March 2010 ISSN : 0974-7419 Volume 9 Issue 1

Trade Science Inc.

Analytical CHEMISTRY

An Indian Journal

Review

ACAIJ, 9(1) 2010 [161-164]

Angiotensin converting enzyme inhibitors-impurity profiling: An overview

Gaurav Sharma*, Mukesh Chand

Department of Chemistry, D.A.V. (P.G.) College, Muzzaffarnagar, (INDIA)

E-mail: gaurav_isll@rediffmail.com

Received: 10th February, 2010 ; Accepted: 20th February, 2010

ABSTRACT

ACE Inhibitors (ACEIs), or inhibitors of Angiotensin-Converting Enzyme, are a group of pharmaceuticals that are used primarily in treatment of hypertension and congestive heart failure. During the synthesis or manufacturing of ACE inhibitors (API substances), some side products may be formed which may be closely related to the product and called as impurities of the drug substances. The chromatographic detection as well as structure elucidation of these impurities is very important. So there is an urgent need of sensitive and accurate analytical methods to detect and isolate these impurities from the API substances. Impurities present in the API substances which are more than 0.1%, should be identified and characterized by using various analytical techniques.

KEYWORDS

Angiotensin converting enzyme inhibitors;
HPLC;
Semipreparative HPLC;
LCMS;
API;
NMR.

INTRODUCTION

Angiotensin converting enzymes (ACE) inhibitors are the medicines that block the conversion of the chemical angiotensin I to a substance that increases salt and water retention in the body.

Angiotensin converting enzymes (ACE) inhibitors are the highly specific drugs, which have found extensive use in therapies of hypertension and lately in the treatment of heart failure.[1,2] ACE inhibitors are also used in the treatment of high blood pressure. They also make blood vessels relax, which helps lowering the blood pressure and allows more oxygen rich blood to reach the heart.

ACE inhibitors are used in the treatment of high blood pressure. They may be used alone or in combination with other medicines for high blood pressure. The mechanism of action of ACE inhibitors is to prevent the conversion of angiotensin I to angiotensin II, resulting in a drop in blood pressure and rise in plasma rennin[5].

ACE inhibitors may also be prescribed for other conditions. For example, Captopril (Capoten) is used to treat kidney problems in people who take insulin to control diabetes. It is also given to some patients after a heart attack. Heart attacks damage and weaken the heart muscle, and the damage continues even after a person recovers from the attack. This medicine helps slow down further damage to the heart. ACE inhibitors also may be used to treat congestive heart failure.

People taking ACE inhibitors are encouraged to drink sufficient liquids during exercise or while outside in hot weather. Physician's orders about exercise, activity levels and diet should also be followed exactly. In addition, anyone taking ACE inhibitors or any other antihypertensive need to be careful about spending too much time in the heat.

Review

Classification of ACE inhibitors

ACE inhibitors represent a family of structurally analogues compounds. Since the development of captopril in 1977, many other synthetic peptides of improved properties have found their way to the market: Lisinopril, Enalapril, Ramipril, Quinapril, Benazepril, Trandolapril, Perindopril.

Captopril (Figure 1) a thiol containing compound caused some side effects and researchers believed that the thiol group was responsible for these effects; the next step was the development of non thiol containing ACE inhibitors.[3]

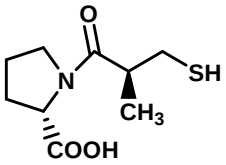

Figure 1 : Captopril

There are three classes of these new ACE inhibitors according to the particular moiety that enhance their bindings to the zinc ion of the angiotensin converting enzyme.[3,4,6,7]

The first class has a second ionizable carboxyl group; Lisinopril (Figure 2) is the only representative drug in this class, differing from other inhibitors because it is not a prodrug.

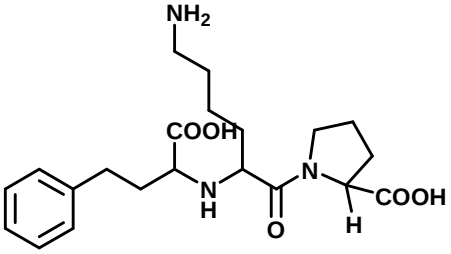

Figure 2 : Lisinopril

Fosinopril (Figure 3), a phosphorous containing ACE inhibitor, belongs to the second class[3,4]. Fosinopril is inactive but serves as a prodrug, being completely hydrolyzed to the active diacid fosinoprilat.

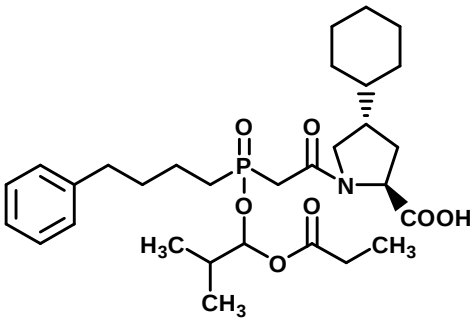

Figure 3 : Fosinopril

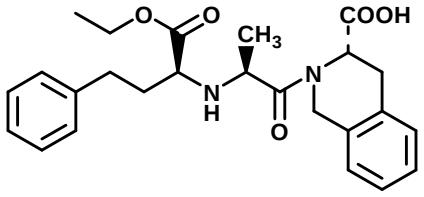

Figure 4 : Quinapril

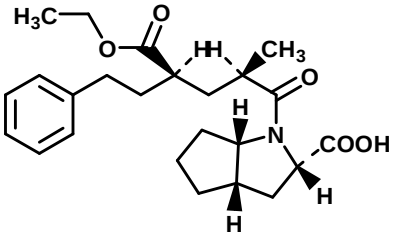

Figure 5 : Ramipril

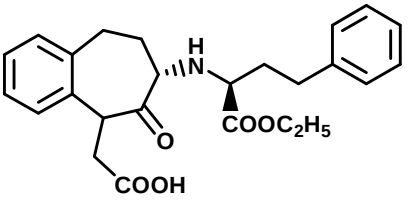

Figure 6 : Benazepril

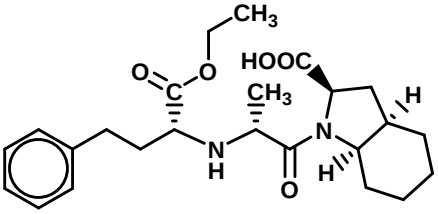

Figure 7 : Trandolapril

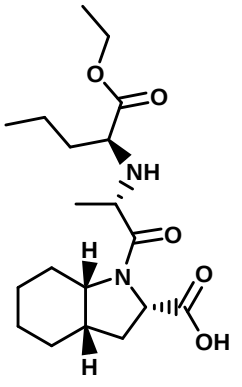

Figure 8 : Perindolapril

Agents in the third class comprise all remaining ACE inhibitors viz, Enalapril maleate, Quinapril (Figure 4), Ramipril (Figure 5), Benazepril (Figure 6), Trandolapril (Figure 7), Perindopril (Figure 8)[3,4].

Classification of impurities

Impurity can be defined as "Something that is impure or makes something else impure" or "A substance of interest mixed or impregnated with an extraneous or usually inferior substance"

Impurity is defined as any substance coexisting with the original drug, such as starting material or intermediates or that is formed, due to any side reactions.

Impurity can be of three types:

Impurities closely related to the product and coming from the chemical or from the biosynthetic route itself.

Impurities formed due to spontaneous decomposition of the drug during the storage or on exposure to extreme conditions.

The precursors which may be present in the final product as impurities.

Impurities present in excess of 0.1% should be identified and quantified by selective methods. The suggested structures of the impurities can be synthesized and will provide the final evidence for their structures, previously determined by spectroscopic methods. Therefore it is essential to know the structure of these impurities in the bulk drug in order to alter the reaction condition and to reduce the quantity of impurity to an acceptable level. Isolation, identification and quantification of impurities helps various ways, to obtain a pure substance with less toxicity and, safety in drug therapy.

Impurity profiling by analytical methods

The use of antihypertensive drugs increased rapidly in the last few years, with a corresponding increase in analytical investigations. In fact, the structural features of this class of drugs calls for specific analytical studies aimed to improve their detectability. Therefore, there is an urgent need of new and more effective analytical methods the involved impurities along with the drug substances. The increasing importance of impurity profiling within the pharmaceutical analysis is demonstrated by two books[10,11].

Identification of the impurities by retention matching with potential impurities using different separation methods with different retention mechanisms. According to the ICH Guideline[8], "potential impurity is an impurity that theoretically can arise during manufacture or storage". This means that the thorough grounding of organic and analytical chemists dealing with impurity profiling greatly determines the success of this step. The better their expertise in this field, the higher the number of predicted potential impurities which can be made available for this very simple and least labor-extensive method for the identification of impurities.

If the retention matching is not successful, the identification/structure elucidation is carried out by means of the joint application of chromatographic and spectroscopic techniques like LCMS. NMR spectroscopy is also necessary for the structure elucidation, somewhat larger sample size is necessary. These samples are usually obtained by semi-preparative HPLC

CONCLUSION

The increasing use of ACE inhibitors has pushed analytical chemists to develop new analytical methods for their determination either in biological fluids or in pharmaceutical preparations. In the light of above discussion, it is necessary to produce good quality of active pharmaceutical ingredients (APIs), and to achieve this, all the impurities present which are more than 0.1% should be isolated and characterized[8]. The efforts should be made to isolate or synthesize these impurities in pure form using different analytical approach and synthesis strategies.

REFERENCES

[1] J.G.Hardman, L.E.Limbird; A.G.Gilman; 'The Pharmacological Basis of Therapeutics', 10th, Ed., McGraw-Hill, New York, 809-835 **(2001)**.

[2] J.F.Reynolds, K.Praffit, A.V., S.C.Sweetman; 'The Extra Pharmacopoeia', J.F.Reynolda, Ed., The Pharmaceutical Press, London, 339-392 **(1993)**.

Review

[3] A.R.Gennaro, N.G.Popovich, A.D.Marderosian, R.L.Schnaare, J.B.Schwartz, G.R.Hanson, T.Medwick, H.S.White; 'The Science & Practice of Pharmacy', 20th Ed., Lippincott Williams & Wilkins, Philadephia, New York, **II**, 1279-1282 **(2000)**.

[4] G.H.Cocolas, J.N.Delgado, W.A.Remers; 'Text Book of Organic, Medicinal & Pharmaceutical Chemistry', 10th Ed., Lippincott-Raven, Philadephia, New York, 603 **(1998)**.

[5] V.Bele; 'Pharmacology' 1st Ed., Carrer Publication, Nasik, India, 138-141 **(2001)**.

[6] United State Pharmacopoeia XXIII; US Pharmacopeial Convention, Rockville, M.D., 895-896 **(1995)**.

[7] J.D.Demarco, M.A.Brooks; 'Analytical Profiles of Drug Substances', Academic Press, New York, **21**, 234-275 **(1992)**.

[8] ICH Harmonized Tripartite Guideline; Impurities in New Drug Substances Q3A®.

[9] 'European Pharmacopoeia' 5th Ed.; Strasbourg, 1922-1923 **(2005)**.

[10] S.Gorog; 'Trends in Analytical Chemistry', 22nd Ed., 407-415 **(2003)**.

[11] S.Ahuja; 'Impurities Evaluations in Pharmaceuticals', Marcel Dekker, New York, **(1998)**.