СЕКЦІЯ 2. СТАНДАРТИЗАЦІЯ І ЗАБЕЗПЕЧЕННЯ ЯКОСТІ НА ЕТАПАХ ЖИТТЄВОГО ЦИКЛУ ЛІКАРСЬКИХ ЗАСОБІВ (ВІД РОЗРОБКИ Й ДОСЛІДЖЕНЬ – ДО ВИРОБНИЦТВА, РЕАЛІЗАЦІЇ ТА ЗАСТОСУВАННЯ)

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Iodometric determination of Donepezil by oxidation with hydrogen peroxymonosulfate

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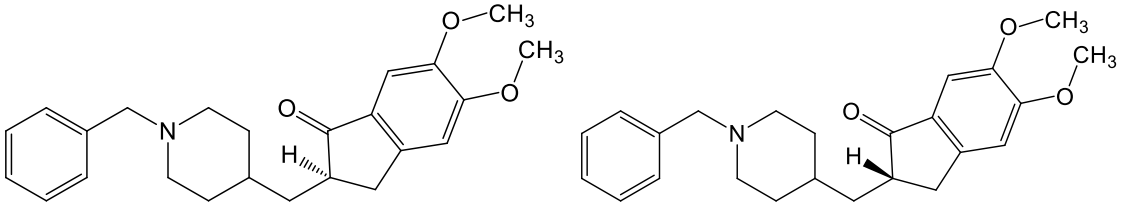
Introduction. Donepezil hydrochloride, 2-[((1-benzylpiperidin-4-yl)methyl)]-5,6-dimethoxy-2,3-dihydoinden-1-one monohydrochloride (**DPZ**) is a centrally active, reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil is a racemate, that is, a 1:1 mixture of the following two enantiomers, The structural formula is shown below (Fig. 1).



(*R*)-Enantiomer (*S*)-Enantiomer

Fig. 1 The structural formula of Donepezil

It is clinically used worldwide for patients with mild to severe Alzheimer disease. The most commonly used techniques for the determination of Donepezil hydrochloride are LC, RP-HPLC and spectrophotometric methods. The official Pharmacopeia of United States monographed a HPLC assay procedure for DPZ in tablets. From the literature references to analytical methods reported for DPZ in pharmaceuticals, it is envisaged that titrimetmetry has practically not been employed so far.

The aim of the study. The main purpose of this study was to develop a selective, simple, and reliable titrimetric method to quantitate donepezil hydrochloride in pure solutions and in pharmaceutical formulations.

Research methods. The proposed red-ox titrimetric method is indirect and is based on the iodometric determination of the excess PMS after allowing the reaction between drug and measured amount of PMS to be complete.

Preparation of $KHSO_5$ (PMS) *solution*. The commercial triple salt of Caro's acid − «Oxone», $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (ACROS ORGANICS, "extra pure", CAS70693-62-8) was used as a reagent. The active substance is potassium hydrogen peroxymonosulfate ($KHSO_5$, PMS). The choice of the reagent is due to its availability, satisfactory solubility in water, high oxidizing capacity, as well as sufficient stability during use and storage. «Oxone» (calculated weight 0.3074 g) was weighed on an analytical balance, the flask was quantitatively transferred to 100.0 ml, dissolved in 70 ml of double-distilled water while stirring, and the volume was brought up to the mark with double distilled water. The concentration of such a solution is 0.01 mol/L.

Donepezil hydrochloride, empirical formula: $C_{24}H_{29}NO_3 \cdot HCl$, molecular weight: 415.95 g/mol. Donepezil HCl Basics 5 mg 98 film-coated tablets (A SUN PHARMA company) Approval number: 77803.00.00 CODE No.: HP/DRUGS/MNB/95/2 PZN -08845263 Each film-coated tablet contains 5 mg donepezil hydrochloride, Equivalent to 4.56 mg donepezil. Composition based on 1 tablet 5 mg donepezil hydrochloride 4.56 mg donepezil; 87.512 mg lactose-1 water, 83.14 mg lactose, cornstarch, Hyprolose, Cellulose, microcrystalline, carboxymethyl starch, sodium type A, Magnesium stearate (vegetable), Hypromelosis, Titanium dioxide, Macrogol 400, talc, Iron (III) oxide hydrate, yellow.

Twenty tablets (Donepezil HCl Basics 5 mg) were accurately weighed, finely pulverized and thoroughly mixed. The powder equivalent to twenty tablets in 5 mg of Donepezil declared active principle (accurately weighed mass) was transferred into 100 mL volumetric flask and about 70 mL of methanol was added, the contents of the

flask were sonicated for 30 min. and then filtered. Aliquots containing suitable concentration of the studied drug was analyzed.

Method of assay. 20 ml of buffer with pH 9.2 was successively added to a 100 ml volumetric flask; 20.00 ml of the solution (or a solution of the substance Donepezil HCl with a concentration of about 1 mg/ml, prepared from an accurately weighed sample) and 20 ml of 0.01 mol/L PMS. It was kept for 15 minutes and diluted to the mark with double distilled water water. Using a pipette, 20.00 ml of the solution was taken into a 100 ml Erlenmeyer flask, 2 ml of 0.1 mol/L HCl solution and 2 ml of 5% potassium iodide solution were added, and the released iodine was titrated with a 0.0100 mol/L (or 0.005 mol/L) standard sodium thiosulfate solution.

Main results. Chemical oxidation is a well-known reaction that has been extensively exploited for the determination of drugs. The proposed method is based on the fact that HSO_5^- ions in an alkaly medium directly oxidise of Donepezil to its *N*-oxide. A proposed mechanism is presented in Fig. 2 in conformity with the 1:1 reaction ratio observed.

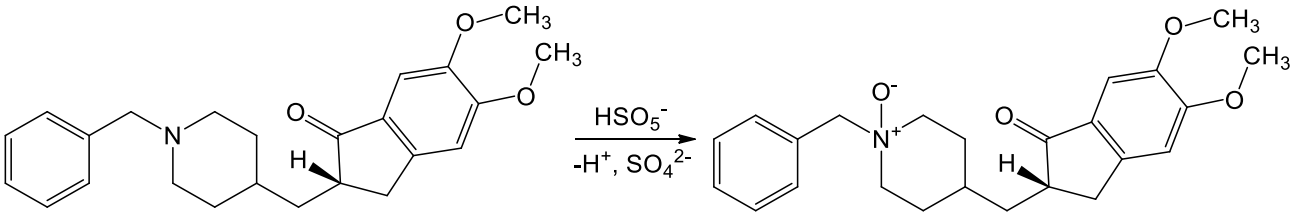


Fig. 2 Scheme of the oxidation process of Donepezil with PMS

Phosphate buffer solution was found to be convenient medium for this method. It was found that the maximum reaction rate was achieved when using a buffer solution with a pH of 9.2-9.5, so a volume of 20 ml of 0.2 mol/L was used for all measurements. The time required to complete the reaction was found to be 15 min: constant volumes readings of sodium thiosulfate titrant were obtained when the reaction times were extended up to 15 min. The measured volume was stable for 20-25 min even in the presence of reaction product. A new method was given for the *determination* of *Donepezil* drug in pure solutions and in tablet pharmaceutical

formulation.

LOQ = 0,01 mg. The maximum RSD in the results is ±2%.

Conclusions. The proposed method for determination of *Donepezil* hydrochloride is simple and economic with good precision and accuracy. With this method one can do analysis simply with cheap chemicals without losing accuracy. Hence this method can be employed as alternatives for routine analysis of bulk sample and tablets. This method is greener approaches due to the non-usage of any organic toxic solvent and pre-treatment and extraction steps' absence.