

# Surfactant-based potentiometric method for quantification of sildenafil citrate

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## Introduction

Sildenafil citrate (SLC) is a vasoactive agent which is widely used for treatment of erectile dysfunction and pulmonary arterial hypertension (PAH). It is a potent, selective, reversible enzyme inhibitor of phosphodiesterase type 5 that acts by elevating cGMP levels and causing smooth muscle relaxation (Ouranidis et al., 2021).

SLC is a substance that is slightly soluble in water, with amphoteric properties due to its structural moieties such as the moderately strong basic piperazine nitrogen, and weak acidic pyrimidinone amide (Gobry et al., 2000). As a result, most of the proposed potentiometric methods for quantification of SLC employ a non-aqueous environment (Silva et al., 2017). The non-aqueous titrations have several drawbacks including the use of expensive organic solvents that are volatile and harmful for both the analyst and the environment, as well as the need to control the moisture, temperature and carbon dioxide levels (Aggarwal et al., 2022). On the other hand, the method for determination of SLC described in the Ph. Eur. monograph 07/2017:2270 for Sildenafil citrate is high performance liquid chromatography (HPLC).

Given that potentiometry as a technique offers many advantages, such as high precision, speed and simplicity, the potentiometric titration plays an important role in quantitative determination of drug substances. In fact, whenever the identification and purity tests are satisfactorily specific, it is more suitable to apply a non-specific, but precise method for quantitative determination of active substances.

In order to overcome some of the disadvantages of non-aqueous titrations, this study shows an alternative aqueous acid-base titration method for quantification of

SLC, using low concentrations of the nonionic surfactant Tween 80 as a solubilization agent.

## Materials and methods

### Materials

SLC was kindly donated by Replek Farm Ltd, Skopje. Sodium hydroxide 0.1 M volumetric solution (VS) was obtained from Fisher Chemical. Standardization of the volumetric solution was performed against a primary volumetric standard, potassium hydrogen phthalate, RV (KHP) purchased from Merck KGaA (100.00% ± 0.05%, k = 2, for approximately 95% level of confidence). Tween 80 (p.a.) was obtained from Sigma-Aldrich (Germany). Water of HPLC grade was used (TKA-AB Reinstwasser system).

### Methods

The potentiometric titration was carried out on Mettler Toledo DL 50 potentiometric titrator, equipped with automatic burette with capacity of 10 mL, qualified according to the OMCL guideline for qualification of automatic titrators (OMCL Network/EDQM of the Council of Europe, 2020d). The end-point was detected using a DG111-SC combined glass pH electrode. The samples were weighed using a calibrated and verified analytical balance (Mettler Toledo).

For the determination of content of SLC, 160.0 mg drug substance was dissolved in 50 mL 1% (v/v) Tween 80 solution. The sample solutions were titrated with 0.1 M NaOH VS, determining the end-point potentiometrically. The content of SLC was calculated according to the stoichiometric ration: 1 mL of 0.1 M

NaOH VS is equivalent to 22.22 mg SLC (Badwan et al., 2001).

## Results and discussion

In this study, Tween 80 (nonionic surfactant) was chosen as a solubilization agent for potentiometric aqueous determination of SLC. Based on the literature data, nonionic surfactants in low concentrations showed no interference with the ionization of certain poorly soluble drugs (Ravichandiran et al., 2011).

In order to optimize the concentration of the surfactant, the potentiometric determination of SLC was performed using four different concentrations of Tween 80 as solvent (0.5%, 1%, 1.5% and 2% (v/v)). The titrations were performed in triplicate. In addition, a blank titration (with zero analyte) was performed for each concentration of Tween 80. The proposed method showed repeatability over the whole concentration range of Tween 80 used as a solubilizer. However, 0.5% (v/v) Tween 80 was insufficient to enable drug solubilization, whereas 2% (v/v) Tween 80 showed significant blank interference.

1% (v/v) Tween 80 was chosen as the ideal surfactant concentration, since it enabled optimal drug solubilization, while the blank titration encompassed insignificant titrant consumption.

The optimized method regarding the concentration of Tween 80 as a solubilization agent was validated according to the Technical guide for the elaboration of monographs of European pharmacopeia (EDQM of the Council of Europe, 2022).

The average content results comply with the established assay limits (98.0% - 102.0%) for active ingredient, described in the individual Ph.Eur. monograph 07/2017:2270 of Sildenafil citrate. The RSD values were satisfactory (<1,0%), thus confirming that the proposed method is precise.

## Conclusion

The proposed potentiometric method presents an inexpensive, fast and simple method for quantitative determination of SLC.

This eco-friendly method could be a suitable alternative to sophisticated and time-consuming instrumental methods such as HPLC and could be easily employed in the quality control of this active substance.

The use of Tween 80 as a solubilization agent in the potentiometric determination of SLC brings to attention the possible use of nonionic surfactants in low concentrations as solvents for determination of other

poorly soluble drug substances and could potentially be a replacement for the non-aqueous titrations.

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