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Review Article

Chiral Analysis of Captopril Derivatives by Hplc Methods

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Abstract

Captoppril is a drug used for the treatment of arterial hypertension, the drug active ingredient possesses in its chemical structure asymmetric carbons. The separation methods presented for captopril can be classified into two main categories; Quality control of pharmaceuticals containing captopril and determination of captopril in biological fluids. Captopril and its ester derivative are separable on the normal stationary phases based on amylose as the case of CHIRAL PACK IB and based on cellulose as the case CHIRACEL OD-H and CHIRACEL OJ, and therefore according to these results the captopril derivatives Can be better solved on the same types of phases used in this work but in reverse mode.

Keywords: Captopril; Chiral Sepatration; Enantiomer; CHIRAL PACK; CHIRACEL

Introduction

Chirality is now a very important topic for academic research as well as for pharmaceutical development. Accounting for the important role of chiral separation, the 2001 Nobel Prize in Chemistry was awarded to three scientists: Dr. William S. Knowles and Prof. K. Barry Sharpless in the United States and Professor Ryori Nyori in Japan, by Their development of asymmetric synthesis using chiral catalysts in the production of drugs or simple enantiomeric chemicals [6,7]. To a wide range of new technologies for chiral separation. The American Drug Organization (FDA) recently recommends evaluations of each enantiomeric activity for racemic drugs and promotes the development of novel chiral drugs in the form of pure enantiomers [7].

In this work, we study the chiral separation of captoppril, a drug used for the treatment of arterial hypertension, the drug captopril has a chiral active principle with two asymmetric carbons. The chiral separation of these isomers is carried out by HPLC methods on chiral columns. Captopril is a drug used in the treatment of high blood pressure. It acts by preventing the production by the organism of molecules which regulate the tension in Causing vaso constriction (Figure 1).

Among other things, blood pressure is controlled by the regulation of the blood volume, that is to say the volume of the vascular system. Angiotensin II is the peptide that is responsible for this mechanism, resulting from the conversion of Angiotensin I. The latter is manufactured as an inactive precursor, angiotensinogen, by the liver. Lecaptopril blocks the conversion of angiotensin [17]. Captopril in its structure has two asymmetric carbons directly linked to two methylenes which makes their protons chemically non-equivalent, which are called diastereoisotopic protons. The difference between the integration of the split signals gives information on the purity and the enantiomeric or diastereoisomeric composition of this product. Several GC methods have been reported for the determination of captopril. Matsuki., *et al.* developed a GC method to determine captopril in dog blood and urine, photometric detection was successful after derivation with N-ethylmaleimide (NEM) [18]. Capillary electrophoresis is a separation technique based on the relative mobility difference of charged species under the effect of the applied electric field. The various methods have been reported to determine captopril. Ling., *et al*. Used to determine a mixture of several thiols of pharmacological interest, in particular captopril, in human blood.

Chiral analysis of captopril

Captopril analysis by UV spectroscopy

The UV-Vis spectrum has two characteristic absorption bands, an intense band at 225 nm corresponds to the electronic transition

π - π* which indicates the presence of a double bond, and a low intensity band located at 288 nm corresponds to the electronic transition n - π* of the two carbonyls of the acid and of the amide.

Analysis of captopril on column C18

Analysis of captopril on column C-18 by simple elution with methanol shows that this product appears at 8.86 min in 99.58%, peak 02 at 10.2 min assigned to the excipient and since this analysis was carried out with detection at Wavelength of 288 nm or captopril has a low absorption which escapes exploration of the other transparent excipients in this detection position.

Figure 1: Chemical structure of captopril.

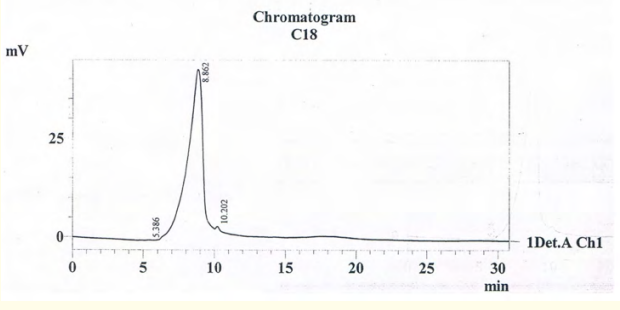

Figure 2: Chromatogram of HPLC analysis of captopril on C-18 column.
Eluent: MeOH, FR: 0.4 mL mn-1

N	t_R (min)	K'	Composition %	α	Rs
01	8.86	0.645	99.58	1.26	0.894
02	10.20	0.894	0.42		

Table 1: HPLC Analysis results of captopril on C-18 column.

Chiral analysis of captopril

Selection of the appropriate chiral column is the most essential and most challenging part of developing chiral separation method. Indeed, the chiral discrimination process is sensitive not only to the structures of the analyte and the PSCs but also to the separation conditions (nature, speed and pH of the mobile phase, temperature). Currently, the implementation of new technologies, such as automated systems, multi-column screening stations, mobile phase gradient has significantly accelerated the process of choice of chiral column is allows to develop and optimize the chiral separation [27,28].

The diasterioisomers, enantiomers and rotational isomers of captopril were successfully separated using chiral stationary phases.

Colonne	N	t_R (min)	K'	Composition %	α	Rs
CHIRAL PAK IB	1	8.47	0.099	9.61	-	-
	2	9.59	0.246	11.94	2.47	1.751
	3	9.84	0.278	62.33	1.13	0.456
	4	10.77	0.399	3.92	1.43	1.388
	5	11.23	0.458	1.82	1.82	0.450
CHIRACEL OD-H	1	7.17	0.181	50.309	-	-
	2	10.40	0.715	32.532	3.95	1.279
	3	14.59	1.405	11.741	1.18	1.737
	4	17.06	1.812	0.816	1.29	2.264
	5	17.76	1.928	0.482	1.04	0.299
	6	19.28	2.178	0.031	1.10	0.759
	7	20.29	2.344	0.322	1.08	1.005

Table 2: Results of Chiral analysis of captopril by HPLC methods on CSPs.

In normal phase liquid chromatography, a polar stationary phase is used with a less polar mobile phase [18]. Amini., *et al.* [18] can determine captopril in human plasma using a silica-NH2-based column and a mobile phase composed of n-hexane/2 propanol/ methanol/acetic acid (68: 15: 15: 2, volume). Captopril was first derived from 2-bromo-2-acetophenone to improve UV absorption properties and improve the sensitivity of the method. Benzoic acid 3,5-dinitro was used as an internal standard which allowed UV detection at 246 nm. The limit of quantitation of captopril in plasma was 10 ng/mL.

The chiral analysis of captopril shows the efficacy of the two chiral columns CHIRAL PAK IB and CHIRACEL OD-H which have allowed the isolation of the four isomers of captopril which has two asymmetric carbons (Figure 2). The immobilized cellulose column pressures a higher selectivity (3.47) with a good resolution which will reach 1.812.

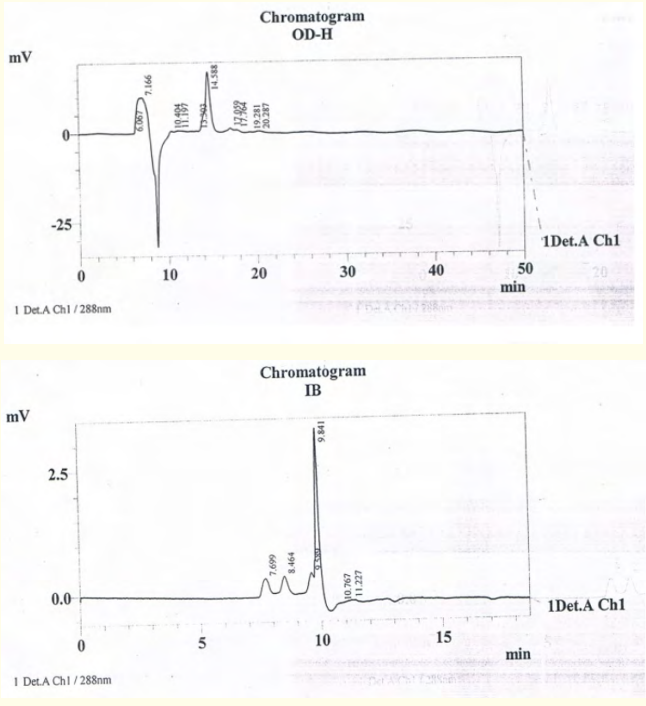

Figure 3: Chromatograms of chiral analysis of captopril by HPLC methods
a) CHIRACEL OD-H and b) CHIRAL PAK IB,
Eluent: MeOH, FR: 0.4 mL mn-1

Chiral analysis of captopril ester derivative

TLC analysis of the captopril ester derivative:

The follow-up of the esterification reaction is carried out by thin-layer chromatography, this reaction is incomplete reversible which arrives at an infinite kinetic under heating and under acid catalysis to displace the acid-ester equilibrium (esterification-hydrolysis) with a yield of 66.6% (Figure 4).

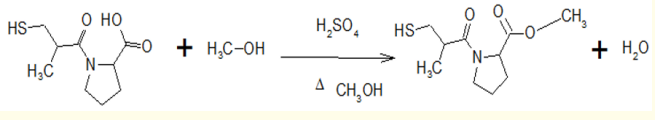

Figure 4: Esterification reaction of captopril.

The TLC analysis of the drug captopril shows the presence of two spots located respectively at Rf 0.39 and 0.59, or Rf = 0.59 is attributed to captopril and Rf = 0.39 assigned to the excipients. Two products were obtained by esterification reaction corresponding to the Rf towards 0.67 and 0.87 attributed to the esters of the captopril isomers (Table 3).

Number of spots	*Rf* (Hexane: Acetic acid (60: 40) v: v	Time (h)
2	0.39 0.59	0 h (at the begining of the reaction)
4	0.39 0.59 0.67 0.87	8 h (at the end of the reaction)

Table 3: TLC analysis of captopril ester derivative.

Analysis of the captopril derivative ester on the C18 column

Analysis of the residue shows the formation of two novel molecules derived from captopril, so the esterification was carried out on two isomers of captopril which appeared respectively at 5.05 min (32.14%) and 5.57 min (6.56%) (Table 4).

N	t_R (min)	K'	Composition %	α	Rs
1	5.05	1.19	32.14	-	-
2	5.57	1.21	6.56	1.017	0.215
3	6.82	4.16	61.29	3.45	1.822

Table 4: HPLC analysis results of captopril ester on C-18 column.

The esterification is regioselective which passes in parallel with different rate constants according to the operating conditions applied. The esters obtained are separable diastereoisomers on column C18 (Figure 5).

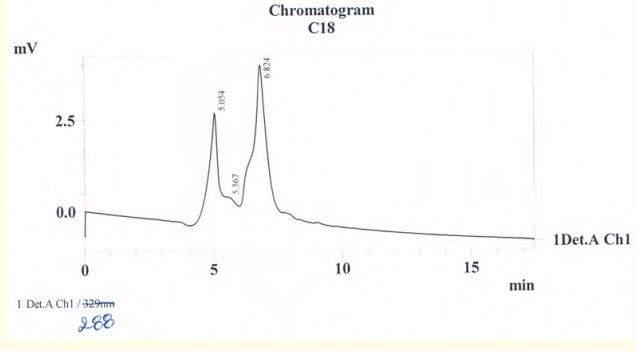

Figure 5: Chromatogram of HPLC analysis of captopril ester on C-18 column.
Eluent: MeOH, FR: 0.4 mL mn-1

Chiral analysis of the captopril ester derivative

The chiral analysis of the captopril ester was carried out on a chiral cellulose-based column, CHIRACEL OJ, under the same operating conditions followed in the analysis of captopril. The ester also has four isomers well resolved with a selectivity factor tending to 1.5 with a resolution of 0.601 (figure 6).

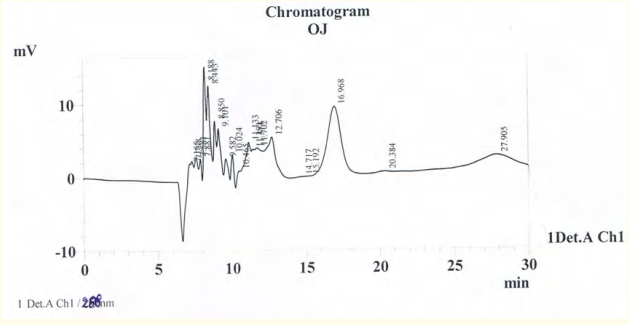

Figure 6: Chromatogramme d'analyse de l'ester du captopril par HPLC sur la colonne.
CHIRACEL OJ, Eluent : Hex-IPrOH (80: 20) ,
Debit: 0.4 mL mn-1

N	t_R (min)	K'	Composition %	α	Rs
1	7.30	0.02	2.78	-	0.035
2	7.58	0.06	3.70	2.18	0.111
3	7.88	0.102	2.62	1.70	0.215
4	8.19	0.144	6.24	1.42	0.415
5	8.44	0.180	6.86	1.25	0.428
6	8.85	0.237	3.89	1.32	0.601
7	9.10	0.272	5.29	1.50	0.304
8	9.58	0.339	4.03	1.25	0.425
9	10.02	0.401	3.12	1.18	0.524
10	10.46	0.463	2.19	1.15	0.163
11	11.13	0.556	7.43	1.20	0.173
12	11.39	0.592	1.57	1.06	0.056

Table 5: Les résultats d'analyse chirale du dérivé ester du captopril par HPLC sur une phase chirale normale (CHIRACEL OJ).

According to the chiral analysis results presented in Table 5, it is noted that captopril is less retained with respect to the ester, which explains the absence of hydrogen bonding interaction of the acid, Elution of the latter on the CHIRACEL OJ chiral column.

Chiral Discrimination Mechanism

The first chiral recognition model was proposed by Dalgliesh and then modified by Pirkle. It assumes the existence of a minimum of three points of interaction between the solute and the selector. These interactions, determined by the chemical composition of these two protagonists, can be attractive or repulsive. This model allows two interactions for each enantiomer, the third, of a stereoselective nature, is possible only for one of them. Interactions that may participate in the chiral discrimination process may include coulombic attractions or repulsions, hydrogen bonds, hydrophobic effects, steric hindrance, inclusion phenomena in cavities, charge transfers, π-π interactions, and of dipole-dipole interactions [1-29].

Conclusion

Captopril is the first inhibitor of high blood pressure and is still widely used in various cardiac disorders. The separation methods presented for captopril can be classified into two main categories; Quality control of pharmaceuticals containing captopril and the determination of captopril in biological fluids, including blood, plasma, urine and tissues. The requirements for each category of analysis are different in terms of sample preparation and analysis protocol. For the analysis of pharmaceutical products, a simple, robust and automated analytical technique is particularly important for coping with high sampling frequency and routine analysis by HPLC methods. Direct UV detection in normal phase mode (NP-LC) is possible and easy, but sensitivity and selectivity may require too detailed screening work. Captopril and its ester derivative are separable on the normal stationary phases based on amylose as the case of chiral pack IB and based on cellulose as the case chiracel OD-H and chiracel OJ, and therefore according to these results the captopril derivatives Can be better solved on the same types of phases used in this work but in reverse mode.

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