focused on the elimination (or reduction) of the consumption of reagents from analytical procedures; proper management of analytical waste; minimization of energy consumption and last but not least increased safety for the analyst[1],[2]. In that direction, the implementation of green (eco-friendly) methods for quality control of medicines that fulfill the GAC criteria is required in the pharmaceutical industry. The implementation of the green methodology is especially important for methods used for the determination of the content of active pharmaceutical ingredient (API), because this parameter is a part of every release and shelf-life specification[3]. Therefore, the use of green, simple, and fast methods for quality control of medicines would bring benefits to analysts and the pharmaceutical industry as well to the environment.

Sildenafil citrate (SC) is pyrazolopyrimidinone derivative salt and it acts as a cGMP-specific phosphodiesterase type 5 (PDE5) inhibitor by minimizing the breakdown of cyclic guanosine monophosphate (cGMP). This medicine is used for treating male erectile dysfunction or impotence as well as for management of pulmonary arterial hypertension[4]. Different pharmaceutical companies produce this medicine in a variety of dosage forms such as tablets, film-coated tablets, or chewable tablets under various names, leading to a great

number of manufactured and controlled batches of SC tablets worldwide. Hence, the development and implementation of a green, simple, and fast method for the determination of the content of SC in tablets will be a step forward to the fulfillment of the GAC goal of the pharmaceutical industry.

According to the literature data, several conventional (non-green) chromatographic[5],[6],[7] and spectrophotometric methods[8][9][10][11][12],[13][14] are used for determination of the SC content in bulk, as well in tablets.

Most of the potentiometric methods for determination of SC are based on non-aqueous titration[9] due to the slight solubility of SC in water[15]. The potentiometric methods are fast, reproducible, and low-cost, therefore they are suitable for the determination of API in dosage forms. However, the non-aqueous potentiometric titrations require toxic organic solvents such as methanol, consequently, this kind of method does not comply with the concept of green analytical chemistry (GAC). The additional shortcomings of non-aqueous titration are the need for strict moisture control, as well as control of the other environmental conditions such as temperature and carbon dioxide concentrations[16].

Surfactants have broad applications in analytical chemistry[17]. These molecules are nontoxic, biodegradable, and have low environmental bioconcentration factors, thus are used as an option for greening the mobile phase for liquid chromatography[18]. In addition, the literature data show that low concentration of non-ionic surfactants could be used for aqueous potentiometric determination of dissociation constant of sparingly soluble APIs[19].

Considering the low solubility of SC in water, the aim of this study was to demonstrate the use of polysorbate 80 as a nonionic surfactant, as an approach for optimization of a green analytical method based on potentiometric titration for quantitative determination of sildenafil citrate in API and in pharmaceutical dosage form (tablet).

II. Materials And Methods

Reagents and Materials: Sildenafil citrate, API, was kindly donated by Replek Ltd, Skopje. The 100 mg film-coated tablets were purchased locally from Pharmacies. Polysorbate 80 p.a. (Sigma-Aldrich), 0.1 M Sodium hydroxide VS (Fisher), Potassium hydrogen phthalate (100.00% purity, Merck) and HPLC grade water were used. 1% (v/v).

Instruments: All potentiometric measurements were performed on a potentiometric titrator Mettler Toledo DL 50 (10 mL automatic burette), with a DG111-SC combined glass pH electrode. The samples were weighed on analytical balance (Mettler Toledo AL204, d = 0.1 mg). All used equipment was suitably calibrated/qualified before use[20],[21].

Standardization of 0.1 M Sodium hydroxide: The volumetric solution (0.1 M sodium hydroxide) was standardized prior to use by titrating 0.150 g of potassium hydrogen phthalate in 50 mL purified water (in accordance with European Pharmacopoeia, 4.2.2).

Sample solution: Average weight from 20 film-coated tablets was determined. Quantity of finely powdered tablets equivalent to the average weight was weighed and dissolved in 50 mL 1% (v/v) Polysorbate 80 solution. Samples were titrated with 0.1 M Sodium hydroxide VS, determining the end-point potentiometrically.

Validation of the method:

Linear regression analysis

Eleven different quantities of sildenafil citrate (46.7, 56.1, 66.3, 92.6, 103.1, 113.0, 136.0, 149.4, 150.5, 152.4, 181.1, mg), using 50 mL 1% (v/v) Polysorbate 80 solution as a solvent, were titrated with 0.1 M sodium hydroxide.

Specificity, accuracy, and precision

Specificity: 50 mL 1% (v/v) Polysorbate 80 was titrated as a blank titration. Placebo powder, dissolved in 50 mL 1% (v/v) Polysorbate 80 was titrated was titrated to evaluate the effect of the excipients.

Precision: Six independent determinations of the content of sildenafil citrate in film-coated tablets were performed in two different days.

Accuracy: Powdered tablet mass equivalent to 100 mg sildenafil citrate was weighed and spiked with three different quantities (10 mg, 30 mg, and 50 mg) of the reference substance sildenafil citrate and dissolved in 50 mL 1% (v/v) Polysorbate 80 solution. Three independent determinations of the content of sildenafil citrate were performed at each level, and the recovery value was calculated.

III. Results

Validation of the method for determination of active substance sildenafil citrate

The method for quantitative determination of sildenafil citrate in API and in finished product (tablets) based on potentiometric titration with sodium hydroxide, was developed and optimized. The water-solubility problem of SC was overcome with the use of polysorbate 80[22]. The optimized method was validated in accordance with the requirements for volumetric titrations defined in Technical guide for the elaboration of monographs of European pharmacopeia[23]. In order to demonstrate the applicability of the method for

determination of SC in tablets, additional testing was performed to confirm specificity, accuracy and precision of the method, according to the ICH guideline Q2(R2)[24].
The obtained results from linear regression analysis of the dependence of the end-point volumes (subtracted by the end-point volume of the blank titration), versus mass of the API, given in Table 1, confirm the linearity of the method. Statistical evaluation of the obtained data from regression analysis confirms the fulfilment of the criteria for the volumetric titrations[23], indicating that the proposed titration procedure is acceptable for determination of the content of SC API.

Table no 1: Results from regression analysis

Parameter	Results	
Regression equation	y =0.046·x+0.0012	
Coefficient of determination (R2)	0.9999	
Parameter	Results	Limits
Proportional systematic error (bias)	0.22%	< 0.3 %
Additional systematic error (bias)	0.02 %	< 0.4 %
Precision (statistical error)	0.28 %	< 0.3 %
Practical relative error	0.24 %	< 0.67 %
Relative standard deviation (n=6)	0.33 %	< 0.5 %
Relative accuracy	-0.004 mL	< 1.0 mL

The end point volume obtained from titration of the placebo enabled subtraction of the effect of the excipients, providing specificity of the method. The recovery values (98.0 % - 102.0 %) given Table 2, obtained by analysis on samples (sildenafil citrate film-coated tablets) spiked with three different quantities (10 mg, 30 mg, and 50 mg) demonstrate the accuracy of the method for assay of sildenafil citrate in the finished product (film-coated tablets). The obtained results for the relative standard deviation (below 0.5%) and F value confirm the repeatability and intermediate precision of the method. The results obtained from the method validation study comply with the defined acceptance criteria, confirming the applicability of the proposed method.

Table no 2: Results from accuracy and precision

Accuracy	Recovery (n=3)	RSD %	
80 %	98. 6%±0.7 %	0.3 %	
100 %	98.5%±0.6 %	0.3%	
120 %	98.8%±0.6 %	0.1 %	
Precision	Assay (n=6)	RSD %	F-test
Day 1	98.2 %	0.3 %	F= 2.65
Day 2	99.3 %	0.4 %	(F_{crit} = 5.05)

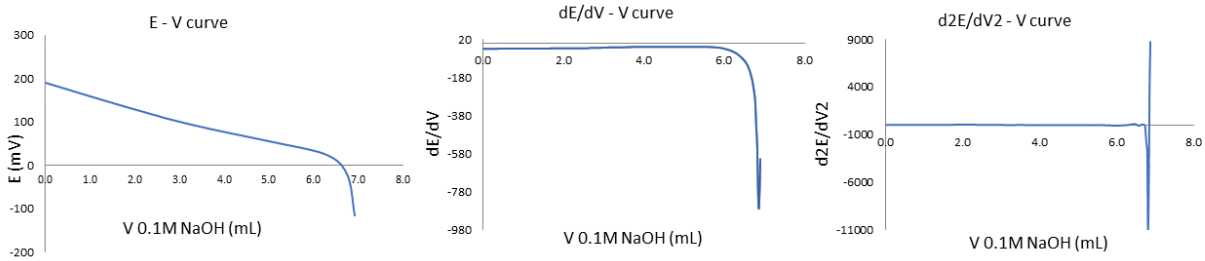

Figure no 1: Potentiometric titration curves of sildenafil citrate with 0.1M NaOH

Applicability of the method

The applicability of the method was confirmed by determining the content of SC in film-coated tablets (Fig 1). The content of SC, active substance, was calculated using equation (Eq. 1), according to the stoichiometric ratio: 1 mL of 0.1 M NaOH VS is equivalent to 22.22 mg SLC[25].

$$Content\ of\ SC\ (\%) = \frac{(V_{eq} - V_{blank}) \cdot Titer_{NaOH} \cdot 22.22\ mg}{m_{SC}} \cdot 100 \quad (1)$$

where: m_{SC} is mass of SC (mg), V_{eq} is titrant consumption (mL) for sample solution, V_{blank} is titrant consumption (mL) for blank titration.

The content of SC in finished product, film-coated tablets was calculated using following equation (Eq. 2):

$$Content\ of SC\ (\%) = \frac{(V_{eq} - V_{placebo}) \cdot \mathrm{Titer_{NaOH}} \cdot 22.22\ \mathrm{mg} \cdot m_{avg}}{m_{tbl} \cdot \mathrm{LC}} \cdot 100 \quad (2)$$

where: m_{tbl} is mass of powdered tablets (mg), m_{avg} is average tablet mass (mg), LC is label claim of SC in tablets (mg), V_{eq} is titrant consumption (mL) for sample titration, $V_{placebo}$ is titrant consumption (mL) for titration of placebo.

IV. Conclusion

The proposed approach for the use of polysorbate 80 as a non-ionic surfactant for solubilization of SC, enabled development of specific, accurate and precise method based on potentiometric titration in aqueous environment, for determination of content of SC in API and in film-coated tablets. The use of polysorbate 80 as a solubilization agent enabled elimination of the toxic organic solvents needed for non-aqueous potentiometric titration of active pharmaceutical ingredients with low solubility. The method implements the principles of green analytical chemistry, providing one possible approach for overcoming the challenges of the pharmaceutical industry for transfer of non-green methods used in quality control into green and environment friendly methods.

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