Eka Yuniara Yopa *et al*, Int. Journal of Pharmaceutical Sciences and Medicine (IJPSM),
Vol.8 Issue. 8, August- 2023, pg. 11-17

ISSN: 2519-9889
Impact Factor: 5.9

Overview of Determination of Imidapril Content in Pharmaceutical Preparations and Biological Matrices

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DOI: 10.47760/ijpsm.2023.v08i08.002

Abstract
Imidapril hydrochloride (IMD) is a kind of ACE inhibitor that has high activity in inhibiting angiotensin-converting enzymes. Imidapril is a new angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension. It is a prodrug-type ACE inhibitor, which means that it converts to its active form in the body. Imidapril has much higher activity compared to the ester form of imidapril. This review provides analytical methods for determining imidapril levels collected from the last twenty-one years of literature (2002–2023) through web sources such as Science Direct, Google Scholar, and PubMed, with the search keywords Analysis of Imidapril in Pharmaceutical Preparations and Biological Matrices. The methods reported are for the analysis of imidrapil in bulk, pharmaceutical preparations, and biological matrices. The analytical methods used include High-Performance Liquid Chromatography (HPLC) and UV-vis spectophotometry. Overall, the most widely used method is high-performance liquid chromatography because, not only for pharmaceutical preparations, this method can also be used for biological matrix samples that require a small amount of sample analysis.
***Keywords**:* imidapril, spectrophotometry, HPLC, pharmaceutical preparations, biological matrices.

1. Introduction
Imidapril hydrochloride (IMD) is a kind of ACE inhibitor that has high activity in inhibiting angiotensin-converting enzymes. Imidapril is a new angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension. It is a prodrug-type ACE inhibitor, which means that it converts to its active form in the body. Imidaprylate has much higher activity compared to the ester form of imidapril (Hegazy, 2014). ACE inhibitors have been shown to have cardiovascular protective effects beyond their antihypertensive properties, making them effective therapeutic agents for various cardiovascular diseases. Potential of ACE inhibitors in preventing left ventricular dysfunction after myocardial infarction (Hosoya, 2002)

Imidapril inhibits ACE by competitively binding to and inhibiting ACE, thereby blocking the conversion of angiotensin I to angiotensin II. This inhibition leads to vasodilation and decreased angiotensin II-induced aldosterone secretion by the adrenal cortex. The active metabolite of imidapril, imidapril, is responsible for its pharmacological effects. The treatment of hypertension has been shown to reduce the incidence of stroke and coronary heart disease, as well as the risk of major cardiovascular events, cardiovascular death, and total mortality. Imidapril is one of the drugs in the ACE inhibitor class. The chemical name of imidapril is (4S)-1-methyl-2-oxoimidazolidine-4-carboxylic acid, 1-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]ethyl ester. The chemical formula of imidapril is C20H28N2O5. The molecular weight of imidapril is 405.48 g/mol. The chemical structure of imidapril is shown in Figure 1. (Sasongko, 2002)

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Impact Factor: 5.9

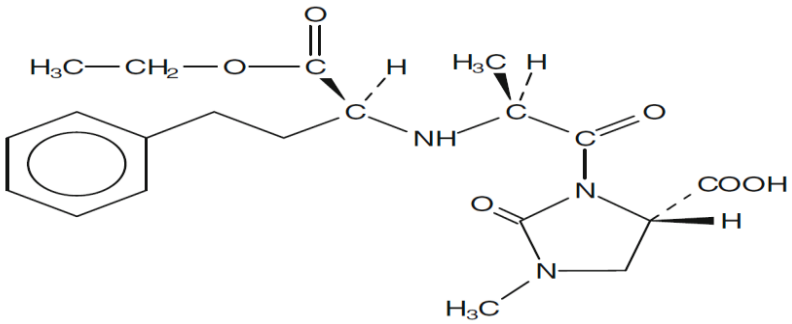

Figure 1. The Chemical Structure Of Imidapril

2. Data Collection Methods

In the preparation of this article, the technique used was a literature study by searching for sources or literature from international journals for the last 21 years (2002–2023). The keywords used for data search were imdapril, pharmaceutical preparation, biological matrix, HPLC, and spectophotometry. The main reference search for this review article was conducted through trusted sites such as Science Direct, Google Scholar, and PubMed.

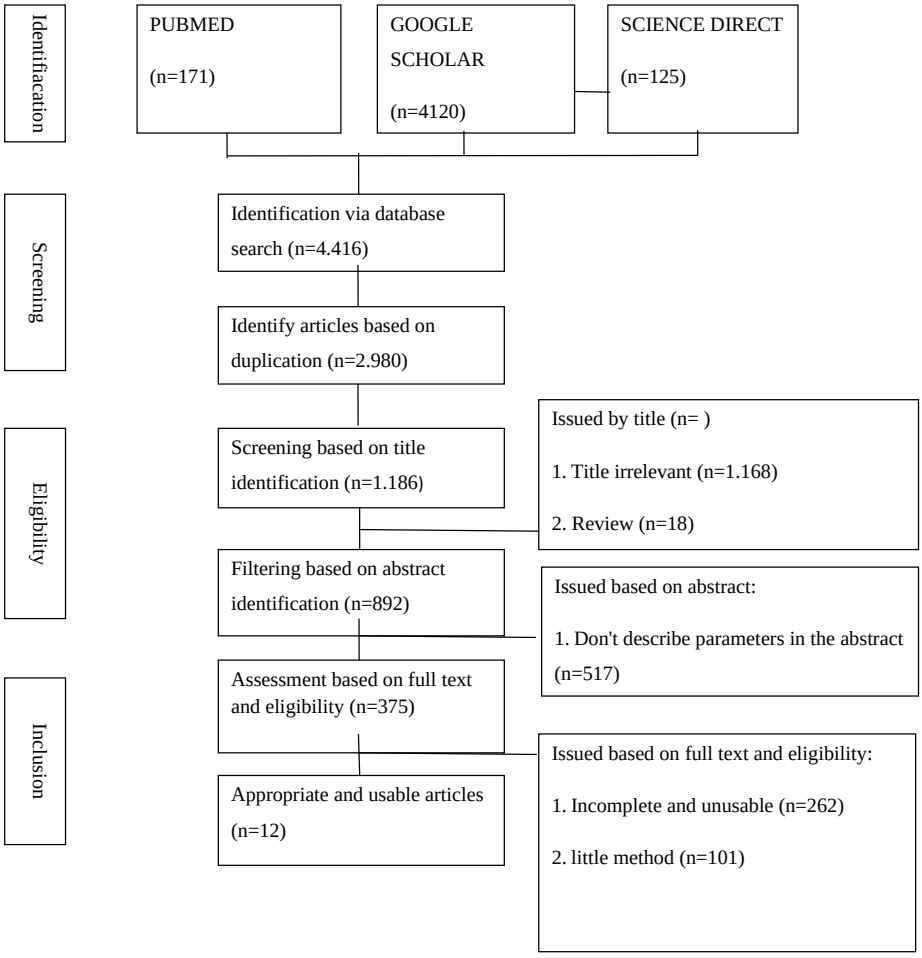

Figure 1. Method of Search Article Review

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3. Analytical methods on imidapril

3.1 High Performance Liquid Chromatography (HPLC)

The high-performance liquid chromatography method is widely used in quantitative analysis to determine the levels of imidapril in pharmaceutical preparations and biological matrices (Table 1).

Sample	Column	Mobile Phase	Detectors	Chromatograhic Conditions	Ref
Imidapril tablet	ACE Generix 5C8	Buffer:Asetonitril (60:40 v/v)	210 nm	Flow rate 0,7 mL/minute	(Abdulla,2016)
Imidapril tablet	Pheny (250x4.6mm)	Buffer:Asetonitril (75:25 v/v)	210 nm	Flow rate 1,0 mL/minute	(Dayyih, 2013)
Imidapril reagen 99,6%	Hypersil-gold C8(100.4,6mm)	Buffer:Asetonitril :Metanol (58:25:17 v/v)	215 nm	Flow rate 1,0 mL/minute	(Dawud, 2019)
Bulk imidapril tablet	Lichros-pher RP18(5nmx4mm)	Acetonitril:Metanol:Phosphate(60:10:30v/v)	218 nm	Flow rate 1-2 mL/minute	(Stanisz, 2011)
Imidapril tablet	(LiChrospherRP1 8.5µm (250 mm × 4 mm)	Methanol:Buffer phosphate (30:70 v/v)	216 nm	Flow rate 1.2 mL/minute	(Regulska, 2013)
Imidapril tablet	Lichrospher 100 RP-18 (10nm size 250x4mm)	Metanol:Air:Formaldehida (49:50:0,5 v/v)	216 nm	Flow rate 0,5 mL/minute	(Regulska, 2013)
Human plasma	XTerra MS C18 (3.5nm, 2.1x150mm)	Acetonitril:Formic acid (67:33 v/v)	API-ES (Atmospheric Pressure Ionization-Electrospray)	Flow rate 0,2 mL/minute	(Yu, 2004)

The HPLC test parameters for the chromatographic method were carefully optimized, including the choice of column, mobile phase conditions, and detection wavelength. An ACE Generix 5C8 column with a particle size of 5 m was shown to provide suitable resolution for IMD and its degradation products. At room temperature, separation was performed on the ACE Generix 5C8 column with a particle size of 5 m used in this study. The mobile phase used in this study consisted of a buffer solution containing 0.1 M potassium dihydrogen phosphate and 0.02 M tetra-n-butyl ammonium hydrogen sulfate, which was adjusted at pH 4.5 with 1 N phosphoric acid, and acetonitrile in a ratio of 60:40 (v/v) at pH 4.5 adjusted with 1 N phosphoric acid. The prepared mobile phase was filtered through a 0.45-mm sieve under vacuum, degassed, and sonicated for 5 minutes. The flow rate was kept at 0.7 mL per minute. The injected volume was 20 mL, and the eluent was monitored at 210 nm. (Abdulla,2016)

The chromatographic method was performed using a mixture of acetonitrile and phosphate buffer in a ratio of 25:75 v/v as the mobile phase. The detection of prescription drugs was carried out at a wavelength of 210 nm with a flow rate of 1.0 mL/min. In this study, equipment such as a constant solvent delivery system (P580), a 100-L fixed volume injector (Rheodyne 7125), a UV detector (UVD 340S), an autosampler (ASI-100) with a Chromeleon chromatography management system, a BDS-l Phenyl column (250 x 4.6 mm), and a STH 585 column oven were used. Materials used in this study included pharmaceutical-grade captopril, lisinopril, and imidapril provided by Hikma Pharmaceutics-Jordan. All chemicals and reagents used were HPLC- and

ISSN: 2519-9889
Impact Factor: 5.9

analytical-grade. Stock solutions of each drug (lisinopril, captopril, and imidapril) were prepared by dissolving 10.9 mg, 10 mg, and 10.9 mg, respectively, in 10 mL. (Dayyih, 2013)

Chromatographic system and conditions The prominent UFLC system consisted of a 20-AD UFLC pump, DGU-20A 3 degasser, SIL-20A auto-sampler, SPD-M20A photo diode array detector, and CBM-20A communication bus module (All from Shimadzu, Kyoto, Japan). Signals were captured using an LC-solution version 1.25 (2009–2010) workstation (Shimadzu, Japan) operating under the Micro-Soft Windows 7 (32-bit) platform. pH measurements were performed using a WTW 720 pH meter equipped with a coupled electrode (with an ATC probe) calibrated using standard buffer solutions of pH 4.0, 7.0, and 9.0. Chromatographic separations were performed on Hypersil-Gold C18 (100–4.6 mm, 3 m, Thermo Fisher Scientific, USA) columns at 25°C using an optimized mobile phase consisting of 58% buffer (5 mM KH2-PO4, containing 0.25 mL/L triethylamine) and 25% acetone. Mobile phase: 58% buffer (5 mM KH2PO4, containing 0.25 mL/L triethylamine), 25% acetonitrile, and 17% methanol (pH 2.8 ± 0.1). Mobile phase flow rate of 1.0 mL/min, injection volume of 10 l, and detection wavelength of 215 nm. (Dawud, 2019)

The HPLC method developed in this study showed good selectivity, sensitivity, and linearity for the determination of imidapril (IMD) in solid formulations. The method utilized a LiChrospher RP-18 column and a mobile phase consisting of acetonitrile, methanol, and phosphate buffer at pH 2.0. The HPLC method was considered suitable for qualitative analysis and indicative test of IMD stability in solid formulations. m Preparation of phosphate buffer at pH 2.0 The exact amount of 0.0681 g potassium dihydrogen phosphate (KH2PO4) was weighed and transferred into a 500 mL volumetric flask, 400 mL of water was added and the flask was shaken until dissolution of the salt. The column used LiChrospher Column RP-18 (5µm, 25 cm × 4 mm). IMD was isocratic separation with mobile phases of acetonitrile, methanol and phosphate-buffered saline at pH 2.0 (60:10:30 v/v/v). The injection volume was 20 mL. chromatogram recording took less than 10 minutes). A performance liquid chromatography method was developed for IMD. The selection was activity for IMD (tR = 6 min), its degradation products (tR = 4 min), and IS (tR = 8.5 min). Validation proved that the method was linear in the concentration range tested, discreet, and sensitive, and the flow rate was (1.0-1.2 mL/min). (Stanisz, 2011)

High Pressure Liquid Chromatography Method A liquid chromatograph consisting of a Rheodyne 7125, 100 µL fixed loop injector, UV-VIS SPO-6AV detector, LC-6A pump, and C-RGA chromatograph integrator was used at operating conditions. The detector used was UV-VIS SPO-6AV. The column used LiChrospher 100 RP-18 (5 µm size) 250×4 mm ID column and the mobile phase was a mixture of acetonitrile and phosphate buffer (0.001 mol L--1 adjusted to pH 2.0 with ortho-phosphoric acid) (30:70 v/v). Chromatographic separation was achieved isocratically at a flow rate of 1.2 mL/min. The detector wavelength was set at 216 nm and the injection volume was 25 µL. The mobile phase was filtered through a 0.22 µm filter and degassed with ultrasound before use. The technique used an internal standard (0.020% benzocaine methanol solution; IS). The optimum HPLC resolution of IMD and its degradation products was influenced by the ratio of organic components in the mobile phase and the mobile phase flow rate. (Regulska, 2013)

Electrospray Liquid Chromatography/Ionization- Mass Spectrometry System The LC-MS system used in this study consisted of a Waters Alliance HPLC equipped with a Waters PDA 996 Photodiode Array Detector paired with a Waters Micromass ZQ 2000 Single Quadruple Mass Detector. IMD degradation products were separated on a LiChrospher 100 RP-18 column (10 µm size, 250×4 mm) at 30°C. The mobile phase used was a mixture of methanol, water, and formaldehyde (49:50:0.5 v/v/v). The mobile phase was filtered through a 0.22 µm filter and removed by ultrasound before use. The flow rate of the mobile phase was set at 0.5 mL/min. (Regulska, 2013)

The LC-MS method used in this study employed an API-ES (Atmospheric Pressure Ionization-Electrospray) detector. LC-MS analysis was performed using an LC/MSD trap system, with an XTerra MS C18 column (3.5 µm, 2.1x150 mm, Waters, USA) used for HPLC separation. The mobile phase consisted of acetonitrile-0.1% formic acid in distilled water (67:33, v/v) and flowed at a rate of 0.2 mL/min. The LC/MSD trap system was operated in positive ion mode, with nitrogen used as the sheath gas and auxiliary gas. The temperature of the heated capillary was maintained at 350°C, and the ESI interface spray voltage was set at 4.5 kV. The molecular ions of imidapril and ramipril (internal standard) were selected at m/z 406 and m/z 417, respectively. HPLC separation was performed using an XTerra MS C18 column (3.5 µm, 2.1x150 mm, Waters, USA), at a column temperature of 40°C using acetonitrile-0.1% (v/v) formic acid in distilled water (67:33, v/v) as the mobile phase

ISSN: 2519-9889
Impact Factor: 5.9

at a rate of 0.2 ml/min. The LC/MSD trap system was operated in positive ion mode under the following conditions: nitrogen (>99%) was used as the sheath gas and auxiliary gas at 40 psi pressure. The temperature of the heated capillary was maintained at 350°C and the ESI interface spray voltage was set at 4.5 kV. Collision-induced dissociation (CID) was achieved using helium as the collision gas at a pressure >1.8 mTorr; the applied collision offset energy was set at 220 eV. Data were acquired with a scan rate of 5 s for all scans. Imidapril and ramipril molecular ions were selected at m/z 406 and m/z 417, respectively. (Yu,2004)

3.2 Spectrophotometry

Spectrophotometry methods have been used in imidapril analysis in bulk and pharmaceutical preparations (Table 2.)

Sample	Solvent	Wavele-ngth	Mode	Concentration ranges	Ref
Imidapril tablet	KMno4	610 nm	UV-VIS Spectrophotometers	6-16 mg/ml	(Ashour, 2010)
Bulk dan imidapril tablet	HCl 0,1 N	217 nm	UV-VIS Spectrophotmeters	2-20 g/ml	(Method, 2018)
Bulk dan imidapril tablet	Distilled water	293 nm	UV-VIS Spectrophotometers	2-20 g/ml	(Method, 2018)
Bulk dan imidapril tablet	NaOH 0,1N	236 nm	UV-VIS Spectrophotometers	2-20g/ml	(Method, 2018)
Imidapril tablet	Etil alkohol 96%	517 nm	UV-VIS Spectrophotometry	50 mg/ml	(Juszczak, 2019)

Imidapril is a potent and long-lasting, non-active sulfhydryl angiotensin-converting enzyme inhibitor. imidapril used tablets (Tanatril 10, Hikma Pharmaceutical, Jordan). The literature reveals several methods for its analysis, such as UV-vis spectroscopy. A Jasco V-530 UV-Vis dual beam spectrophotometer was used for all absorbance measurements with a matched 1 cm silica cell. All chemicals and reagents used were of analytical grade. Standard stocks for an IMP content of 200 g/mL were prepared separately in distilled water, and Potassium manganate (VII) (5x10-3M) and NaOH (1M) were prepared in distilled water. A commercial penny form of imidrapil (Tanatril 10, Hikma Pharmaceuticals, Jor-dan) obtained from the local market over the concentration range was pipetted and loaded into 10 ml calibration flasks. For each flask, the optimal volumes of 1M NaOH and 5 x 10-3M KMnO4 were consequently added regularly over the concentration range of 6–60 mg/mL. Absorbance measurements were measured at 610 nm against a reagent blank prepared in the same way without the drug. (Ashour,2010)

Ultraviolet spectroscopy is concerned with the study of the absorption of UV radiation that ranges from 200 to 400 nm, but compounds that do not absorb radiation in the UV region are also not studied in UV spectroscopy because only valence electrons absorb energy, so molecules undergo a transition from the ground state to the excited state. Dual-beam spectrophotometer technology analysis with UV Probe software version 2 was used to develop the analysis method. Imidapril hydrochloride was obtained from Aurabindo Pvt. Ltd., Hyderabad, India. Commercially available Tindamax 500 mg tablets, Humanity, India In this experiment, using 0.1 N hydrochloric solvent The dose of imidrapil used was 100 mg.The absorbance obtained in this solvent with

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a concentration range of 2-20 (µg/mL) was concluded that the drug Imidapril HCl showed maximum absorption (λmax) in 0.1 N Hydrochloric Solvent which is 236 nm. (Method, 2018)

In this experiment, distilled water solvent used from water purification unit. Standard working spectra were obtained by scanning from 200-400 nm against the solvent as a blank to establish the maximum absorption using a dual beam UV-Visible spectrophotometer. Still using the same sample as above, 100 mg imidrapril was used with a concentration range of 2-20 (µg/mL).It was concluded that the drug Imidapril HCl showed a maximum absorption (λmax) of 293 in distilled water solvent. (Method, 2018)

In this experiment, we used the same method and the same sample, but the last solvent was 0.1 N sodium hydroxide. The absorbance obtained in 0.1 N NaOH solvent, imidrapil used 100 mg. The absorbance obtained in this solvent with a concentration range of 2-20 (µg/mL) and concluded that the drug Imidapril HCl showed maximum absorption (λmax) in 0.1 N sodium hydroxide solution which is 236 nm. (Method, 2018)

Chemical structure of DPPH and localization of unpaired electrons DPPH was used as a solution of ethyl alcohol. DPPH powder (394.32 g/mol) was dissolved at 19.71 mg in 100 cm3 ethyl alcohol, and the maximum absorbance was 517 nm. The solution obtained was diluted so that the absorbance was at a wavelength of 517 nm. DPPH spectra in ethyl alcohol are presented in Characterization of ACE The samples tested were: imidapril (supplied by Jelfa Pharmaceuticals), lisinopril (supplied by FarmSpania), perindopril (supplied by Bachem), and quinapril (supplied by Biofarm). In the experiment, 50 mg of ACE-I was mixed with 1.5 mL of 0.5 mm DPPH in an ethyl alcohol solution. (Juszczak, 2019)

CONCLUSION

Hypertension is one of the most common cardiovascular disorders. It is considered a social disease because of its high incidence, contributing to the development of arteriosclerosis and its clinical forms, including coronary disease, cardiac infarction, and cerebral stroke. Imidapril is indicated for the essential treatment of hypertension as well as for the treatment of parenchymal hypertensive kidneys and diabetic nephropathy. For the method that I summarize, there are two methods, namely the method using HPLC and spectophotometry. In the HPLC method, many studies use various types of columns, such as ACE Generix 5C8 (15 cm, 4.6 mm id, practical size 5 mm), Rheodyne 7125, Hypersil-Gold C18, and others in the widely used solvent method of acetonitrile, water, methanol, and buffer. In the summary results, the wavelength in this method is from 210 to 280 nm, and in the UV-VIS spectrophotometry method, there are those that use single and double beams with various solvents such as KMnO4, 0.1 HCl, 0.1N NaOH, and 96% ethanol. In this method, the highest wavelength is 610 nm with KMnO4 solvent.

SUGGESTION

In carrying out the task of reviewing the journal entitled Training on imidapril levels in pharmaceutical preparations and biological matrices, There are two methods that I used, namely HPLC (High-Performance Liquid Chromatography) and UV-Vis spectrophotometry. The HPLC method does cost more, but the results obtained are more accurate and don't take a long time. Spectrophotometry does require a small fee. but a lot of time is wasted because they have to do it to get the wavelength of the drug imidapril. In carrying out this journal review assignment, it is hoped that there will be more books and journals related to imidrapil so that students have no difficulty finding literature or reference sources as reading material, and more research is being done for research on imidrapil because, when I was doing this assignment, there were still many methods that had not been tested on the drug imidapril.

References

[1]. Abdulla, SA, Frag, EY, & Ahmed, HE (2016). Kinetic study of the alkaline degradation of imidapril hydrochloride using a validated stability indicating HPLC method. *RSC Advances* , *6* (73), 69239–69250. https://doi.org/10.1039/c6ra11953k

[2]. Ashour, S., Bahbouh, M., & Khateeb, M. (2010). Kinetic spectrophotometric determination of fluvastatin in pharmaceutical preparations. *International Journal of Biomedical Science* , *6* (1), 19–26.

[3]. Dawud, ER, & Shakya, AK (2019). HPLC-PDA analysis of ACE-inhibitors, hydrochlorothiazide and indapamide utilizing design of experiments. *Arabian Journal of Chemistry* , *12* (5), 718–728. https://doi.org/10.1016/j.arabjc.2014.10.052

ISSN: 2519-9889
Impact Factor: 5.9

[4]. Dayyih, WA, Alsaid, S., Hamad, M., Al Akayleh, F., & Mallah, E. (2013). Development and validation of a reverse phase HPLC method for simultaneous estimation of some prills in drug forms. *International Journal of Pharmacy and Pharmaceutical Sciences* , *5* (1), 203–213.

[5]. Hegazy, MAM, Eissa, MS, Abd El-Sattar, OI, & Abd El-Kawy, MM (2014). Determination of a novel ACE inhibitor in the presence of alkaline and oxidative degradation products using smart spectrophotometric and chemometric methods. *Journal of Pharmaceutical Analysis* , *4* (2), 132–143. https://doi.org/10.1016/j.jpha.2013.09.006

[6]. Hosoya, K., & Ishimitsu, T. (2002). Protection of the cardiovascular system by imidapril, a versatile angiotensin-converting enzyme inhibitor. *Cardiovascular Drug Reviews* , *20* (2), 93–110. https://doi.org/10.1111/j.1527-3466.2002.tb00185.x

[7]. Juszczak, A., Ramos, P., Szczolko, W., Pilawa, B., & Stanisz, BJ (2019). Can angiotensin-converting enzyme inhibitors interfere with the free radicals? Measurement of antioxidant capacity using DPPH radical reduction examined by UV-Vis method. *Acta Poloniae Pharmaceutica - Drug Research* , *76* (2), 233–239. https://doi.org/10.32383/appdr/95136

[8]. Method, S., & Different, IN (2018). *ESTIMATION OF IMIDAPRIL HYDROCHLORIDE BY UV - VISIBLE SPECTROSCOPIC METHOD IN DIFFERENT SOLVENTS* . *7* (10), 572–582. https://doi.org/10.20959/wjpr201810-12269

[9]. Regulska, K., & Stanisz, B. (2013). Kinetics and mechanism of solid state imidapril hydrochloride degradation and its degradation impurities identification. *Open Chemistry* , *11* (5), 754-762.

[10]. Sasongko, L., Harahap, Y., Prasaja, B., Lusthom, W., Setiawan, EC, Meliala, RS, & Lipin. (2010). Comparative bioavailability of two irbesartan/hydrochlorothiazide tablet formulations in Indonesian healthy subjects. *Arzneimittel-Forschung/Drug Research* , *60* (12), 749–753. https://doi.org/10.1055/s-0031-1296350

[11]. Stanisz, B., Regulska, K., & Kolasa, K. (2011). UV derivative spectrophotometric and RP-HPLC methods for the determination of imidapril hydrochloride in tablets and for its stability assessment in solid state. *Acta Poloniae Pharmaceutica - Drug Research* , *68* (5), 645–651.

[12]. Yu, JH, Kim, HJ, Lee, S., Hwang, SJ, Kim, W., & Moon, CJ (2004). LC-MS determination and bioavailability study of loperamide hydrochloride after oral administration of loperamide capsule in human volunteers. *Journal of Pharmaceutical and Biomedical Analysis* , *36* (2), 421–427. https://doi.org/10.1016/j.jpba.2004.06.020

