INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors help relax blood vessels. ACE inhibitors prevent an enzyme in your body from producing angiotensin II, a substance in your body that narrows your blood vessels and releases hormones that can raise your blood pressure. This narrowing can cause high blood pressure and force your heart to work harder. Many ACE inhibitors are available. Which one is best for you depends on your health and the condition being treated. People with chronic kidney disease may benefit from having an ACE inhibitor as one of their medications.

Since 1981, ACE inhibitors have been commonly prescribed to treat hypertension. This is because they tend to be well-tolerated by those who take them. They’re usually taken just once a day, often in the morning. They may be prescribed along with diuretics or calcium channel blockers, which are also used to treat high blood pressure. ACE inhibitors have two primary functions. First, they decrease the amount of sodium retained in the kidneys. Secondly, they stop the production of a hormone called angiotensin II. This hormone usually causes blood vessels to narrow. When this hormone isn’t produced, production of a hormone called angiotensin II. This hormone usually causes blood vessels to narrow. When this hormone isn’t produced, it allows blood to flow more effectively. This helps the blood vessels to relax and expand, which lowers blood pressure [1].

The quantity of medication brought into the marketplace is growing each year. Analytical method development is increasingly being introduced into fundamental pharmaceutical research and pharmaceutical analysis practice, taking into account their high sensitivity, accuracy, specificity and expressiveness. Search criteria was analytical method development for medicines from group of ACE inhibitors. Literature survey has been done in range of years 1990-2018 to make the review updated and comprehensive and to show the new approaches to the development of the methods of analysis ACE inhibitors. The sources were world recognized journals and key words used as filter were angiotensin-converting enzyme inhibitors, captopril, enalapril, method development, spectrophotometry, HPLC, UHPLC. The current review is created with an intended to focus on the advantage of HPLC. Literature survey revealed that a number of methods have been reported for estimation of ACE inhibitors individually or in combination with other drugs. However, there is very few analytical methods reported for the simultaneous analysis of these drugs in a combined dosage formulation by HPLC. In additional, analysis of approaches to the development of the methods of analysis of ACE inhibitors in drugs and biological liquids has been shown that HPLC is the most suitable method for analyses ACE inhibitors in substances, drugs, biological liquids to performe routine analysis of medicines, pharmacokinetic (bioequivalence in vivo), dissolution test for final doses forms (bioequivalence in vitro, bioequivalence procedure).

Keywords: Angiotensin-converting enzyme inhibitors, Captopril, Enalapril, Spectrophotometry, HPLC, UHPLC, Pharmacokinetic, Bioequivalence

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The quantity of medication brought into the marketplace is growing each year. Analytical method development is increasingly being introduced into fundamental pharmaceutical research and pharmaceutical analysis practice, taking into account their high sensitivity, accuracy. Search criteria was analytical method development for medicines from group of ACE inhibitors. Literature survey has been done in range of years 1990-2018 to make the review updated and comprehensive and to show the new approaches to the development of the methods of analysis ACE inhibitors. The sources were world recognized journals and key words used as filter were angiotensin-converting enzyme inhibitors, captopril, enalapril, method development, spectrophotometry, HPLC, UHPLC.

Analytical method development of captopril

Captopril is an angiotensin-converting enzyme (ACE) inhibitor used in the therapy of hypertension and heart failure. Captopril is associated with a low rate of transient serum aminotransferase elevations and has been linked to rare instances of acute liver injury [2]. Chemical name of captopril is (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid (fig. 1).

![Chemical structure of captopril](Image)

**Fig. 1:** The chemical structures of captopril

The State Pharmacopoeia of Ukraine (SPHU) has the monograph on the substance of captopril and on tablets of captopril [86-94]. For identification of captopril substance, the SPhU proposes to determine the specific optical rotation and the method of absorption spectrophotometry in the infrared region, the quantitative determination–iodometry potentiometric titration using the combined platinum electrode. For identification of captopril in tablets, the SPhU proposes TLC (mobile phase–a mixture of methanol P, ice acetic acid P, toluene P (1:25:75). For quantitative determination of captopril in tablets–HPLC/UV (mobile phase–a mixture of phosphoric acid of concentrated P, water P and methanol P (0.5:450:550), mobile phase rate–1.0 ml/min, detection of wavelength 220 nm).

The United States Pharmacopeia regulates the definition of captopril in substances, tablets and combined tablets with hydrochlorothiazide. For identification of captopril in the substance, the method of absorption spectrophotometry in the infrared region and the determination of specific optical rotation is proposed, for quantitative determination–iodometry. For the identification of captopril in tablets, the United States Pharmacopeia offers TLC (mobile phase–a mixture of the SPhU), for quantification–HPLC/UV. According to this monograph, the following chromatographic conditions are used: chromatographic column of category L1 (with
fixed phase C18 size 4.6 mm x 250 mm; mobile phase – methanol P: water P: phosphoric acid P (55:45:0.5); wavelength – 220 nm, flow rate – 1.0 ml/min.

The European Pharmacopoeia suggests for identification of captopril substance to determine the specific optical rotation and the method of absorption spectrophotometry in the infrared region, the quantitative determination – iodometry, potentiometric titration with the use of a combined platinum electrode.

Methods of quantitative determination of captopril in the drug and biological fluids by spectrophotometry and chromatography [3-25] methods are described in the scientific literature.

Captopril has three analytical and functional groups in its structure (carboxyl group, keto group and mercapto group), which determine the methods of captopril analysis. Titrimetric methods have not been widely used in the analysis of medical form of captopril, since the drugs have auxiliary substances that would interfere with the determination of captopril titrimetrically in medical form. Spectrophotometric methods of analysis are widely used in the analysis of drugs containing captopril. The scientific literature describes methods for determining captopril by spectrophotometry using various reagents to determine the mercapto group.

The authors S. M. El-Ashry, F. A. Ibrahim developed two spectrophotometric methods for the determination of captopril in tablets, which were based on the reaction of thiol group. In the first method, promethazine hydrochloride during interaction with the solution of N-Bromophthalimide in orthophosphate acid was oxidized to the free radical of promethazine, which had a maximum absorption at 516 nm. Red color of promethazine was quantitatively reduced by captopril to colorless promethazine. Adding captopril to the red solution of promethazine resulted in reduction in absorption in direct proportion to the amount of captopril, which was the basis of spectrophotometric determination of captopril in tablets. The second method involved the use of molybdenum phosphoric acid as an oxidant to determine captopril. When captopril interacted with molybdenum phosphate acid, there was formed a reaction product of blue color during heating and the maximum of absorption was 685 nm [3, 4].

Jovanović T et al. proposed spectrophotometric determination of captopril in interaction with palladium (III) chloride in the Britton-Robinson buffer solution at different pH values (2.14-9.10) with the formation of yellow reaction product with the maximum absorption at 380 nm. Developed spectrophotometric method has been successfully applied for the determination of captopril in the drug [5].

Spectrophotometric method for the determination of captopril in the drug using 2,3-dichloro-1,4-naphthaquinone (dichloro) in a neutral environment with forming a product of yellow reaction with the maximum absorption at 347 nm is described by Dawood H. et al. [6, 7]. Scientists H. Chandru and A. C. Sharada developed a spectrophotometric method for the determination of captopril in the drug using hexaammineruthenium (III) as a reagent. Solutions of the complex have absorption maxima at 510 nm and are subject to the Bouguer-Lambert-Beer’s law in the concentration range of 0.25-12.00 μg/ml. The proposed method has been successfully applied to determine this API in tablets [8].

Scientists A. Gumieniczek, D. Kowalczuk and L. Przyborowski proposed chromatographic and spectrophotometric methods of determination of captopril in tablets. The method of reverse HPLC/UV detection of captopril was developed using the chromatography column LiChrosorb RP-18 column, mobile phase – a mixture of phosphate buffer solution pH 2.4 and acetonitrile (7:3, v/v) at wavelength of 211 nm and internal standard – cephradine. The spectrophotometric method was based on the interaction of captopril with tetrazolium blue with the formation of a product of blue reaction having a maximum absorption at 526 nm [9-14].

Jebasliehepzybai B. et al. developed HPLC/UV method for captopril determination in tablets using the chromatography column LC1 (C18) column (250 × 4.6 mm; 5 μm) and mobile phase – a mixture of methanol and water (55:45 v/v), flow rate – 1 ml/min, detection wavelength – 220 nm. The method was linear in the range of concentrations of 80-120 μg/ml, the correlation coefficient was 0.999. The developed method has been successfully applied for routine analysis of captopril in drugs [15].

Scientists Leanpokharameajh J. and Sukrisiwarong J. described the HPLC/UV method for the determination of captopril in extemporaneous medical form for use in pediatrics. In solution, captopril is oxidized to captopril disulfide, therefore the developed method involves the simultaneous determination of captopril and captopril disulfide in medical form. Chromatography was carried out using the mobile phase – a mixture of methanol and 0.1% phosphoric acid. Captopril holding time was 5.1-5.4 min and captopril disulfide – 12.2-12.9 min. The method was linear in the concentration range 0.75-20 ng/ml, the correlation coefficient was 0.9995. The developed method was fully validated [16].

Reverse-phase HPLC/UV method for the simultaneous determination of captopril with antagonists of H-2 histamine receptors (cimetidine, ranitidine, famotidine) was described by Sultan N. et al. The proposed method uses the chromatography column Purospher star C18 (5 μm, 250 mm × 4.6 mm) and mobile phase – a mixture of methanol, water and phosphate buffer solution pH 3.0 (60:40 v/v), mobile phase rate – 0.8 ml/min, detection wavelength is 225 nm. Captopril holding time was 5.2 min. The method was linear in the range of concentrations of 9.3-150 μg/ml, correlation coefficient was 0.9993, LOD – 1.75 ng/ml, LOQ – 5.3 ng/ml. The developed method has been successfully applied to study the bioavailability of captopril in the presence of antagonists of H-2 histamine receptors [17].

Huang T. et al. developed the reverse-phase HPLC/UV method for the simultaneous determination of captopril and hydrochlorothiazide in blood plasma using the chromatography column C18 column (DIAMONSIL 150 mm × 4 mm i.d., 5 microm) and mobile phase – a mixture of acetonitrile, fluoracetic acid and water in gradient elution mode, mobile phase rate –1.2 ml/min, detection wavelength is 263 nm. Captopril holding time was 6.8 min, hydrochlorothiazide – 16.9 min, respectively. The method is linear in the range of concentrations of captopril 20-4000 ng/ml and hydrochlorothiazide – 10-1200 ng/ml. The correlation coefficient of captopril was 0.9993, hydrochlorothiazide was 0.9999. LOQ of captopril was 7 ng/ml, of hydrochlorothiazide was 3.3 ng/ml, respectively. The developed method has been successfully applied for the determination of captopril and hydrochlorothiazide in blood plasma [18].

Scientists N. Sultan, M. S. Arayne, S. Naveed proposed HPLC/UV method for the determination of captopril and API from the group of nonsteroidal anti-inflammatory drugs (flurbiprofen, ibuprofen, diclofenac sodium, mafenamic acid) in drug formulation blood plasma using the chromatography column Purospher star C18 (250 mm × 4.6 mm i.d., 5 microm) and mobile phase – a mixture of methanol, water, orthophosphoric acid pH 2.8 (80:20 v/v), mobile phase rate – 1.0 ml/min, detection wavelength – 227 nm. LOD of captopril was 1 ng/ml, whereas fluoxetine – 0.2 ng/ml, ibuprofen 1 ng/ml, diclofenac sodium 2 ng/ml, mafenamic acid 0.4 ng/ml. LOQ of captopril was 3.5 ng/ml, fluoropropene – 0.9 ng/ml, ibuprofen – 2.9 ng/ml, diclofenac sodium – 8 ng/ml, mafenamic acid – 1 ng/ml, respectively. The retention time of all analytes was less than 12 min [19].

Scientists N. Aykin, R. Neal, M. Yusof, N. Earl developed the method for the determination of captopril in biological fluids with ThioGlo 3 derivatization due to the presence of thiol group. Captopril was derivatized by ThioGlo 3 [3H-naphtho [2,1-b]pyran-9-oxo-2-4-[2.5-dihydro-2,5-dioxo-1H-pyrrol-1yl)phenyl-3-oxo]-]. Chromatography was performed using the chromatography column Astec C (18) column and mobile phase – a mixture of water, acetonitrile, acetic acid, phosphoric acid (50:50, 1 ml/l of acids) per concentration of excitation of 365 nm and wavelength of radiation of 445 nm. The developed method was used to determine captopril in biological fluids [20, 21].

Li K. et al. described HPLC/UV method for the determination of captopril in blood plasma and the use of this method for the study of pharmacokinetics. The proposed method uses the chromatography column Spherisorb C18 column and mobile phase – a mixture of...
A simple, rapid, sensitive, and specific method was developed for the determination of captopril by UHPLC in mono-medicines and pharmaceutical dosage forms in combination with hydrochlorothiazide without previous separation. Satisfactory resolution was achieved using Fused-Core® technology Ascentis Express C18 column (4.6 x 150 mm) and a mobile phase consisting of methanol and water (60:40% v/v) with the addition of phosphoric acid to pH 3.0, mobile phase rate 2.0 ml/min, column temperature 30 °C, detection wavelength 220 nm. Captopril holding time was 8 min. The method is linear in the range of concentrations of captopril 25-200 μg/ml, correlation coefficient 0.9997. LOD of captopril was 7 μg/ml, LOQ–3 μg/ml, Tmax–0.56 h, Cmax–266.5 μg/ml, AUC0-t–3068.1 μg/ml/h.

The method was successfully applied for the determination of captopril in drugs [25-47].

Aalytical method development of enalapril

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor widely used in the therapy of hypertension and heart failure. Enalapril is associated with a low rate of transient serum aminotransferase elevations and has been linked to rare instances of acute liver injury [2]. Chemical name of enalapril is (2S)-1-[(2S)-2-[(1S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl] pyrolidine-2-carboxylic acid (fig. 2).

The State Pharmacopeia of Ukraine (SPU) has the monograph on the substance of enalapril maleate and on enalapril tablets. For identification of the substance of enalapril maleate, the SPU offers the method of absorption spectrophotometry in the infrared region, quantitative determination–alkalimetry potentiometric titration. For identification of enalapril in tablets, the SPU proposes TLC (mobile phase–a mixture of acetic acid of 0.1% v/v, water, 1-butanol, P 15:25:60). For the quantitative determination of enalapril in tablets–HPLC/UV (mobile phase–a mixture of acetonitrile P and solvent (40:60), solvent–potassium dihydrogen phosphate solution P, mobile phase rate–1.0 ml/min, detecting by wavelength at 215 nm).

The United States Pharmacopoeia regulates the determination of enalapril maleate in substances and tablets. For the identification of enalapril maleate in the substance, the method of absorption spectrophotometry in the infrared region and HPLC/UV, for the quantitative determination–HPLC/UV is proposed. For the identification and quantification of enalapril in tablets, the United States Pharmacopoeia offers HPLC/UV. According to this monograph, the following chromatographic conditions are used: chromatographic column of category L1 (fixed phase C18) with size 4.6 mm x 250 mm; mobile phase–a mixture of buffer solution (solution of sodium dihydrogen phosphate with the addition of phosphoric acid to pH 2.2): acetonitrile P (75:25); wavelength–215 nm, flow rate–2.0 ml/min.

The European Pharmacopoeia [3] suggests the method of absorbing spectrophotometry in the infrared region for the identification of substance enalapril maleate, quantitative determination–alkalimetry potentiometric titration.

Methods of quantitative determination of enalapril maleate in drugs and biological fluids. The methods of spectrophotometry and chromatography [48-75] are described in the scientific literature.

Scientists Papanov S., Hadjieva B., N. Koleva developed the reverse-phased HPLC/UV method for the determination of captopril in tablets using the chromatography column LiChrosorb® RP-18 (10 μm, 250x4 mm) and mobile phase–a mixture of methanol and water (60:40% v/v) with the addition of phosphoric acid to pH 3.0, mobile phase rate–2.0 ml/min, column temperature–30 °C, detection wavelength–220 nm. Captopril holding time was 8 min. The method is linear in the range of concentrations of captopril 25-200 μg/ml, correlation coefficient–0.9997. LOD of captopril was 7 μg/ml, LOQ–3 μg/ml, Tmax–0.56 h, Cmax–266.5 μg/ml, AUC0-t–3068.1 μg/ml/h.

The method was successfully applied for the determination of captopril in drugs [25-47].

Baraka M. M. et al. proposed spectrophotometric methods for the determination of ramipril, enalapril, and fosinopril drugs, which were based on the formation of complex compounds in the interaction with molybdenum (V) thiocyanate, which was extracted with chloroform. The solutions of complex have absorption maxima at 517 nm and are subject to the Bouguer-Lambert-Beer’s law in the range of enalapril concentrations of 4-36 μg/ml, ramipril concentrations of 3-27 μg/ml, and fosinopril–10-90 μg/ml. Another way was direct determination of the complex compound after adding benzalkonium chloride as surfactant. Solutions of complex have absorption maxima at 545 nm and are subject to the Bouguer-Lambert-Beer’s law in the range of enalapril concentrations of 3-27 μg/ml, ramipril and fosinopril–10-72 μg/ml. The developed methods were successfully applied for the determination of ramipril, enalapril, and fosinopril in drugs [50].

Scientists Ayad M. M., Shababy A., Abdellatif H. E., Hosny M. M. developed spectrophotometric methods for determination of enalapril and timolol in drugs. The first method was based on the formation of a complex compound with palladium (II) chloride in buffer media, while the second method was the formation of colored complexes in interaction with palladium (II) salt, eosin and detectable APIs using methylcellulose as surfactant to increase the solubility of complex compounds. Solutions of complex have absorption maxima at 545 nm and are subject to the Bouguer-Lambert-Beer’s law in the range of enalapril concentrations of 3-27 μg/ml, ramipril and fosinopril–10-72 μg/ml. The developed methods were successfully applied for the determination of timolol and enalapril in medical form [49].
method was linear in the range of concentrations of enalapril 5-50 μg/ml and hydrochlorothiazide 5-30 μg/ml, respectively [53, 54].

Scientists Rahman N., Manirul Haque S. K. developed spectrophotometric methods for determination of enalapril maleate in drugs. The first method was based on the interaction of enalapril with potassium iodate and potassium iodide to form a yellow reaction product with a maximum absorption at 352 nm. Other methods were based on the reaction of complexation with dichloro-5,6-dicyano-1,4-benzoquinone in environment of acetonitrile-1,4-dioxane, with potassium iodide in environment acetonitrile-dichloromethane. Subjected to the Bouguer-Lambert-Beer's law was in the range of concentrations of 2.5-50, 20-560, 5.75 and 10-200 μg/ml, respectively. The developed methods were successfully applied for the spectrophotometric determination of enalapril maleate in drugs [55].

Simona Gherman et al. offered the spectrophotometric method of determination of enalapril maleate in drugs of different manufacturers. The method was based on the dissolution of enalapril in buffer solution of pH 4, the maximum absorption was observed at 208 nm. The method was linear in the range of concentrations of 1-20 μg/ml LOD =0.3721 μg/mL, LOQ =0.9019 μg/mL [56].

Scientists Manindra M., Zafar H. S. and Ankur K. described HPLC/UV method for the determination of enalapril maleate in tablets using the chromatography column Hypersil MOS, 5 μm (250 mm x 4.6 mm) and mobile phase—a mixture of buffer solution and acetonitrile (40:60, v/v), flow rate—1.5 ml/min, wavelength detection—215 nm. Enalapril holding time was 9.72 min. The method was linear in the range of concentrations of 150-250 μg/ml, correlation coefficient was 0.9992. The developed method was successfully applied for the control of the quality of drugs that contain enalapril maleate [57].

Scientists Al-Momani F. developed the HPLC/UV method for determination of enalapril maleate and hydrochlorothiazide in tablets using the chromatography column Supelcosil LC-8 (5 μm, 150 mm x 4.6 mm id), internal standard—thophylline and mobile phase—tetrahydroxalammonium hydrogen sulfate in acetonitrile, water, tetraamine (14:85:6.6, v/v/v) with addition of ice acetic acid to pH 4,1, detection wavelength=220 nm. The developed method was used to determine enalapril maleate and hydrochlorothiazide in drugs [58].

Reverse-phase HPLC/UV method for the simultaneous determination of enalapril maleate and hydrochlorothiazide in drugs was proposed by Suryadevaa Vidyadharaa et al. The developed method uses the chromatography column C18 column (ODS C18 column 250 mm x4.5 mm) and mobile phase—a mixture of acetonitrile, methanol and acetonitrile (60:20:20 V/V/V, pH 5), mobile phase rate—0.8 ml/min, detection wavelength=232 nm. Enalapril maleate holding time was 2.8 min, hydrochlorothiazide—4.1 min. The method was linear in the range of concentrations of 10-30 μg/ml, correlation coefficient was 0.999. LOD enalapril—0.16 μg/ml, LOQ enalapril—0.49 μg/ml. The developed method was successfully applied for the determination of enalapril maleate and hydrochlorothiazide in drugs [59].

The scientist Bharat G. described the HPLC/UV method for determining enalapril maleate and amloidipine in drugs using the chromatography column Phenomenex C18 (5 μm, 250 mm x6 mm) and mobile phase—a mixture of methanol, acetonitrile, water (40:50:10, v/v/v), mobile phase rate—1.0 ml/min. Enalapril holding time was 2.27 min, amloidipine was 5.07 min. The method was linear in the enalapril concentration range of 0.5-60 μg/ml, correlation coefficient was 0.9999. LOD of enalapril—0.04 μg/ml, LOQ of enalapril—0.4 μg/ml. The method was linear in the amloidipine concentration range of 0.5-80 μg/ml, correlation coefficient was 0.9983. LOD of amloidipine was 0.04 μg/ml, LOQ of 0.4 μg/ml. The developed method was successfully applied for the determination of enalapril maleate and amloidipine in drugs [60].

Scientists Sultana N., Saeed A. and Naveed S. developed the method of reverse-phase HPLC/UV determination of enalapril maleate in the presence of API from the group of statins (rosuvastatin, atorvastatin, simvastatin). Chromatography was performed using the chromatographic column Purospher Star, C18 (5 mm, 250 x 4.6 mm) and mobile phase—a mixture of acetonitrile and water (60:40 v/v), detection wavelength=230 nm. The holding time of all analytes was less than 10 min. The method was linear in enalapril concentration range of 2.5-100 μg/ml, correlation coefficient—0.9995 whereas the method was linear in the range of concentrations of API 0.625-25.0 μg/ml of statins group, correlation coefficient was 0.9990. LOD of enalapril was 3.9 ng/ml, while rosuvastatin was 0.03 ng/ml, atorvastatin 0.04 ng/ml, simvastatin was 0.02 ng/ml. LOQ was 12 ng/ml, while rosuvastatin—not 0.09 ng/ml, atorvastatin—not 0.1 ng/ml, simvastatin—not 0.07 ng/ml. The developed method was successfully applied for the determination of enalapril maleate in the presence of API from the group of statins [61, 62].

Nagarajan G. et al. proposed the HPLC/UV method for determination of enalapril and ramipril in drugs using the chromatographic column Oyster BDS C18 column (250x4.6 mm, 5μm) and mobile phase—a mixture of buffer solution A (aqueous solution of sodium perchloride with the addition of triethylamine, with phosphoric acid pH 3.6±0.1 and addition of acetonitrile) and buffer solution B (aqueous sodium perchloride solution with addition of triethylamine, formation of phosphoric acid pH of 2.6±0.1 and addition of acetonitrile) (50:50, v/v), mobile phase rate—1.0 ml/min, detection wavelength=208 nm. Enalapril holding time was 4.197 min, ramipril—5.819 min. The method was linear in the range of concentrations of 5-30 μg/ml of both analytes, limits of enalapril and ramipril detection—3.25 and 1.09 μg/ml, respectively. The limit of enalapril and ramipril detection—1.733 μg/ml and 3.303 μg/ml, respectively. The developed method was successfully applied for routine analysis of enalapril and ramipril in drugs [63].

Scientists Wally A. M., Belal S. F., Heaba E. A., Kersh A. E. described the determination of enalapril maleate and hydrochlorothiazide by UV spectrophotometry and HPLC/UV methods (mobile phase—a mixture of acetonitrile and water (20:80, v/v), detection wavelength=215 nm for enalapril and 275 nm for hydrochlorothiazide) [64].

Scientists Tajerzadeh H. and Hamidi M. developed HPLC/UV methods for enalaprilat determination. The method was linear in the range of concentrations of 1-200 μg/ml, LOD of enalaprilat—0.125 μg/mL, LOQ of enalaprilat—0.5 μg/ml. The developed method makes it possible to clearly separate the peaks of enalaprilat and enalapril, so it can be used to determine enalapril in the presence of enalaprilat [65].

Scientists Ush B. and Ozden T. proposed HPLC/UV and UHPLC/UV methods for enalapril and hydrochlorothiazide determination in drugs using chromatographic columns Waters μ-Bondapak C 18 (300 x 3.9 mm, 10 μm) and Waters Acquity BEH C18 (100 x 2.1 mm, 1.7 μm). Enalapril holding time by UHPLC/UV method was 5.2 min, while by UHPLC/UV method was 1.95 min. The HPLC/UV method was linear in the range of enalapril concentrations of 0.270-399 μg/ml and hydrochlorothiazide 0.260-399 μg/ml. The UHPLC/UV method was linear in the range of concentrations of enalapril 0.270-399 μg/ml and hydrochlorothiazide 0.065-249 μg/ml. The developed method was successfully applied for the determination of enalapril and hydrochlorothiazide in drugs. It can also be used as an example of increasing the expressiveness of methods for the determination of various APIs [66].

Scientists Hossein Danafar and Mehrdad Hamidi described the bioanalytical method for enalapril and enalaprilat in blood plasma by the HPLC/MS method using the chromatographic column C (18) column and mobile phase—a mixture of methanol, water, formic acid (74:24:2 v/v/v), mobile phase rate—0.2 ml/min. Total chromatography time was 1.25 min. The method is linear in the range of concentrations of 0.1-20 ng/ml of both analytes, the correlation coefficient was more than 0.999. LOD was 0.08 ng/ml, LOQ was 0.1 ng/ml, respectively. The developed method was successfully applied for the determination of enalapril and enalaprilat in blood plasma [67-71].

Qi Gu et al. developed the HPLC/MS method for enalapril and enalaprilat determination in blood plasma using the chromatographic column Zorbax Extend-C (18). Total chromatography time was 3.45 min. The method was linear in the range of concentrations of enalapril 5-50 μg/ml and hydrochlorothiazide 5-30 μg/ml, respectively [53, 54].
min. The method was linear in the range of concentrations of 0.1-100.0 ng/ml for both analytes, LOQ=0.1 ng/ml, respectively. The developed method was successfully applied for the determination of enalapril andenalaprilatumin blood plasma and conducting of pharmacokinetic studies [72, 73].

Scientists Niopas I., Daftsios A. C., Nikolaidis N. described the bioanalytical method of enalapril determination using the developed method for study the bioequivalence of two tablet drugs with enalapril (Antiprex (Elpen, Greece) and Renitec (Vianex, Greece)) [74].

Siddiqui F. A. et al. proposed the HPLC/UV method for the determination of metformin in the presence of ACE inhibitors (captopril, lisinopril, enalapril) in drugs and the use of developed method for the study of pharmacokinetics. Chromatography was performed using the chromatography column Purospher® StarRP-18 endcapped (250 mm x 4.6 mm id) and mobile phase–a mixture of methanol and water (50:50 v/v) with the addition of phosphate acid to produce pH 3.1, mobile phase rate–1.0 ml/min, and detection wavelength-208 nm. The method was linear in the range of concentrations of metformin 10-10000 ng/ml and 30-10000 ng/ml API from the ACE inhibitors group, correlation coefficient 0.9964. The developed method was successfully applied to study the pharmacokinetics of metformin, captopril, lisinopril and enalapril [75].

Among the disadvantages of spectrophotometry, low selectivity, low sensitivity and relatively high variability of the results of the analysis can be noted. The current review is created with an intended to focus on the advantage of HPLC for determination of ACE inhibitors. In the design of HPLC and UHPLC techniques, it is necessary to consider many factors that will influence the results of the analysis, namely the size of the chromatographic column, the type of the stationary phase and the size of its particles, the temperature of the column, the composition of the mobile phase and the rate of its feed, the method of detection, conditions of sample preparation of solutions and others. The choice of the column type is made taking into account the physical and chemical properties of the analyzed analytes. Development of chromatographoc conditions for HPLC and UHPLC under analytical method development presents on fig. 3.

Literature survey revealed that a number of methods have been reported for estimation of ACE inhibitors individually or in combination with other drugs. However, there is very few analytical methods reported for the simultaneous analysis of these drugs in a combined dosage formulation by HPLC. In additional, analysis of approaches to the development of the methods of analysis of ACE inhibitors in drugs and biological liquids has been shown that HPLC is the most suitable method for analyses ACE inhibitors in substances, drugs, biological liquids to performe routine analysis of medicines, pharmacokinetic (bioequivalence in vivo), dissolution test for final dosages forms (bioequivalence in vitro, biowaiver procedure).

CONCLUSION

In light of the benefits discussed in this review, we can conclude that analysts are constantly working on developing new methods of analysis of ACE inhibitors in drugs and biological liquids and on their optimization in order to save time and consumables, which also ensures the efficiency of the developed methodology. Among the disadvantages of spectrophotometry, low selectivity, low sensitivity and relatively high variability of the results of the analysis can be noted. Therefore, the advantage is provided by HPLC. Literature survey revealed that a number of methods have been reported for estimation of ACE inhibitors individually or in combination with other drugs. However, there is very few analytical methods reported for the simultaneous analysis of these drugs in a combined dosage formulation by HPLC. The way of solving the outlined problem lies in the plan of creating unified approaches to the development and validation of analytical methods of determination, taking into account their features, goals and objectives.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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