AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

The Degradations Routes of Ramipril and Its Products

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ABSTRACT

Ramipril is a prodrug of the active metabolite ramiprilat, it inhibits angiotensin-converting enzyme and consequent raise in blood pressure. Its pharmacologic effect aids the treatment of hypertension, congestive heart failure and reduces mortality in post myocardial infarction patients. As for other drugs, Ramipril might degrade upon storage and compromise the quality, efficacy and safety of the product. In order to avoid deterioration, it is important to characterize the degradation products and source of stress (temperature, water content, oxidizers, etc). This review aims to summarize the data concerning the subject and serve as a guide for further studies.

Keywords: Ramipril, Impurities, Stress testing, Degradation Pathways

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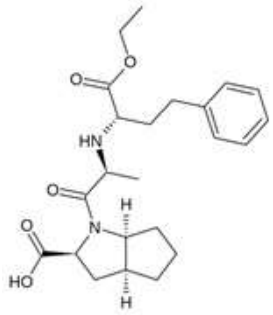
Received 27January 2015, Accepted 1 March 2015

Please cite this article as: Aschar GD., The Degradations Routes of Ramipril and Its Products. American Journal of PharmTech Research 2015.

INTRODUCTION

Ramipril is a pro drug and its active metabolite is ramiprilat. The mechanism of antihypertensive action seems to be due to competitive inhibition of the angiotensin converting enzyme (ACE) which causes a reduction in the conversion of angiotensin I to angiotensin II ratio, which is a potent vasoconstrictor. The decrease in concentration of angiotensin II results in secondary increase in plasma renin activity, due to the elimination of the negative feedback of renin release and direct reduced aldosterone secretion.[1]



Chemical Structure of Ramipril

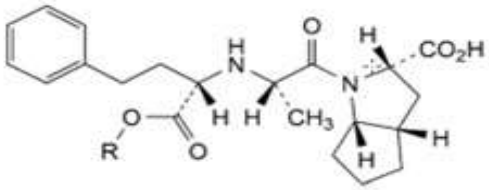
Although it is one of the most widely used ACE inhibitors, the drug has considerable degree of instability, and the degradation shown by two major pathways: hydrolysis, forming ramipril-diacid and cyclization by internal nucleophilic attack leading to the formation of diketopiperazine (DKP)[2]. Currently have been much explored the issue of degradation products. It is important to demonstrate the quality of the pharmaceutical product and for this is necessary prove its safety and efficacy. The effectiveness is guaranteed through physical-chemical tests, as the assay of active, and performance, as the dissolution test. The security is proven through tests of degradation products and the monitoring of the product stability studies during their period of validity. To ensure that the method is indicative of stability it is indispensable perform the forced degradation study, in which the product is studied degradation pathways and products generated by this degradation, as well as study into the drug and its known impurities, synthesis, manufacturing process or degradation. Knowledge of the stability of molecule helps in selecting proper formulation and package as well as providing proper storage conditions and shelf life, which is essential for regulatory documentation.

Impurities

Impurities are generally classified as organic or inorganic. The inorganic impurities can be heavy metals (treated in the USP general chapter <231> or other free carbon residue. The organic impurities can be classified according to their origin and they are studied separately in each

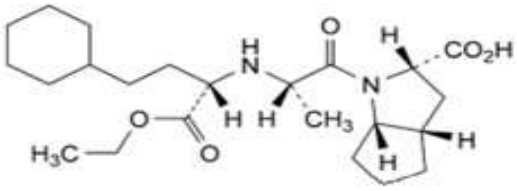
specific asset or product monograph of the pharmacopoeias. In the active pharmaceutical ingredient (IFA) may exist impurities from the starting material synthesis or the manufacturing process IFA, incomplete or partial reactions, remaining intermediate molecules, or from degradation.[3,4]

The Ramipril can have the follow impurities, as described by european pharmacopeia[5]:

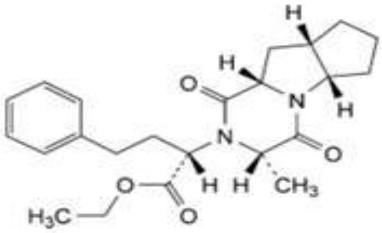


A. R = CH_3: (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(methoxycarbonyl)-3-phenylpropyl]amino]propanoyl] octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril methyl ester),

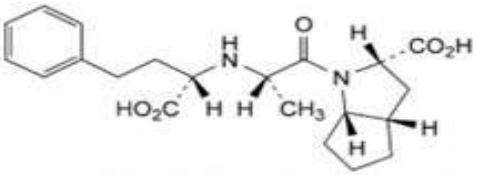
B. R = $CH(CH_3)_2$: (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(1*S*)-1-[(1-methylethoxy)carbonyl]-3-phenylpropyl]amino] propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril isopropyl ester),



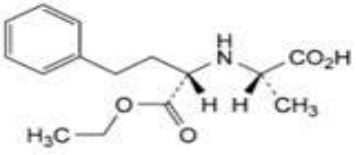
C. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(*1S*)-3-cyclohexyl-1-(ethoxycarbonyl)-propyl]amino]propanoyl] octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (hexahydroramipril),



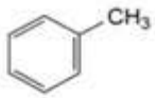
D. ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoate (ramipril diketopiperazine),



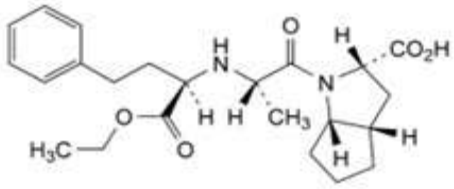
E. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (ramipril diacid),



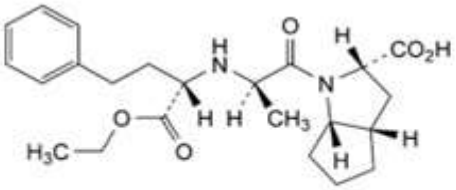
F. (2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoic acid,



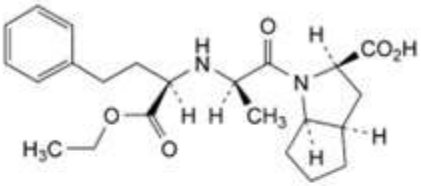
G. methylbenzene (toluene),



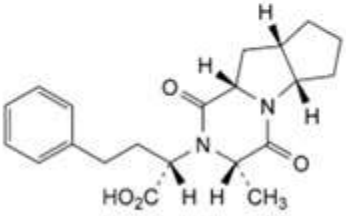
H. (2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*] pyrrole-2-carboxylic acid ((*R*,*S*,*S*,*S*,*S*)-epimer of ramipril),



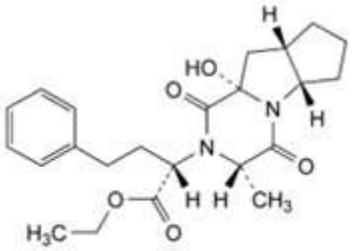
I. (2*S*,3a*S*,6a*S*)-1-[(2*R*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*] pyrrole-2-carboxylic acid ((*S*,*R*,*S*,*S*,*S*)-epimer of ramipril),



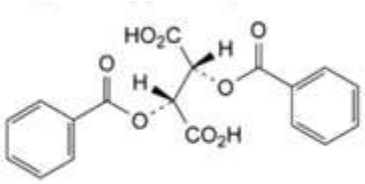
J. (2*R*,3a*R*,6a*R*)-1-[(2*R*)-2-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*] pyrrole-2-carboxylic acid (enantiomer of ramipril),



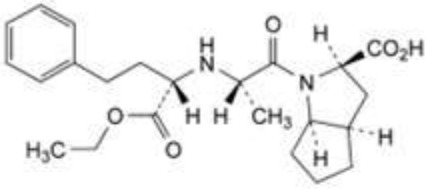
K. (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenylbutanoic acid (ramipril diketopiperazine acid),



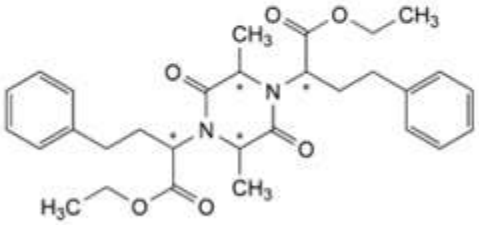
L. ethyl (2S)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-9a-hydroxy-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-*a*] pyrazin-2-yl]-4-phenylbutanoate (ramipril hydroxydiketopiperazine),



M. (2*R*,3*R*)-2,3-bis(benzoyloxy)butanedioic acid (dibenzoyltartric acid),



N. (2*R*,3a*R*,6a*R*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[*b*] pyrrole-2-carboxylic acid ((*S*,*S*,*R*,*R*,*R*)-isomer of ramipril),



O. diethyl 2,2'-(2,5-dimethyl-3,6-dioxopiperazine-1,4-diyl)bis(4-phenylbutanoate).

The impurities A, B, C and D are specific impurities of Ramipril, while the others are detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. The control of impurities is essential in substances for pharmaceutical use.[5]. The ICH Q3b defined the impurity is any component of the new drug product that is not the drug substance or an excipient in the drug product. The united states pharmacopeia show in the chapter 1086 to the limits of the sum the ordinary impurities to 2.0%[3, 6]. When do not have in an official monograph, the impurities limits must are stipulated considering the maximum daily dose and also the level of knowledge we have of each substance. The ICH stipulates in its Q3a guides (active pharmaceutical ingredient) and Q3b (pharmaceutical product) the following values:[6]

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

[1] The amount of drug substance administered per day

[2] Higher reporting thresholds should be scientifically justified

[3] Lower thresholds can be appropriate if the impurity is unusually toxic

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Notes on Attachment 1

1 The amount of drug substance administered per day

2 Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

3 Higher thresholds should be scientifically justified.

Stress Testing

The ICH guideline states that stress testing is intended to identify the likely degradation products which further helps in determination of the intrinsic stability of the molecule and establishing degradation pathways, and to validate the stability indicating procedures used.[7]

Forced degradation studies are carried out to achieve the following purposes:[7]

- To establish degradation pathways of drug substances and drug products.
- To differentiate degradation products that are related to drug products from those that are generated from non-drug product in a formulation.

- To elucidate the structure of degradation products.
- To determine the intrinsic stability of a drug substance in formulation.
- To reveal the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substance and drug product.
- To establish stability indicating nature of a developed method.
- To understand the chemical properties of drug molecules.
- To generate more stable formulations.
- To produce a degradation profile similar to that of what would be observed in a formal stability study under ICH conditions.
- To solve stability-related problems.

Forced degradation studies provide knowledge about possible degradation pathways and degradation products of the active ingredients and help elucidate the structure of the degradants. Degradation products generated from forced degradation studies are potential degradation products that may or may not be formed under relevant storage conditions but they assist in the developing stability indicating method. It is better to start degradation studies earlier in the drug development process to have sufficient time to gain more information about the stability of the molecule. This information will in turn help improve the formulation manufacturing process and determine the storage conditions. As no specific set of conditions is applicable to all drug products and drug substances and the regulatory guidance does not specify about the conditions to be used, this study requires the experimenter to use common sense. The aim of any strategy used for forced degradation is to produce the desired amount of degradation i.e., 5–20%. A properly designed and executed forced degradation study would generate an appropriate sample for development of stability indicating method[7]. Currently, there is not described in the literature or official guides a standard way to perform stress testing studies. This becomes clear when we read the master's thesis of Itu, K (2012), where a table with various literary sources and guides was shown, demonstrating the divergence of opinions on how to conduct these tests. The United States Pharmacopeia and ICH suggest that degradation of 5 is reached to 10% in order to have results consistent with reality. The National Health Surveillance Agency (ANVISA) in Brazil recommends degradation reached 10-30%. When it degrades very active, may have secondary degradation, wherein the degradation compounds are degraded leading to other compounds that are not of interest for the study. Another interesting fact presented in that study was that most publications related to stress testing studies are related to the validation of analytical methodology, and the least amount of work are related to the formulation and preformulation studies.[8]

Degradation pathways and its products

Although it is a commonly used ACE inhibitor, the drug has a considerable degree of instability being manifested by the two major degradation pathways: hydrolysis, forming ramipril-diacid (ramiprilat), Figure 2, and cyclizing by internal nucleophilic attack leading to the formation Ramipril diketopiperazine (DKP), figure 3.[9,10]

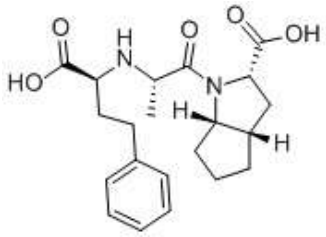


Figure 2: Chemical structure of Ramipril di-ácido (Ramiprilate)

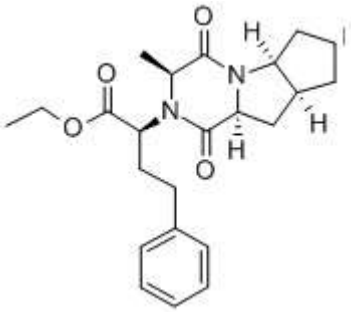
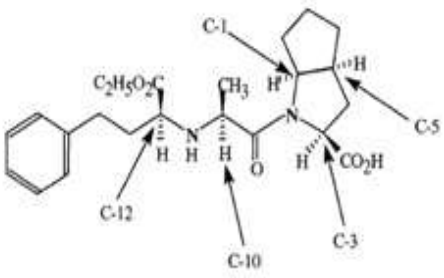


Figure 3: Chemical structure of Ramipril DKP

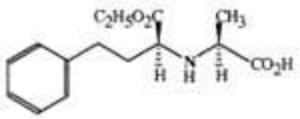
Is reported that mechanical stress, heat, moisture, pH, storage conditions and interaction with others ingredients lead to degradation of fármaco[10]. The Ramipril-DKP formation is strongly dependent on pH, especially at low pH, and that increasing the pH of the formulation leads to a decrease in the formation of DKP. The ideal pH of a formulation should be between 6.1 to 6.3. It is improve active stability[10,11] . Because of the presence of the ester group in its structure, Ramipril is highly likely to suffer degradação[11]. According to a study conducted in 2010 at the University of Conception, Chile, the Ramipril is degraded by various routes, among them the thermal degradation, alkaline hydrolysis, acid hydrolysis and oxidative[12]. Stress testing was performed on drug substance under hydrolysis (0.1 N HCl, water and 0.1 N NaOH), oxidation (3% H_2O_2), heat (70ºC) and photolysis (UV and VIS radiation). The drug was degraded under acidic, neutral, alkaline, oxidation and thermal stress conditions but it was stable under photolysis. Chromatographic separation of ramipril from its degradation products was achieved on a RP-18 column, using a mobile phase consisting of methanol – tetrahydrofuran – phosphate buffer (pH 2.4; 0.01M) (55:5:40, v/v/v) at a flow rate of 1.0 mL min^{-1} and UV detection at 215 nm. The assay was linear for ramipril concentrations of 50-300 µg/mL. The developed method was stability indicating, specific, accurate and precise for ramipril determination. This method was used to quantify ramipril in tablets. The results showed that the method described here is suitable for quantitative determination and the stability study of ramipril[12]. The principal degradation product for acidic hydrolysis was ramipril diketopiperazine. It was observed in the alkaline hydrolysis the formation of the diacidic form of the drug; ramiprilat. In the oxidative degradation it was observed

the formation of ramiprilat and ramipril diketopiperazine. Stress by heat produced ramipril diketopiperazine. The results obtained in stress tests show that the drug ramipril is strongly unstable in alkaline conditions. The drug is also unstable under acidic and neutral conditions for hydrolysis, oxidation and can undergo thermal degradation[12]. The stability of ramipril in the buffer solution with different pH and the influence of acid, alkaline and oxidative medium on ramipril stability were studied. The ramipril degradation products were determined by high-performance liquid chromatography (HPLC) method. Acetonitrile: sodium perchlorate was used as the mobile phase, at a flow rate of 1.0 ml/min (linear gradient elution). A Nucleosil 100-S 5 µm C18, 250 mm × 4.6 mm i.d. was utilized as stationary phase. Detection was affected spectrophotometrically at 210 nm. The drug substance was dissolved in the ammonium phosphate buffer (pH 3, 5 and 8) and these solutions were stored at 90 °C for 1 h. The other series of test solutions were prepared from stock solution (drug substance dissolved in solvent A of the mobile phase) by dilution in acid (0.1 M HCl), alkaline (0.1 M NaOH) and oxidative (hydrogen peroxide solution) medium. More then 0.2% of impurity D (ramipril–diketopiperazine) was detected in the buffer of pH 3 and pH 5. In the buffer of pH 8 there was detected more then 1% of impurity E (ramipril–diacid). No peaks for degradation products appeared in the chromatograms above limit of quantification. The alkaline medium has the greatest effect on degradation of ramipril into impurity E (more than 50%)[13]. A study conducted in the quality control department at Aventis Pharmaceutical in 2010, demonstrates the various diatereomers from the ramipril.[14]

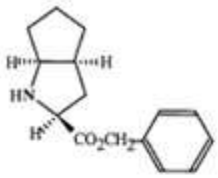


Diastereomer Abbreviation	Configuration at Listed Carbon Center				
	1	3	5	10	12
SSSSS (Ramipril)	S	S	S	S	S
SRSSS	S	R	S	S	S
SSSRS	S	S	S	R	S
RRRSS	R	R	R	S	S
SSSSR	S	S	S	S	R

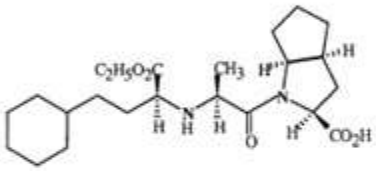
In addition to the diastereomers were also mentioned the following compounds:[13]



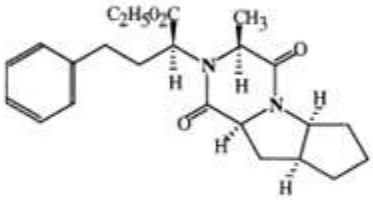
Precursor I



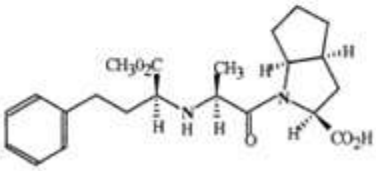
Precursor II-8



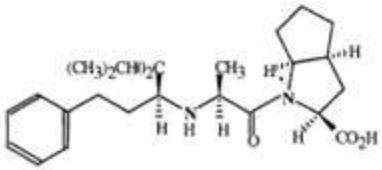
Hexahydro-ramipril



Ramipril-Diketopiperazine



Ramipril Methyl Ester



Ramipril Isopropyl Ester

Samples of ramipril capsules were exposed to stress conditions in acidic, alkaline and oxidative solutions, were also exposed to heat and light. The stressed samples were compared to those not exposed (time zero). The objective test was demonstrated the selectivity of the analytical method proposed, and the ability to separately quantify the Ramipril and their degradation compounds (known and unknown). Samples were accepted with no less than 10% degradation. The degraded samples by heating have produced ramipril diketopiperazine. In other stress conditions were not found degradation products in significant levels. Other impurities mentioned in the article were considered to synthesis impurities. These impurities were studied in the validation of the analytical method, and the samples were spiked with impurities standards.[14]. In his article he describes the synthesis, isolation and elucidation of impurity D and other compostos.[15]. A study of stress testing was make in China by Shi-Ying Dai et al. Samples were subjected to stress conditions of light, heat, acid, base and oxidation in order to evaluate the ability of the proposed method to separate Ramipril and Anlodipine from both known and unknown degradation products. All stressed

samples were compared with an un-stressed sample solution. The proposed chromatographic conditions were found to be specific under all applied stress conditions[16]. This study did not demonstrate clearly the origin of degradation compounds, showed only some chromatograms that are not clearly identified. The objective was only to show that the developed method is suitable for analytical application of ramipril tablets associated with amlodipine. The degradation of ramipril is believed to occur mainly via two pathways: hydrolysis to ramipril-diacid; and cyclization or condensation to ramipril-diketopip erazine, also referred herein as ramipril-DKP. These ramipril-diacid and ramipril-DKP compounds form, as indicated above, as a result of cyclization, condensation and/or break down arising from exposure to heat, air, moisture, stress, compaction or other interactions or events.[17]

DISCUSSION

US20060177498 describes a process to formulate ramipril compositions that utilizes excipients with low water content and processing parameters and packaging material that prohibit water or moisture uptake. Although the excipients include glyceryl behenate, microcrystalline cellulose and starch[18]. This proposal avoids hydrolysis of the drug, but does not solve the problem of thermal degradation and mechanical friction. US20080058404 A1 does not teach pre blending or co-milling the ramipril with glyceryl behenate or substantially coating the ramipril With glyceryl behenate. Moreover, the ramipril compositions taught have a high rate of ramipril-DKP formulation of 9.56% after two months at ambient temperature and humidity. Additionally, even when placed in air-tight packaging, the ramipril compositions have a rate of ramipril-DKP formation of 2.0%, after one month at 400 C and at 75% humidity[19]. US20050169981 A1 describes solid ramipril capsules that comprise a mixture of ramipril and lactose monohydrate as the diluent.[20] According to US20060177498, the process includes lactose monohydrate as the major excipient to formulate ramipril compositions in an attempt to improve ramipril stability. However, immediately after for mation of the described capsules, ramipril-DKP formation is already at 1.10%[18]. The lactose monohydrate can is crystalline or amorphous, depending on the water of hydration may be more or less reactive (available) to promote hydrolysis. In sensitive drugs such as ramipril, should be avoided amorphous form or to use excipients with little humidity. US20050069586 A1 describes ramipril tablets that have an admixture of ramipril and sodium stearyl fumerate with reduced ramipril DKP formation, but does not teach pre-blending or comilling the ramipril with glyceryl behenate or substantially coating the ramipril with any blending agent[21]. In particular, the inventors have demonstrated that by utilizing glyceryl behenate

as a blending agent, ramipril decomposition into degradant products, such as ramipril DKP and ramipril diacid, can be significantly reduced. Indeed, the inventors have demonstrated that the rate of decomposition of ramipril in compositions of the invention is less than 0.05% of the total weight of ramipril on average per month for at least 36 months from the date that the ramipril compositions are first formulated. The present invention also relates to methods of making the pharmaceutical compositions, of the present invention. Such methods comprise first pre-blending or co-milling ramipril with a blending agent (hydroxypropyl methylcellulose). The methods of the present invention also comprise first coating ramipril with a blending agent prior to formulation of ramipril into a dosage form[17]. Through the active precoating with hydroxypropyl methylcellulose can minimize thermal degradation, physical and hydrolysis friction because the drug is surrounded by this polymer that prevents the action of degrading agents.

CONCLUSION

Stress testing studies is very important, they provide knowledge about the degradation pathways of the drug and enables to understand what is required to produce a stable product. Through the stress testing can of deciding what excipients and packaging are more appropriate to the product, and to evaluate whether the method is indicative to stability. The ramipril is a drug sensitive to temperature, hydrolysis and oxidation, so it has been studied by many people. Its molecule ester group, this is related to its instability and reactivity. Various impurities are mentioned in official compendiums and articles, but the impurities were seen in major part of items were ramipril diketopiperazin and ramipril diacid. Ramipril diketopiperazin is formed by thermal degradation and ramipril diacid by hydrolysis. The drug is stable to light, but is strongly degradation by alkaline hydrolysis. Considering the data presented in the study it is concluded that articles should take special care in the manufacturing process and storage of the product in order to avoid degradation, since the degraded drug can result in decreased efficacy and safety of pharmaceutical. Metal packaging or others that are good heat conductors must be avoided to not lead to thermal degradation. The idea of the coat active before formulating the product is very effective according to data presented at the US 2006/0134213 A1 patent, then it is a proposal to be considered in others products that lead unstable active pharmaceutical ingredient as ramipril.

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