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PHARMACEUTICAL SCIENCES

UDK 615.1

INVESTIGATION OF NITRENDIPINE BY HPLC STANDARDIZED METHOD

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Annotation: Nitrendipine is a representative of dihydropyridines class and used in medicine as calcium channel blocker for the treatment of hypertension. IUPAC name of nitrendipine is 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. Nitrendipine has an effect on peripheral blood vessels. Despite the fact that nitrendipine in therapeutic doses does not affect the function of the kidneys and heart, cerebral and peripheral circulation, the toxic effect on this substance on the body is present. It can manifest as peripheral vasodilation and prolonged arterial hypotension. Therefore, an important aspect of the pharmaceutical analysis of this medicinal substance is a thorough check for the presence of unacceptable impurities, the presence of which will affect the enhancement of the toxic effect of the drug on the body.

Keywords: nitrendipine, dihydropyridine, HPLC, standardization, pharmaceutical analysis

The molecule of 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate exists as two enantiomers, it is a racemic mixture.

It is aromatic conjugated system with pharmacophores and active functional groups in positions 2, 3, 4, 5 and 6 (fig.1).

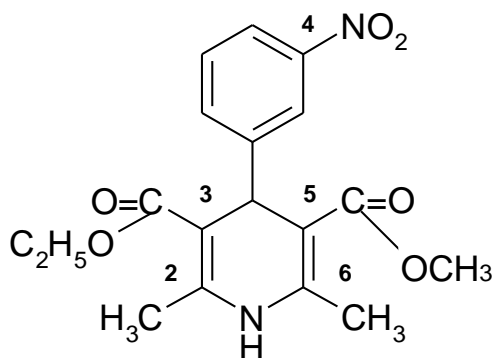


Figure 1. Chemical formula of 5-O-ethyl-3-O-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Attempts to chemically modify this molecule were carried out in order to reduce the toxicity of the substance and enhance or, even expand, the spectrum of its pharmacological activity. It is known that the introduction of fluorine-containing substituents into the structure of the molecule led to a decrease in toxicity and an increase in pharmacological action [1, p. 42-45]. These changes are explained by lipophilicity of the fluorine-containing substituents, as well as by the high-strength carbon-fluorine bond (fig.2).

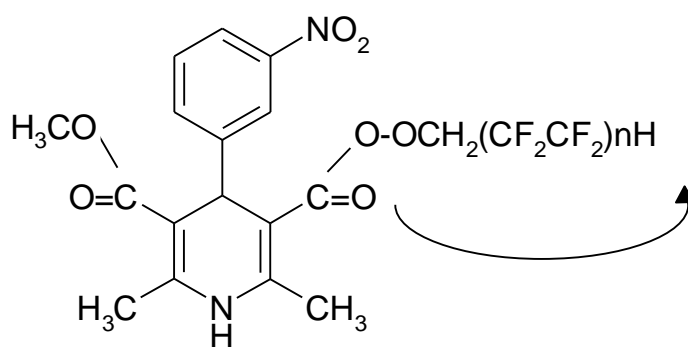
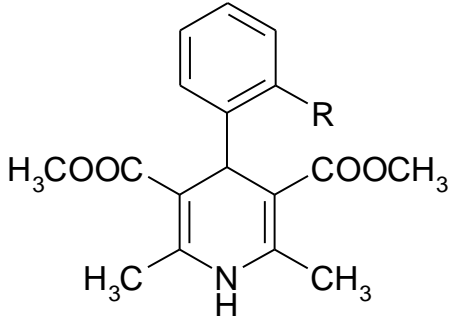
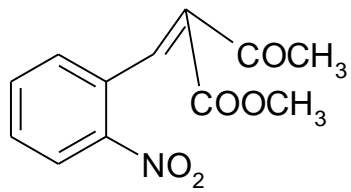
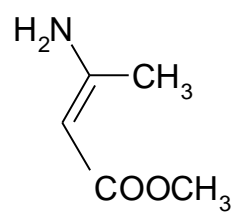


Figure 2. Chemical formula of modified 5-O-ethyl-3-O-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

The State Pharmacopoeia of Ukraine describes the analysis of an analogue of Nitrendipine – *the drug Nifedipine* (dimethyl ester 2,6-dimethyl-4-(2-nitrophenyl)-

1,4-dihydropyridine-3,5-dicarboxylate) [2, p. 504]. Accompanying impurities, namely specific impurities A, B, C and D, are determined by liquid chromatography:

 <p>R = NO₂ (A), NO (B)</p>	<p>A – nitrophenylpyridine analogue</p> <p>B – nitrosophenylpyridine analogue</p>
 <p>C</p>  <p>D</p>	<p>C – methyl 2-(2-nitrobenzylidene)-3-oxobutanoate</p> <p>D – methyl 3-aminobuto-2-enoate</p>

The purpose of the investigation is to study the use of HPLC method to detect the permissible and not permissible impurities in the substance of 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine). This will allow testing the HPLC method in the analysis of the test substance in a comparative characteristic with the standardized method for the analysis on Nifedipine described in SPhU.

Materials and methods. An Agilent 1260 Infinity II chromatograph with a UV detector was used for the studies.

HPLC method, conditions:

- column – InfinityLab Poroshell 120 EC-C18, 150x4,6x4 (or equivalent);
- flow rate – 0.9 mL/min;
- detection – 235 nm;
- injection volume – 20 µl;
- column temperature – 25°C;
- Solvents: deionized water phosphate buffer solution pH 3.0 (A), methanol (B) and tetrahydrofuran (D) in the ratio 60:16:24.

Solvent: deionized water phosphate buffer solution pH 3.0 (A), methanol (B) and tetrahydrofuran (D) in the ratio 60:16:24. Used solutions of two 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine) substances (conc. 1.0 mg/mL in solution). Standard was the sample of SPU 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine) (conc. 0.01 mg/mL in solution). For computer analysis, the program OpenLab CDS (impurities determination) by HPLC method was used. The following reagents were used: water (HPLC purity), methanol (HPLC purity), THF (HPLC purity).

Results and discussion. Chromatographic data showed that the standard sample of 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine) substance contains only acceptable impurities within acceptable limits (fig.3).

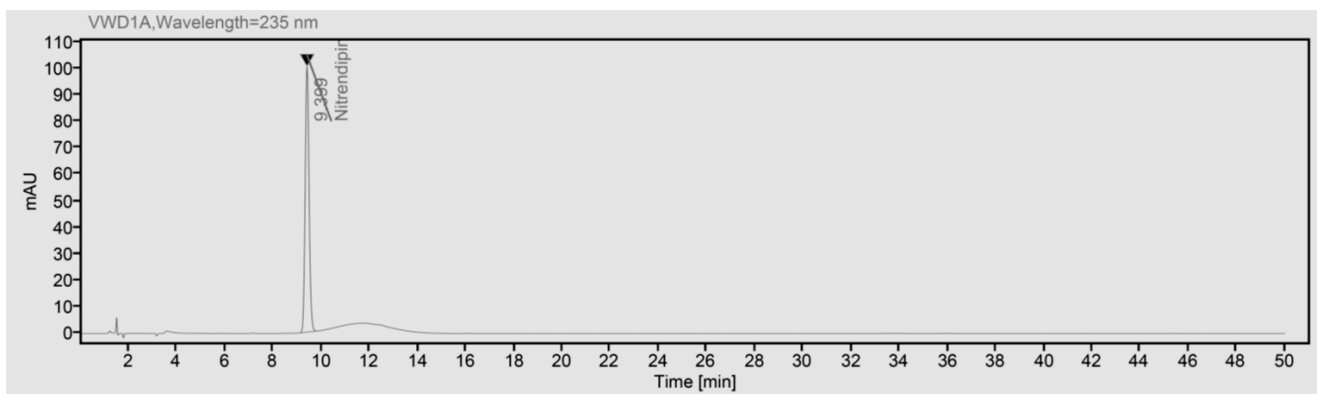


Figure 3. Chromatogram of standard sample of 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine) substance (retention time 9.399).

It was established that three identified and two unidentified impurities were present in the studied samples of two substances of 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine), however, their sum does not exceed the established level in comparison with the standard sample (fig.4).

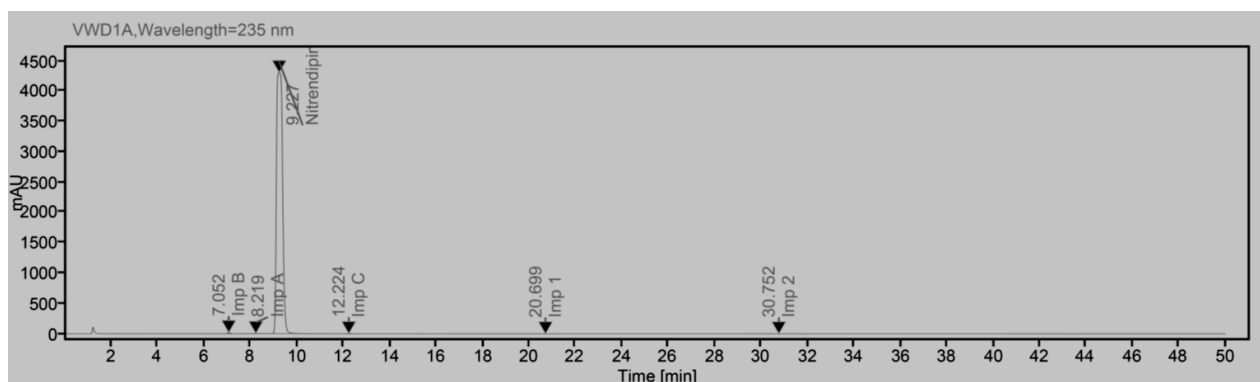


Figure 4. Chromatogram of 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine) substance with identified impurities (retention time 7.052 (Imp A), retention time 8.219 (Imp B), retention time 12.224 (Imp C), and unidentified impurities retention time 20.699 (Imp 1), retention time 30.752 (Imp 2).

Conclusions. HPLC method allows to perform a very thorough analysis of 5-*O*-ethyl-3-*O*-methyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nitrendipine) substance, as a result of which not only specific and non-specific or permissible and not permissible impurities are detected, but also

unidentified impurities, the structure of which can only be determined by mass spectrometry method.

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