Original scientific papers UDK 615.225.2
doi: 10.7251/COMEN1702164K

STRESS DEGRADATION OF LISINOPRIL DIHYDRATE IN DIFFERENT AQUEOUS MEDIA

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Abstract: Lisinopril is an antihypertensive drug from the ACE inhibitor group. It is often used in practice and, in oral administration is characterized by very low percentage of resorption (~25%). Therefore, it is important to ensure the stability of this drug, since any degradation leads to a decrease in the percentage of resorption and an increased risk of subdosage of patients. In accordance with modern trends of pharmaceutical analysis, the chemical stability of lisinopril under the influence of various aqueous media was tested: distilled water, 0.1M HCl, 0.1M and 0.01M NaOH and 3% hydrogen peroxide solution. In order to clearly define the effect of elevated temperature on the stability of this drug, tests were carried out at 25 °C and 50 °C. High-pressure liquid chromatography was used as the method for stability testing. The obtained results clearly define that lisinopril is the most sensitive to hydrolysis in the base environment, where at 25 °C, in the first minute, it degrades ~100%. In this paper, kinetic parameters (degradation constant rate, half-life of degradation, order kinetics, and activation energy) were also determined, which enabled clear definition of the stability and identification of degradation products of lisinopril under the influence of various stress agents. In the degradation of lisinopril in neutral and acidic medium, impurity D is identified as the main degradation product.

Keywords: lisinopril dihydrate, stress studies, degradation products, kinetic parameters of degradation

1. INTRODUCTION

Stress studies or forced degradation studies are an important part of the drug development process. These studies are conducted in order to develop and validate the Stability Indicating Method (SIM), then to detect pathways of drug degradation and define their stability in various pharmaceutical dosage forms, as well as identify potential degradation products. In this way, useful information for defining the conditions of storage of the drug but also the production method and compatibility with certain excipients is obtained [1−3].

Forced degradation studies are conducted on pure active pharmaceutical ingredient (standard substance) and pharmaceutical dosage forms: in solid form, solutions or suspensions (due to possible interaction with some of the excipients). Thus, the origin of any degradation product can be determined, and whether the impurities resulting from the instability of the pharmaceutically active ingredient or interaction with excipients are formed. These studies are conducted according to the ICH Guidelines Q1A (R2) which proposes the following stress test conditions: elevated temperature (50°C or 60°C), relative humidity 75% or more, hydrolysis in a wide range of pH values, oxidation and photolysis [4]. Besides the ICH guidelines, there are also additional recommendations describing the conditions for conducting stress studies [5−8].

The experimental conditions for carrying out the forced degradation studies must include testing the drug's sensitivity to hydrolysis, oxidation, thermal degradation, moisture and light. Forced degradation studies are performed on a single product series, and experimental conditions should be much more extreme than in accelerated stability studies. The precise conditions for carrying out the forced degradation studies are chosen based on the physicochemical characteristics of the drug [8], ie. the guideline does not define the process of hydrolysis, photolysis or oxidation. The hydrolytic degradation of the test substance in the acid or base medium can be studied by the action of 0.1 mol L^{-1} HCl/NaOH, for example 8 hours or longer. The oxidative degradation test is performed by dissolving the drug in hydrogen peroxide or by diluting the solution of the active pharmaceutical ingredient

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with a hydrogen peroxide concentration of 3% to 30%.

In stress studies, if moderate degradation is observed, testing can be stopped at that moment by the neutralization process. However, if there is no degradation, the test substance is exposed to the action of a stronger acid/base over a longer period of time or an elevated temperature in combination with a particular stress agent. In contrast, in the case of complete decomposition of the test substance in the initial conditions, the acidity/alkalinity of the medium may be reduced together with the reduction in the reaction temperature. Also, degradation in a neutral environment may be initiated by dissolving the drug in water, and the test may last, for example, 12 hours or, if not degrading, longer. If the drug is completely decomposed, the duration of the test is shortened, and the temperature can be reduced.

What necessarily precedes the experiment is an analysis of the chemical structure of the test substance or functional groups within it. Thus, esters, amides or lactones can be expected to be easily subjected to hydrolysis. Functional groups containing a heteroatom (nitrogen, sulfur), aldehydes and ketones are sensitive to oxidation. Alkene, aromatic and heterocyclic derivatives are photosensitive [1]. The set experimental conditions must be such that the pharmaceutically active ingredient is degraded from 5% to 20%, which is considered to be significant and representative degradation [1, 3]. Degradation of over 20% is useless since this percentage of degradation is sufficient to reliably and completely define the degradation profile expected under the recommended conditions of storage of the tested pharmaceutically active ingredient or pharmaceutical form containing the test substance. On the other hand, degradation below 5% is not taken into consideration because very small quantities of degradation products are produced in stress conditions, and it is considered that under the recommended storage conditions they would not have been generated. If the substance does not break down after the predicted stress-strain period, it is considered to be stable according to the stress test agent.

After stress studies, kinetic studies to calculate the corresponding degradation constant rates (k) and half-lives of degradation ($t_{1/2}$) in the acidic, basic, neutral environment and after exposure to the oxidizing agent were carried out. These studies have enabled the definition of degradation mechanisms and a better insight into the stability of the test compound.

By performing the forced degradation studies at elevated temperatures (at two or more temperature points), the best possible insight into the stability of the test compounds can be obtained, based on the activation energy (E*a*), which is a prerequisite for the initiation of the degradation reaction. Activation energy is the energy needed to bring molecules to interact with each other [9, 10]. In the chemical kinetics, *Ea* is the height of the potential barrier that separates the products from the reactants. The higher *Ea*, the smaller number of molecules can cross the top of the energy barrier and the reaction is slower. *Ea* is a very important indication of the stability of the product, which can, with great accuracy, determine which compound is more stable, which drug formulation is more stable, and whether the analytes tested are more stable individually or mixed with other compounds [9].

This paper describes the performance of a forced degradation study on lisinopril dihydrate (LSDH) (Figure 1) and validated HPLC method was used as a method for monitoring degradation [11].

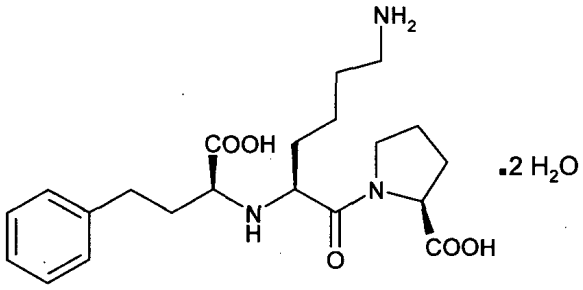

Figure 1. Chemical structure of lisinopril dihydrate

The aim of this study was to conduct a forced degradation study on LSDH in order to test its stability after exposure to various stress agents on two different temperatures. Using the validated HPLC method, a change in concentration at defined time intervals was followed [11]. The aim also was to identify possible degradation product, define the degradation profile of LSDH to carry out kinetic studies, ie. determine the degradation constant rate, the half-life of degradation, and then determine *Ea*, all with the aim of better insight into the stability of LSDH.

Based on the literature review [12-17], it can be seen that until now similar analyses with LSDH have not been performed. This is the first time that this type of experiment was carried out at two temperatures (25°C and 50°C) under the influence of various stress agents, where the stability and degradation profile of the test compound was determined based on kinetic parameters and *Ea*.

2. METHODS AND MATERIALS

Chromatographic system. The experiments were performed on chromatographic system Agilent

Technologies HP 1200, which consists of the HP 1200 pump, HP 1200 UV/VIS detector and Chem-Station Software, Excel 2013 and Windows XP for collection and data analysis.

Other equipment and accessories. pH meter Ciberscan pH 11 (Eutech, Malaysia), a magnetic stirrer (Falco, Italy), a system for filtering water (Whatman, Germany), ultrasonic bath (Bandelin, Sonorex digitec, Germany), Incubator (Binder, Germany). Method: High-performance liquid chromatography (HPLC), previously developed and validated.

Reagents. Acetonitrile HPLC grade (Fisher Scientific, England), Methanol HPLC grade (Fisher Scientific, England), Phosphoric acid 85% (Lachner, Czech Republic). HPLC water quality and distilled water obtained by system Barnstead.

Standards. Lisinopril dihydrate working standards, Lisinopril(R,S,S)-diketopiperazine (impurity D of lisinoprildi dihydrate) reference standard. All standars donated from Hemofarm Banja Luka.

Solutions. Stock solutions of lisinopril dihydrate (c=1 mg mL^{-1}) were prepared in mobile phase. Working solutions of lisinopril dihydrate (c=100 μg mL^{-1}) were prepared by dissolving in different stress agents: distilled water, 0.1M HCl, 0.1M NaOH, 0.01M NaOH or 3% hydrogen peroxide. Basic and working solutions of impurity D of lisinopril dihydrate (c=100 μg mL^{-1} and 10 μg mL^{-1}) were prepared in mobile phase.

Chromatographic conditions. Column – Hypersi ODS C18 (250 mm x 4.6 mm, 5 μm particle size), the mobile phase is a mixture of methanol–water–acetonitrile (pH 3.0 adjusted with concentrated phosphoric acid) at a ratio of 80:17.5:2.5 V/V/V. The flow rate was 1 mL min^{-1} and column temperature was 25°C. UV detection was carried out at 225 nm and the injection volume was 20 μL.

3. RESULTS AND DISCUSSION

By analyzing the chemical structure, it can be seen that LSDH has a heteroatom (nitrogen) in its structure, so it can be assumed to be subject to the oxidation process. Due to the presence of amide group, it is also subjected to the hydrolysis process. Forced degradation of LSDH was performed with the aim of testing its stability and identifying degradation products under the influence of different aqueous media and elevated temperatures. The analyses were done at two temperatures: at room temperature (25°C) and 50°C, in order to define the influence of elevated temperature on the stability study, ie. on the process of degradation of LSDH. The behavior of LSDH and its stability at the specified temperatures and in different aqueous media cannot be accurately predicted. The reason for this is that water-rich mediums with a wide range of pH values are used as stress agents: in 0.1 M HCl pH ~ 2; in 0.1M NaOH pH ~ 13, 0.01M NaOH pH ~ 10; distilled water pH ~ 6 and hydrogen peroxide pH ~ 7. In such analyzes, it is necessary to know p*Ka* and log *P* values in order to define the pH at which LSDH is in ionic and/or molecular form and to define the degree of lipophilicity of the test compound. For this determination, Marvin Sketch program [18] was used (Table 1). The European Pharmacopoeia from 2013 (Ph.Eur. 8.0) in the LSDH monograph prescribes six impurities marked as impurities A, B, C, D, E, and F [19], and therefore it was determined the p*Ka* and log *P* values of LSDH and all listed impurities (Table 1).

Table 1. Display the values for the partition coefficient and the constant of dissociation

Substance	**log *P***	**p*Ka* 1**	**p*Ka* 2**
Lisinopril	1.61	3.17; 3.85	8.01; 10.21
Impurity A	1.52	2.55	9.52
Impurity B	1.67	-2.14	/
Impurity C	1.44	3.79	10.21
Impurity D	1.44	3.79	10.21
Impurity E	1.61	3.17; 3.85	8.01; 10.21
Impurity F	2.07	3.22; 3.88	7.99; 10.21

log *P* - partition coefficient; p*Ka* - constant of dissociation

From the obtained log *P* values (Table 1), it can be concluded that the most lipophilic compound is impurity F (2.07) and that if it occurs in these stress studies, it will show the longest retention in the RP-HPLC column. The lowest log *P* value have impurities C and D (1.44), which means that these compounds are of the lowest degree of lipophilicity and the first will be eluted from the RP-HPLC

column. The order of elution can be predicted in this way, which is very important for easier determination and identification of the resulting degradation product. If a formed degradation product is eluted before LSDH, it is likely that it is a matter of impurity A, C, and/or D. However, if it is eluted after LSDH, it is probably a matter of impurity E, B and/or F. On the basis of the estimate obtained for p*Ka* values, it can be seen that all compounds (except impurity B) have two or more p*Ka* values. This means that LSDH and its principles will be at least 50% in ionic and ~ 50% in molecular form at most pH values. This phenomenon in the use of the HPLC method is not good, as chromatograms with stretched, sloping and asymmetric peaks will be obtained, and this will not produce reliable and accurate data. Based on the presented, it is very difficult to find out which is the ideal pH value that will ensure that LSDH and its impurities are presented only in molecular or ionic form. By reviewing the literature [11, 13-15, 17] various SIM methods with a range of pH values from 2.2 to 7.1 are developed, which is still quite a wide range. By using the estimate obtained in the Marvin Sketch program, LSDH and most impurities at a pH of 3.0 – 4.0 are ~ 100% in molecular form, and this pH value of 3.0 will be used to prepare the mobile phase in a chromatographic analysis of this stress study [11].

Under defined chromatographic conditions [11], the calibration curve for LSDH was made and obtained correlation coefficient was r = 0.9999 (Figure 2). The basic and working solutions of LSDH were dissolved in the mobile phase and served as reference solutions for this type of analysis. The obtained calibration curve was used to monitor the decrease in the concentration of LSDH, due to its degradation, and under the influence of various water stress agents at room and elevated temperature.

The degree of degradation of LSDH, under the influence of all stress agents singularly, was monitored at precisely defined time intervals: in 0 minutes, then after 2, 24, 48 and 72 hours at two temperatures (25°C and 50°C). The obtained results are shown in Table 2.

Degradation in the neutral environment (water) – LSDH proved to be quite stable under the influence of this stress agent. From Table 2, it can be seen that there is no significant degradation (for a total of 72h it degraded ~ 2%). The same data was obtained at an elevated temperature which leads to the conclusion that LSDH is quite stable under distilled water, as a neutral medium, on both temperatures.

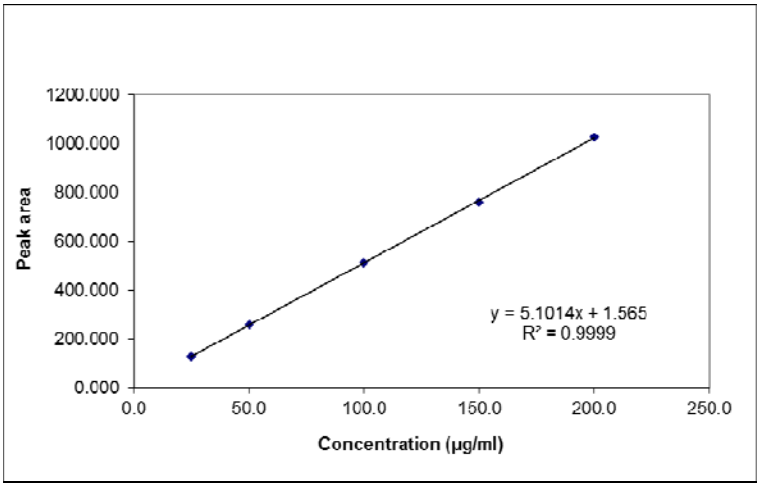

Figure 2. Calibration curve of LSDH

Table 2. Comparative presentation of LSDH degradation degree after stress study at defined time intervals at two temperatures

Degradation time [h]		**0**	**2**	**24**	**48**	**72**
Degradation degree [%]	**H_2O:**					
	25°C	0	0.1	0.3	0.8	1.7
	50°C	0	0	0.3	0.8	1.7
	0.1M HCl:					
	25°C	0	0.4	1.1	1.8	3.0
	50°C	0	0	1.0	1.9	4.6
	0.01M NaOH:					
	25°C	35.2	38.3	44.6	46.7	51.3
	50°C	35.2	78.3	88.3	100	-

Degradation time [h]		0	2	24	48	72
	3% H_2O_2:					
	25°C	7.8	16.6	27.6	98.6	100
	50°C	7.8	100	-	-	-
	mobile phase:					
	25°C	0	8.4	10.1	10.8	10.8
	50°C	0	10.4	12.5	13.0	22.0

The reaction order is experimental value and depends on the reaction mechanism. In different media/stress agents and at different temperatures, different mechanisms of the degradation reaction are obtained. In most pharmaceutical substances, such reactions are carried out by the reaction of zero, first, or pseudo-first order kinetics. However, there is also degradation of the drug substances that occur through the reaction of the second order kinetics, where the process of degradation is a very complex mechanism [9].

From the obtained kinetic parameters (Table 3), it was concluded that the degradation in water takes place by the reaction of second order kinetics, which means that the rate of formation of the degradation product is a very complex mechanism. The half-life of LSDH degradation is 195 hours, which means that the hydrolytic degradation of this compound in water nevertheless occurs, pretty fast.

Degradation in the acidic environment (0.1M HCl) – LSDH proved to be stable on acid hydrolysis. From the obtained data, at both temperatures (Table 2), LSDH degradation for a total of 72 hours was < 5% (at both analyzed temperatures). From the obtained kinetic parameters (Table 3), a better insight into the degradation mechanism can be obtained: the degradation reaction on 25°C is carried out by reaction of the zero order kinetics (the rate of formation of the degradation product is constant value), while at 50°C it is carried out by the reaction of the second order kinetics, which means that the elevated temperature caused the formation of a very complex degradation mechanism. The degradation mechanism itself changes at 25°C, which causes a slower type of degradation. This is confirmed by the $t_{1/2}$ values where it can be seen that degradation of acid hydrolysis takes place 2 times slower at 50°C than at 25°C. The value E*a* (Table 3) in this environment indicates that this is a very stable system and that it is necessary to bring great energy to this system in order to overcome the energy barrier and start the process of degradation product formation.

Table 3. Results of activation energy and kinetic parameters of lisinopril at two temperatures of 25°C and 50°C

Media type		H_2O	0,1M HCl	0,01M NaOH	3% H_2O_2	mobile phase
E*a*		63.13 kJ/mol	98.95 kJ/mol	120.87 kJ/mol	23.26 kJ/mol	32.32 kJ/mol
Kinetic parameters						
k	25 °C	0.0022 $mM^{-1}h^{-1}$	0.0002 $mM\,h^{-1}$	0.0241 $mM^{-1}h^{-1}$	0.0842 h^{-1}	0.0051 $mM^{-1}h^{-1}$
	50 °C	0.0022 $mM^{-1}h^{-1}$	0.0044 $mM^{-1}h^{-1}$	1.0514 $mM^{-1}h^{-1}$	-	0.0140 $mM^{-1}h^{-1}$
n	25 °C	Second order kinetics	Zero order kinetics	Second order kinetics	First order kinetics	Second order kinetics
	50 °C	Second order kinetics	Second order kinetics	Second order kinetics	-	Second order kinetics
$t_{1/2}$	25 °C	195.1 h	580.0 h	282.3 h	8.2 h	830.8 h
	50 °C	195.1 h	979.6 h	6.5 h	-	302.7 h

E*a* - activation energy; k – degradation constant rate; n – order kinetics; $t_{1/2}$ – half-life of degradation.

Degradation in the base environment (0.1M and 0.01M NaOH) – LSDH showed instantaneous degradation with 0.1M NaOH in 0 minutes at 25°C, which confirms the high sensitivity of this compound to base hydrolysis. The tests were continued using 0.01M NaOH and the obtained results are shown in Table 2 and Table 3. From the obtained data showing the degree of degradation at defined time intervals, it can be concluded that even under the action of milder base (0.01M NaOH) degradation occurs very quickly. At 25°C, 35.2% LSDH degraded in 0 minutes, and for 72h ~ 52% overall. This degradation reaction was carried out by reaction of the second order kinetics (Table 3). Elevated temperature significantly accelerated the degradation reaction, LSDH almost completely degraded within

24 hours (Table 2). This can also be seen from the obtained values for $t_{1/2}$ (Table 3). The degradation reaction at 50°C is a second order kinetics reaction, which means that base hydrolytic degradation represents a very complex degradation mechanism. From the obtained *Ea* values, it was concluded that in this system the largest amount of energy to start the degradation process must be brought, but once the degradation process starts, it occurs very quickly. On the obtained chromatograms (Figure 3), the resulting degradation product was identified as impurity D. This is the primary degradation product resulting from intramolecular condensation of LSDH, as confirmed by Beasley et al [15].

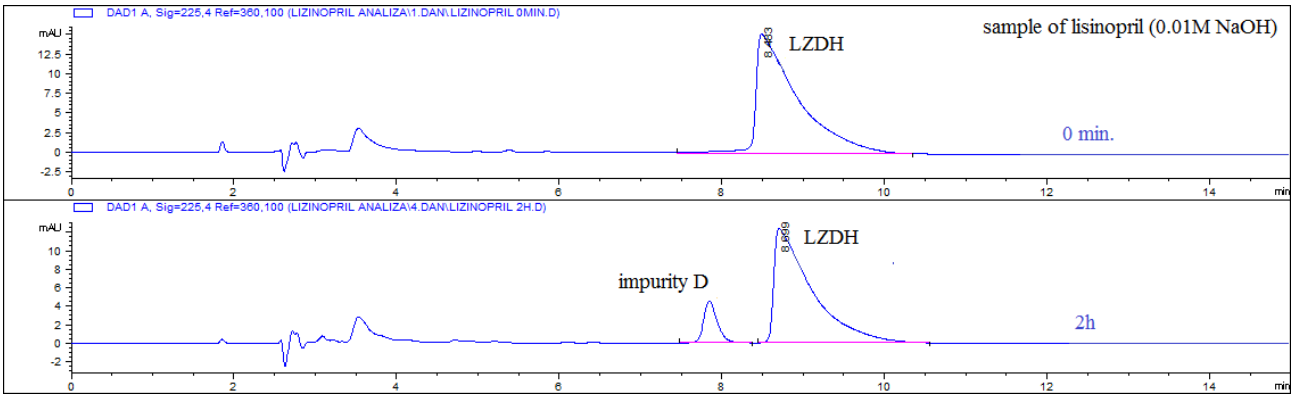

Figure 3. Degradation of lisinopril in 0.01M NaOH and formation of impurity D

Degradation in medium with an oxidizing agent (3% hydrogen peroxide) – LSDH has been shown to be very sensitive to this stress agent, which was also anticipated by a preliminary analysis of its chemical structure. At 25°C, in the 0th minute, ~ 8% degraded, and for a total of 72h 100% (Table 2). The degradation mechanism under the influence of this stress agent occurred very quickly, which can be seen from the obtained value for $t_{1/2}$ = 8.2h (Table 2). The degradation mechanism is carried out by the reaction of the first order kinetics, which means that the reaction of the degradation is directly proportional to the concentration of the reactant. Degradation at an elevated temperature significantly accelerated the degradation reaction – within 2h LSDH was 100% degraded. The *Ea* value was calculated to be 23.26 kJ mol^{-1}, which shows that LSDH is the most unstable to the presence of an oxidizing agent and that very little energy brought to this system is required to start the process of its degradation.

At the end of these experiments, the stability of LSDH in the mobile phase (pH 3.0) was tested at both temperatures in order to obtain LSDH behavior data on this pH too. LSDH proved to be stable at both tested temperatures in the first 2 hours and there was no significant degradation (< 5%). After 72h at 25°C, less than 10% degraded. The elevated temperature accelerated the process of degradation of LSDH in this environment. After 72h, the degradation rate was 22%, which can also be seen from the obtained values for $t_{1/2}$ (Table 3), which show that degradation reaction is significantly faster at elevated temperature. The degradation of LSDH at both temperatures takes place in the second order kinetics reaction. In this degradation, a degradation product is identified as an impurity D (Figure 4).

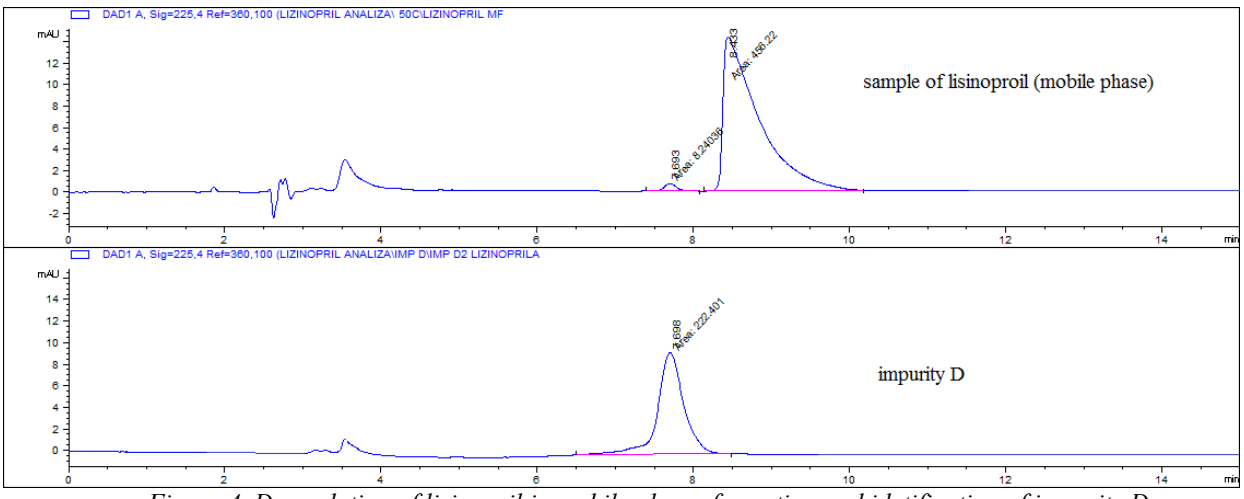

Figure 4. Degradation of lisinopril in mobile phase, formation and idetification of impurity D

4. CONCLUSION

Compounds, such as LSDH, with the very small percent of resorption, used in the treatment of cardiovascular diseases, must be studied in detail in terms of their stability. For these compounds, it is necessary to clearly define what the critical factors for their stability are and to prescribe clear conditions for the preservation of this medicine. It is of great importance to provide an adequate pharmaceutical form of the drug, but also the correct use of the drug, in order to ensure the best possible resorption and to achieve a therapeutically effective dose. This paper clearly defines critical stability factors for LSDH. It is a drug sensitive to the process of oxidative degradation and basic hydrolysis. The elevated temperature in most experiments accelerates the process of its degradation. Under the influence of all stress agents, the process of degradation of LSDH takes place, it only differs in each other from the degradation rate, which again depends on the type of its mechanism. In order to define more clearly the degradation mechanisms, kinetic parameters are defined, as well as *Ea*. It was concluded that the major part of LSDH degradation mechanism is the reaction of the second order, which indicates that all these degradations are very complex and depend on several factors at the same time. The primary degradation product of LSDH was identified as impurity D. After these analyses, it is recommended that all LSDH-containing preparations must be protected from oxidation, hydrolysis and must not be exposed to elevated temperature. It is also recommended to avoid, in the therapeutic use of LSDH *per os*, 1h before and after use, food that can lead to a change in pH value and affect the percent of resorption of this drug, and consequently to achieve an effective dose of LSDH. Special attention should be given to the stability of the LSDH solution for parenteral administration.

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СТРЕС ДЕГРАДАЦИЈА ЛИЗИНОПРИЛ-ДИХИДРАТА У РАЗЛИЧИТИМ ВОДЕНИМ МЕДИЈУМИМА

Сажетак: Лизиноприл је антихипертензивни лијек из групе АЦЕ инхибитора. У пракси се често користи и код оралне примјене одликује се веома малим процентом ресорпције (~25%). Због тога је важно обезбиједити стабилност овог лијека, јер свака његова деградација доводи до смањења процента ресорпције и повећаног ризика од субдозираности пацијената. У складу са савременим трендовима фармацеутске анализе, испитана је хемијска стабилност лизиноприла под утицајем различитих водених медијума: дестилована вода, 0,1M HCl, 0,1M и 0,01M NaOH и 3% раствор водоник-пероксида. Испитивања су спроведена на 25 °C и 50 °C, како би се јасно дефинисао и утицај повишене температуре на стабилност овог лијека. Као метода праћења стабилности лизиноприл-дихидрата коришћена је течна хроматографија под високим притиском. Добијени резултати јасно дефинишу да је лизиноприл најосјетљивији на хидролизу у базној средини, гдје се на 25 °C, у првом минуту, деградира ~100%. У овом раду одређени су и кинетички параметри (константа брзине деградације, полувријеме деградације, ред реакције, али и енергија активације) који су омогућили јасно дефинисање стабилности лизиноприла и идентификацију деградационих производа насталих под утицајем различитих стрес агенаса. При деградацији лизиноприла у неутралном и киселом медијуму идентификована је нечистоћа Д као главни деградациони производ.

Кључне ријечи: лизиноприл-дихидрат, стрес студије, продукти деградације, кинетички параметри деградације.