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ANALYSIS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANTAGONISTS

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The Angiotensin-converting enzyme inhibitors and antagonists are widely used in the management of essential hypertension, stable chronic heart failure, myocardial infarction and diabetic nephropathy, so that specific and sensitive methods are needed for the qualitative and quantitative determinations of these drugs in pharmaceutical dosage forms and in biological material. In the last few years, there was no review published covering all different analytical methods used for the determination of these drugs. The aim of this work is to review the most important recent methods for their analysis in pure forms, in different pharmaceutical dosage forms and in biological fluids due to the great importance of this class of drugs. This review includes two parts: the first part presents the methods applied for the analysis of pharmaceuticals. The second part is devoted to the methods elaborated for the assays in biological material (blood, plasma and urine).

Keywords: Angiotensin converting enzyme inhibitors, Antagonists; Analytical methods; Pharmaceutical dosage forms analysis; Biological fluids analysis.

Abbreviations: ACE, Angiotensin-Converting Enzyme; ACEI, Angiotensin converting enzyme inhibitor; ARBs, Angiotensin Receptor Blockers; Ang II, Angiotensin II; Ang I, Angiotensin I; HCT, hydrochlorothiazide; ACN, Acetonitrile; H_2O, Water.

1. Introduction

The Angiotensin-converting enzyme inhibitors are widely used in the management of essential hypertension, stable chronic heart failure, myocardial infarction and diabetic nephropathy[1-3].

Angiotensin-converting enzyme plays a central role in a cascade of proteolytic reactions, which ultimately control the levels of Angiotensin II, a potent vasoconstrictor[4]. At first, rennin cleaves the inactive substrate angiotensinogen to the decapeptide Angiotensin I. In turn, Angiotensin-converting enzyme catalyses the transformation of Angiotensin I into Angiotensin II, the active octapeptide of the renin-angiotensin system (Fig. 1). Angiotensin II (Ang II) in plasma then binds to AT-receptors.

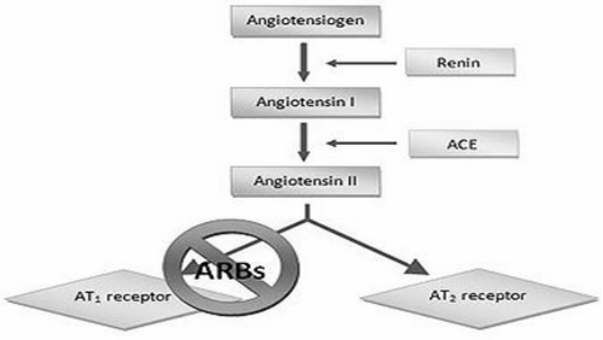

Fig. 1: Renin Angiotensin pathway.

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Angiotensin Converting Enzyme (ACE) inactivates bradykinin, a potent vasodilating agent. ACE inhibitors evoke the opposite action, while the Angiotensin Receptor Blockers (ARBs) block the last part of the renin-angiotensin pathway more specifically than ACE inhibitors[5]. In the 1970s scientists first observed that Ang II harms the heart and kidneys and it was also witnessed that individuals with high levels of renin activity in plasma were at increased risk of myocardial infarction and stroke[6]. Ang II plays an important role in regulating blood pressure and electrolyte and fluid balance[7]. Two compounds, S-8307 and S-8308, were found to be highly specific and promising non-peptide Ang II receptor antagonists but their structures would have to mimic the pharmacophore of AngII[8]. The orally active, potent and selective nonpeptide AT1 receptor blocker Losartan was developed and, in 1995, Losartan was approved for clinical use in the United States. Since then, six additional ARBs have been approved[9]. These drugs are known for their excellent side-effect- profiles, which proved clinically to be similar to that of placebos[10].

Specific and sensitive methods are needed for the qualitative and quantitative determinations of both pharmaceutical forms and in biological material of these widely used drugs. In the last few years, there was no review published covering all different analytical methods used for the determination of these drugs. Monographs in the "Analytical Profiles of Drug Substances", series, were published for Enalapril Maleate[11], Lisinopril[12] and Benazepril[13]. This motivated us to review the most important recent methods for their analysis in pure forms, in different pharmaceutical dosage forms and in biological fluids.

2. Chemistry

2.1. Chemical structures of ACEIs

There are currently 11 ACE inhibitors approved for therapeutic use in the United States. Based on their chemical composition, these compounds can be sub classified into three groups: sulfhydryl-containing inhibitors exemplified by captopril (Fig. 2), dicarboxylate-containing inhibitors exemplified by enalapril (Fig. 3), and phosphonate-containing inhibitors exemplified by fosinopril (Fig. 4). Captopril and fosinopril are the sole representatives of their respective chemical subclassifications, while the majority of the inhibitors contain the dicarboxylate functionality. All of these compounds effectively block the conversion of Ang I to Ang II and have similar therapeutic and physiologic effects. The compounds differ primarily in their potency and pharmacokinetic profile[14]. Additionally, the sulfhydryl group in captopril is responsible for certain effects, not seen with the other ACEIs (The chemical structure of enalapril "Parent of dicarpoxylate containing ACEIs is shown in figure 3", while other dicarboxylate containing drugs are shown in table 1).

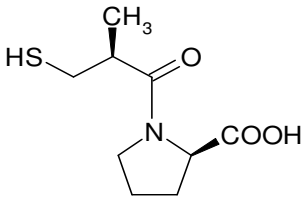


Fig. 2: Captopril
(Sulfhydryl-containing inhibitor)

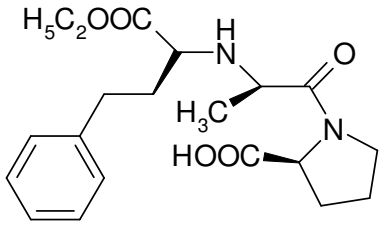


Fig. 3: Enalapril
(The parent dicarboxylate containing inhibitor)

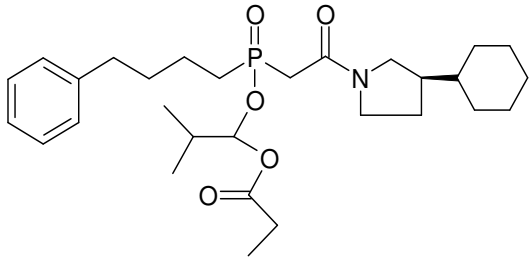
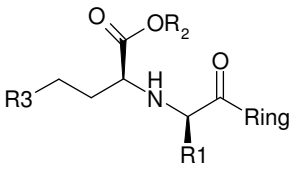


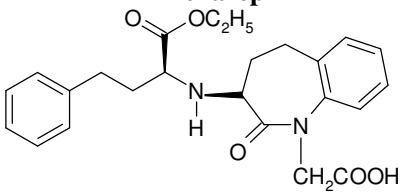
Fig. 4: Fosinopril
(Phosphonate-containing inhibitor)

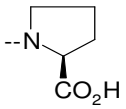
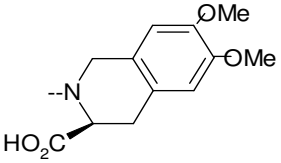
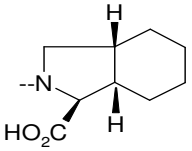
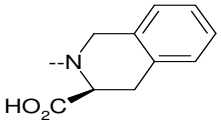
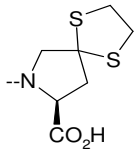
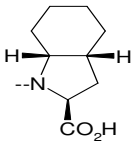
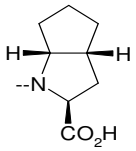
Table 1: Dicarboxylate-containig angiotensin converting enzyme inhibitors.

General structure:



Benazepril

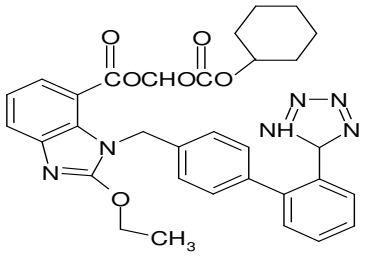


Compounds	Ring	R1	R2	R3
Lisinopril		$(CH_2)_4NH_2$	H	
Moexipril		CH_3	CH_2CH_3	
Perindopril		CH_3	CH_2CH_3	CH_3
Quinapril		CH_3	CH_2CH_3	
Spirapril		CH_3	CH_2CH_3	
Trandolapril		CH_3	CH_2CH_3	
Ramipril		CH_3	CH_2CH_3	

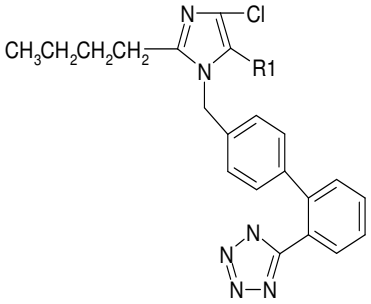
2.2. Chemical structures of ARBs

Losartan, valsartan, candesartan, irbesartan, telmisartan and olmesartan all contain a biphenyl-methyl group. Losartan is partly metabolized to its 5-carboxylic acid metabolite EXP 3174, which is a more potent AT1 receptor antagonist than its parent compound[15] and is a model for the continuing development of several other ARBs. Valsartan, is a nonheterocyclic ARB, where the imidazole of losartan is replaced by an acylated amino acid[5]. Irbesartan is longer acting than valsartan and losartan and it has an imidazolinone ring where a carbonyl group functions as a hydrogen bond acceptor instead of the hydroxymethyl group in losartan. Irbesartan is

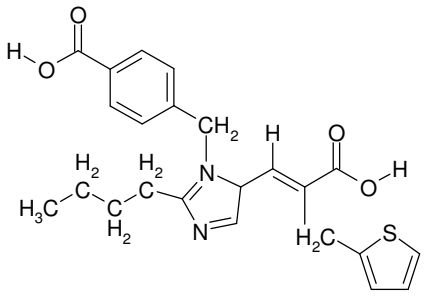
a non-competitive inhibitor. Candesartan cilexetil is a benzimidazole and is an ester carbonate prodrug. In vivo, it is rapidly converted to the much more potent corresponding 7-carboxylic acid, candesartan (CV 11974), Telmisartan has carboxylic acid as the biphenyl acidic group. It has the longest elimination half-life of the ARBs (about 24 hrs)[6]. Olmesartan medoxomil is the newest ARB on the market, marketed in 2002. It is an ester pro-drug like candesartan cilexetil. In vivo, the pro-drug is completely and rapidly hydrolyzed to the active acid form, olmesartan (RNH-6270). It has a hydroxyisopropyl group connected to the imidazole ring in addition to the carboxyl group[5] (The chemical structures are shown in figure 5).



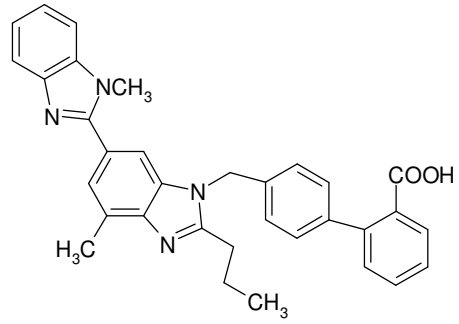
CANDESARTAN
Cilexetil



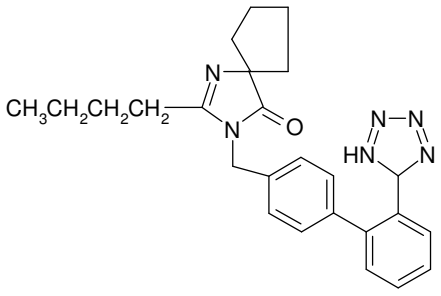
LOSARTAN R1 =CH_2OH R2= K
Potassium
EXP3174 R1=COOH R2=H



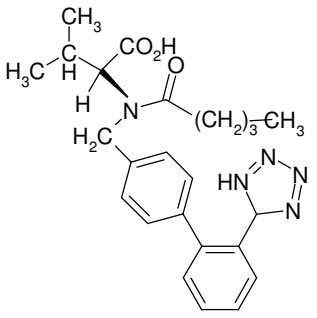
EPROSARTAN



TELMISARTAN



IRBESARTAN



VALSARTAN

Fig. 5: Structures of angiotensin receptor blockers.

3. Physico-chemical and pharmacokinetic properties

The pharmacokinetic parameters for ACEIs are summarized in table 2[16]. The oral bioavailability of this class of drugs ranges from 13-95%, With the exception of enalapril, lisinopril and fosinopril, concurrent administration of food adversely affects the oral absorption of ACEIs. The extent of protein binding also exhibits wide variability among the different compounds, and renal elimination is the primary route of elimination for most ACE inhibitors[17]

The pharmacokinetic parameters for (ARBs) are summarized in table 3[16]. With the exception of irbesartan (60-80%), and possibly telmisartan (42%), all of the compounds have low, but adequate, oral bioavailability (15-33%).The compounds can be taken either with or without food. All of the compounds have similar onsets, are highly protein bound, have elimination half-lives which allow once or twice daily dosing, and are primarily eliminated via the fecal route[17].

Table 2: Physico-chemical and pharmacokinetic parameters of ACE inhibitors.

Drug	Calculated Log P	Oral bioavailability	Effect of food on absorption	active metabolite	Protein binding	Onset of action (hr)	Duration of action (hr)	Major route(s) of elimination
Benazepril	1.74	37%	reduced rate, same extent	Benazepril	>95%	1	24	Renal (primary) Biliary (secondary)
Captopril	1.02	60-75%	reduced	na*	25-30%	0.25-0.50	6-12	Renal
Enalapril	0.71	60%	none	Enalaprilat	50-60%)	1	24	Renal
Enalaprilat	001	na*	na*	na*	_†	0.25	6	Renal
Fosinopril	_†	36%	none	Fosinoprilat	95%	1	24	Renal (50%) Hepatic (50%)
Lisinopril	-1.77	25-30%	None	na*	25%	1	24	Renal
Moexipril	_†	13%	reduced	Moexiprilat	50-90%	1	24	Renal/Fecal
Perindopril	1.26	65-95%	reduced	Perindoprilat	60-80%	1	24	Renal
Quinapril	1.84	60%	reduced	Quinaprilat	97%	1	24	Renal/Fecal
Ramipril	1.59	50-60%	reduced	Ramiprilat	73%	1	24	Renal/Fecal
Spirapril	0.61	50%	_†	Spiraprilat	_†	1	24	Renal (50%) Hepatic (50%)
Trandolapril	2.14	80%	reduced rate, same extent	Trandolaprilat	65-94%	0.5-1.0	24	Renal/Fecal

* Not applicable † Data not available

Table 3: Physico-chemical and pharmacokinetic parameters of ARBs.

Drug	Oral Bioavailability (%)	Effect of Food on Absorption	Active Metabolite	Protein Binding (%)	Time to Peak Plasma Cone. (hrs)	Elimination Half-life (hrs)	Major Route(s) of Elimination (%)
Losartan	33	Reduced	EXP-3174	98,7 (losartan) 99,8%EXP-3174 (EXP-3174)	1 (losartan) 3-4(EXP-3174) (EXP-3174)	1.5-2(losartan) 6-9(EXP-3174) (EXP-3	Fecal (60) Renal (35)
Valsartan	25	Reduced	None	95	2-4	6	Fecal (83) Renal (13)
Irbesartan	60-80	None	None	90	1,5-2	11-15	Fecal (80) Renal (20)
Candesartan Cilexetil	15	None	Candesartan	99	3-4	9	Fecal (67) Renal (33)
Telmisartan	42	None	None	100	5	24	Fecal (97)
Eprosartan	15	Variable	None	98	1-2	5-7	Fecal (90) Renal (10)

4. Official methods of analysis

The United States Pharmacopeia XXX[18] prescribes HPLC methods for the assay of benazepril, enalapril, lisinopril, losartan, quinapril and ramipril, while the British Pharmacopeia[19] prescribes potentiometric methods for the assay of enalapril, losartan and ramipril.

5. Reported methods of analysis

5.1. Analysis in bulk drug and dosage forms

5.1.1. Spectroscopic methods

5.1.1.1. Ultraviolet spectrophotometric methods

Table 4: The most important methods for UV spectrophotometric methods for analysis of ACEIs and ARBs in pharmaceutical dosage forms.

Drug(s)	Method	Wavelength(s)	Ref.
Fosinopril & (HCT)	Multiwavelength UV spectrophotometry using the program QUEST	(210-240 nm)	(20)
Enalapril Maleate & (HCT)	Multi component mode	200-300 nm	(21)
Ramipril, benazepril, enalapril maleate, lisinopril and quinapril	Derivative UV spectroscopy: Ramipril (third order), benazepril (second-order), enalapril maleate (second-order), lisinopril (first- and second-order), quinapril (first-order)	(224-228 nm) (241-259 nm) (228 nm). (268&270 nm respectively) (272 nm)	(22)
Benazepril Hcl and (HCT)	Second order derivative	253.6 and 282.6 nm for benazepril & 282.6 nm for (HCT)	(23-24)
Lisinopril and (HCT)	Ratio-spectra, derivative spectrophotometry & Vierordt & apos method	At 269.6 nm for lisinopril & 279.8 nm for HCT(first drevative), at 253.7 nm and 243.6 nm for lisinopril , at 280.1 nm and 270.8 nm for HCT (ratio spectra). In Vierordt's method at 259.8 nm and 272.7 nm in the zero-order spectra	(25)
Lisinopril	Second-derivative UV spectrophotometry		(26)
Lisinopril and (HCT)	Drugs dissolved in acidic H_2O	At 205 and 225 nm respectively	(27)
Simultaneous determination of (HCT) [I] in binary mixtures with benazepril HCl [II], triamterene [III] and cilazapril [IV]	Vierordt & apos method, and ratio spectra derivative spectro-photometry	At 271.7, 238.1, 234.1 and 210.7 nm for I, II, III and IV respectively (Vierordt & apos method). I in a binary mixture with II, III or IV within 200-350 nm)	(28)
Amlodipine-enalapril maleate & Amlodipine-lisinopril	derivative spectrophotometry	At 251.1 nm for amlodipine and 226.6 nm for enalapril (first derivative), At 216.6 nm for amlodipine and 219.4 nm for lisinopril (second derivative)	(29)
(HCT) and either Spironolactone or ramipril	Vierordt& apos method and ratio-spectra zero-crossing derivative spectrophotometric methods	At 270.7 and 269.9 nm for mixtures of HCT & spironolactone and for HCT & ramipril respectively (first derivative). Combined HCT with spironolactone or ramipril measurement at 237.0 and 253.8 nm, respectively (ratio spectra based on 1st derivative measurement)	(30)

Drug(s)	Method	Wavelength(s)	Ref.
(HCT) and amiloride HCl	Ratio spectra derivative spectrophotometry	At 285.7 nm for HCT and at 302.5 nm for amiloride HCl	(31)
benazepril hydrochloride and (HCT)	Absorbance ratio and Vierordt method	249 nm is the isosbestic point in the absorbance ratio method. At 236 and 269 nm for benazepril & HCT respectively (Vierordt method)	(32)
Losartan potassium & HCT	Tablets dissolved in H_2O	At 205 &272 nm respectively	(33)
Mixture of lisinopril and (HCT)	Third derivative UV zero crossing measurement, second derivative of the ratio spectra, classical least squares and principal component regression, and first derivative spectra	At 217.4 and 233.4 nm (third derivative (3D) UV with zero crossing measurement). At 214.3 and 228.0 nm (second derivative of the ratio spectra)	(34)
Benazepril HCl and (HCT)	Second derivative UV spectrophotometry, second derivative of the ratio spectra and Chemometric methods	At 214.8 and 227.4 nm for benazepril Hcl and (HCT) respectively, at 241.2 and 273.2 nm for benazepril HCl and (HCT) respectively	(35)
Fosinopril and (HCT)	Fourth-derivative UV spectrophotometric method	At zero-crossing wavelengths of 217.7 and 227.9 nm for fosinopril and (HCT) respectively	(36)
Losartan and (HCT)	first-derivative spectroscopy	at 271.6 nm for losartan and 335 nm for (HCT) respectively	(37)
Fosinopril and(HCT)	Derivative-differential spectrophotometry, ratio spectra derivative spectrophotometric method and absorbance ratio method	At 227.6 and 276.4 nm (derivative-differential spectrophotometry) for fosinopril and HCT respectively. At 237.9, 243.8 nm for fosinopril and 262.4, 269.3 and 278.6 nm for HCT (first derivative of the ratio spectra)	(38)
Cilazapril and (HCT)	Chemometric methods	The absorbance measured for 15 wavelength points (from 222 to 276 nm)	(39)
Lisinopril alone & with HCT	By derivatization reaction with 1-fluoro-2, 4-dinitrobenzene (sanger's reagent)	At 356.5 (alone) At 405.5 nm (with HCT)	(40)
Valsartan	Measurement of standard solution, and second derivative-spectrophotometric methods	At 205.6 nm (UV) At 221.6 and 231.2 nm (second drevative)	(41)
Amlodipine besilate and enalapril maleate	Measurement of standard solution dissolved in H_2O	At 238 &208 nm respectively	(42)
Moexipril HCl and (HCT)	Second-derivative UV spectrophotometry with zero-crossing measurements	at 215 and 234 nm for moexipril HCl and (HCT), respectively	(43)
Candesartan cilexetil and (HCT)	First derivative and ratio derivative spectrophotometry	At 270.1 and 255.5 nm (first drevative). At 236, 250, 232, 267 and 280 nm (first derivative of the ratio amplitudes) for Candesartan and HCT respectively	(44)
Losartan potassium	First derivative spectrum	At 234 nm	(45)

Drug(s)	Method	Wavelength(s)	Ref.
Losartan Potassium	Measurement of absorbances of the standard solutions Second derivative spectrophotometry	At 206.6 nm At 219.6 nm and 228.8 nm	(46)
Lisinopril (stability study)	Classic spectroscopy, first-, second-, third derivative UV-spectroscopy methods		(47)
Losartan	First-derivative zero-crossing technique	at 232.5 nm	(48)
Quinapril and (HCT)	Second-order-derivative zero-crossing	At 211.6 nm and 270.8 nm respectively	(49)
Losartan, paracetamol, phenyl-ephrine and quinine	Regression analysis of spectrophotometric data	Determination Of thermodynamic dissociation constant	(50)
Ramipril (kinetic spectro-photometry)	A mixture of potassium iodate (KIO3) and potassium iodide (KI) in aqueous medium at room temperature	At 253 nm as a function of time	(51)
Benazepril and (HCT)	New wavelet method	Multiple wavelengths	(52)
Atenolol and losartan potassium	UV spectrophotometry and calibration models based on artificial neural networks	range 215–275 nm	(53)
Ramipril	By subtracting the absorption due to olmesartan medoxomil using experimentally calculated absorption factor	At 210 nm	(54)
Losartan potassium and (HCT)	Multivariate analysis of spectral data	In the 220-274 nm region	(55)
Mixtures of felodipine and ramipril	A zero-crossing first- and second-order derivative procedure and a derivative compensation technique		(56)
Enalapril and (HCT)	First derivative spectrophotometry		(57) (58)
Enalapril and losartan	Simultaneous equation method	At 222 and 250 nm for Enalapril and losartan respectively	(59)
(HCT) and Olmesartan	(absorbance ratio), Derivative spectrophotometric method at zero crossing wavelengths.	At 264 nm (isobestic point) and at 271 nm. At 257.8 and 240.2 nm	(60) (61)
Amlodipine besilate and olmesartan	Simultaneous equation method The area under curve method	at 237.5 nm and 255.5 at 242.5-232.5 nm and 260.5-250.5 nm for Amlodipine besilate & olmesartan respectively	(62)
Benazepril HCl	The absorbance and first-, second- and third-order derivative UV spectroscopic methods		(63)
Moexipril HCl	First derivative spectroscopy	238 nm	(64)

5.1.1.2. Visible spectrophotometric methods. The reported visible spectrophotometric methods for the determination of ACEIs and ARBs could be classified according to the following reactions:

(a) Metal complexation
(b) Charge-transfer complexation.
(c) Redox reactions
(d) Ion pair formation
(e) Miscellaneous

Table 5: Summarizes some of the recently reported visible spectrophotometric methods for the analysis of ACEIs and ARBs in pure forms and pharmaceutical formulations by:

(a) Metal complexation

Drug(s)	Reagent	Wavelength	Ref.
Enalapril maleate and ramipril	Copper (II), eosin, and enalapril. Iron (III), thiocyanate, and Ramipril) which is extracted with methylene chloride	533.4 nm 436.6 nm	(65)
Timolol and enalapril maleate	Palladium (II) chloride in buffered medium Palladium (II), eosin, and the two cited drugs	369.4 nm, 362.8 nm for timolol and enalapril maleate, respectively 552.2 and 550.6 nm for timolol and enalapril maleate, respectively	(66)
Lisinopril	Hydroxylamine HCl (HAHC) and dicyclohexylcarbodiimide (DCC) forming reddish brown colored iron (III) hydroxamate complex with iron (III) perchlorate in ethanolic solution of perchloric acid	506 nm	(67)
Ramipril, enalapril maleate and fosinopril	Molybdenum (V) thiocyanate. Or measuring the formed ternary complex after addition of benzalkonium chloride as surfactant	517 nm 545 nm	(68)
Ramipril	Copper (II), eosin and ramipril in the presence of methylcellulose as surfactant	543 nm	(69)
Enalapril	Copper (II), and bromothymol blue, in a slightly alkaline environment	426 nm	(70)
Ramipril	Molybdophosphoric acid in acidic medium	361 nm	(71)

(b) Charge-transfer complexation

Drug(s)	Reagent	Wavelength	Ref.
Lisinopril	Chloranil in aqueous solution of pH 9.5. -dichlone	346 nm	(72)
Enalapril Maleate and lisinopril	2,4-dinitrofluorobenzene to form colored products	580 nm	(73)
Losartan and Lisinopril	7, 7, 8, 8, tetracyanoquinodimethane (TCNQ) and p-chloranilic acid	743 and 525 nm respectively	(74)
Losartan potassium	Study of its charge-transfer reactions with σ-acceptor like iodine and various π-acceptors		(75)
Lisinopril	Chloranil in 1, 4-dioxan–ACN medium		(76)

(c) Redox reactions

Drug(s)	Reagent	Wavelength	Ref.
Benazepril HCl	$KMnO_4$ in the presence of sodium hydroxide	609.4 nm	(77)
Ramipril	$KMnO_4$ in alkaline medium	610 nm	(78)
Enalapril maleate, Ramipril, moexipril and lisenopril	$KMnO_4$ in sulphuric acid medium (method A) Reaction with K_2CrO_4 (method B)	520 nm 610 nm	(79)

(d) Ion pair formation

Drug(s)	Reagent	Wavelength	Ref.
Enalapril	Bromothymol blue (Flow-injection spectrophotometry)	430 nm	(80)
Benazepril HCl	Bromocresol green	412 nm	(81)
Losartan potassium	Calmagite (CT) and Orange-II (O-II)	491 nm (CT) and 486 nm (O-II)	(82)

(e) Miscellaneous

Drug(s)	Reagent	Wavelength	Ref.
Lisinopril	Sodium hypochlorite/phenyl hydrazine (condensation product)	362 nm	(83)
Lisinopril	Ninhydrin (0.3% in acetone)	410 nm	(84)
Ramipril	7-chloro-4-nitrobenzo-2-oxa-1, 3-diazole (NBD-Cl)	465 nm	(85)
Lisinopril	(NBD-Cl) in borate buffer of pH 9	470 nm	
Lisinopril	N-bromosuccinimide in acetone medium	353 nm	(74)
Ramipril	1-chlorobenzotriazole reagent in strong alkaline medium	350 nm	(68)

5.1.1.3. Spectrofluorometric methods. The spectrofluorometric methods for the determination of ACEIs and ARBs may be sub-classified into the following categories:

(a) Methods based on measurement of the fluorescence of the hydrolytic products;
(b) Methods depending on reaction with fluorogenic agents;
(c) Fluorescence quenching methods;
(d) Miscellaneous methods.

(a) Methods based on measurement of the fluorescence of the hydrolytic products

Modification of the fluorescent properties of enalapril maleate in solution after exposure to UV-radiation and the degradation mechanisms was studied[86].

(b) Methods depending on reaction with fluorogenic agents

Ramipril, reacts with 7-fluoro-4-nitrobenzo-2-oxo-1,3-diazole (NBD-F) producing the corresponding fluorescent NBD-ramipril, measured at 530 nm after excitation at 465 nm[87], El Gindy *et al.* used o-phthal-aldehyde in the presence of 2-mercaptoethanol in borate buffer (pH 9.5) for the determination of lisinopril[83], lisinopril was also determined by the formation of a derivative formed with 7-chloro-4-nitrobenzofurazan, the fluorescence intensity of the derivative was measured at 528 nm with excitation at 465 nm[88], also sequential injection analysis was used for the determination of lisinopril based on the reaction with o-phthalaldehyde in the presence of 2-mercaptoethanol (borate buffer medium, pH= 10.6) with The emission of the derivative measured at 455 nm upon excitation at 346 nm[89].

(c) Fluorescence quenching methods

A fluorescence quenching method for the determination of ramipril was applied by forming a ternary complex between copper (II), eosin and ramipril measuring the flourescence at 543 and 300 nm respectively[68].

(d) Miscellaneous methods

The acid-base equilibrium constants of losartan, irbesartan, valsartan, candesartan cilexetil, its metabolite candesartan M1 and telmisartan were determined by spectro-fluorimetry[90], Lisinopril was determined by El Yazbi *et al.*[85] depending on the reaction of the drug with acetyl acetone and formaldehyde to form a colored condensation product with a strong fluorescence at 475 nm and excitation at 410 nm. Losartan and valsartan were determined in urine by fractional factorial design and a central composite design[91].

5.1.1.4. Chemiluminescence methods. Ouyang *et al.* proposed a flow-injection analytical method for the determination of (HCT) based on the chemiluminescence reaction of (HCT) with cerium(IV) in sulphuric acid, sensitized by the fluorescent dye rhodamine 6G[92]. A chemiluminescence (CL) method using flow injection has been used for the determination of enalapril maleate, based on the reaction of the drug with tris(2,2'-bipyridyl)ruthenium(II), Ru(bipyridyl)3(2+) and acidic potassium permanganate[93]. Flow injection (FI) was used for determination of enalapril maleate and atenolol, based on the sensitizing effect of these drugs on the Ce(IV)-sulfite reaction[94]. Ramipril can quench the luminescence intensity of the Sm(3+) ion in Sm(3+)-doxycycline complex at 375 nm in sol-gel matrix, with the emission band of ramipril in DMSO at 454[95].

5.1.1.5. Atomic absorption spectrometric methods. Ayad *et al.* determined ramipril and enalapril maleate by the formation of ternary complex with copper (II) and eosin for enalapril, Fe (III) and thiocyanate for ramipril[63]. Ramipril, enalapril maleate and fosinopril were determined by the formation of ternary complex with molybdenum (V) and thiocyanate[69].

5.1.2. Chromatographic methods

5.1.2.1. Thin-layer chromatographic methods. Table 6 summarizes the most important methods for analysis of ACEIs and ARBs in pure forms and in pharmaceutical dosage forms by TLC.

Table 6: The most important TLC methods for analysis of ACEIs and ARBS in pharmaceutical dosage forms.

Drug(s)	Stationary phase	Mobile phase	Ref.
Losartan potassium (stability testing)	Reversed-phase high-performance TLC		(96)
Benazepril HCl and (HCT)	HPTLC aluminum sheets of silica gel 60 F254	ethyl acetate/methanol/ammonia (85:20:10 v/v)	(97)
Benazepril and (HCT)	HPTLC aluminum sheets of silica gel 60 F254	Ethyl acetate-methanol-chloroform (10:3:2 v/v)	(98)
Captopril, enalapril, lisinopril, quinapril, ramipril and cilazapril	Silica gel and polyacrylonitrile sorbent (PANS)	On silica gel sixteen and on PANS thirteen solvents were used	(99)
Lisinopril, cilazapril, captopril, quinapril and Ramipril	thin layers of aminoplast	Several mobile phases were used	(100)
Quinapril and (HCT)	Silica gel 60 F254 HPTLC plates and octadecylsilane (RP-18) TLC plates	Ethyl acetate-acetone-acetic acid, 8:2:0.5 (v/v) and methanol-0.07 M-phosphate buffer, pH 2.5, 6:4 (v/v), respectively	(101)
Benazepril and cilazapril	silica gel 60 F254 HPTLC plates	Ethyl acetate–acetone–acetic acid–H_2O, 8:2:0.5:0.5 (v/v)	(102)
Cilazapril; enalapril; fosinopril; lisinopril; quinapril; and their active degradation products	Silica gel, cellulose, and polyacrylonitrile	Aqueous ammonium sulfate solutions of different concentration as mobile phases	(103)
Simultaneous analysis of amlodipine and benazepril	Silica gel 60 F254 HPTLC plates prewashed with methanol	Ethyl acetate-methanol-ammonia solution (8.5:2.0:1.0, v/v/v)	(104)
Trandolapril and verapamil	TLCSilica gel 60 F254	Ethyl acetate - ethanol - acetic acid (8:2:0.5 v/v)	(105)
Enalapril maleate & HCT	HPTLC silica gel 60 F254 plates	Chloroform- ethylacetate- methanol (10:1:5 v/v/v)	(106)
Moexipril HCl & HCT	HPTLC silica gel 60 F254 plates	Ethylacetate-chloroform-glacial acetic acid (8:2:0.2 v/v/v)	(106)

Drug(s)	Stationary phase	Mobile phase	Ref.
Lisinopril HCl & HCT	HPTLC silica gel 60 F254 plates	Benzene- methanol- glacial acetic acid (8:2.5:0.4 v/v/v)	(106)
Losartan potassium, atenolol, and (HCT)	HPTLC prewashed silica gel silica gel 60 F254 plates	Toluene- methanol- triethylamine 6.5:4:0.5 (v/v)	(107)
Candesartan cilexetil and (HCT)	(HPTLC) silica gel 60 GF 254 plates	Acetone- chloroform- ethyl acetate-methanol 3:3:3:0.5 (v/v)	(108)
Enantiomers of ketamine and lisinopril	TLC silica gel 60 F 254 plates	Various mobile phases using (+)-tartaric acid or (−)-mandelic acid as mobile phase additives and as impregnating agents	(109)
(HCT), valsartan, candesartan, and enalapril	TLC silica gel 60 F254 plates	Ethyl acetate-tetrahydrofuran-acetic acid (8:2:0.5 v/v) (for candesartan and valsartan with HCT). Butane-1-ol-glacial acetic acid- H_2O (12:3:5 v/v/v) (for enalapril and (HCT))	(110)
Atorvastatin calcium, ramipril, and aspirin	HPTLC silica gel 60 F254 plates	Methanol-benzene-ethyl acetate-glacial acetic acid 0.36:5.6:4.0:0.04 (v/v)	(111)

5.1.2.2. High-performance liquid chromatographic methods. The impressive increase in the use of high-performance liquid chromatography in the past thirty years did not pass the ACEIs and ARBs; it has been used frequently in all fields of research, not only as an assay method but also as a tool for separation of the drugs. Table 7 summarizes some of the recently reported HPLC methods for the analysis of ACEIs and ARBs in pure forms and pharmaceutical formulations.

Table 7: Some of the recently reported HPLC methods for the analysis of ACEIs and ARBs in pure forms and pharmaceutical formulations.

Drug(s)	Column	Mobile phase	Detection	Ref.
Enalapril maleate	LiChrosorb RP-18 (7 µm, 25 cm × 4.2mm)	5mmol L-1-$HClO_4$ in aq. 57% methanol (pH 3.5)	UV (213 nm)	(112)
Ramipril (I) and its optical isomers	Nucleosil 50-5 Spherisorb silica (5 µm) or Sumipax OA-1004	0.4% of ethanol in hexane. hexane - THF (4:1) ethanol - hexane (1:49 or 0.5:95, respectively)	UV (210 nm) UV (254 nm) UV (210 nm)	(113)
Enalapril maleate	A column (Silasorb SPH C18 (7.5 µm,25 cm × 4 mm)	0.05 mol L-1-phosphate buffer (pH 3.0) - ACN (3:2)	UV (215 nm)	(114)
Enalapril maleate	A Nucleosil C18 column (25 cm × 4.6 mm)	ACN - H_2O - methanol (2:1:1)	UV (230 nm)	(115)
Ramipril and its precursors	10 µm LiChrosorb RP-18 column (25 cm × 4.6 mm)	ACN - 5% phosphoric acid (3:7)	UV (220 nm)	(116)
Lisinopril and (HCT)	5 µm ODS Hypersil column (26 cm × 4.6 mm)	H_2O -ACN - triethylamine (pH 5 with aq. phosphoric acid)	UV (220 nm)	(117)
Ramipril and enantiomers of its precursors	Chiralcel OT(+) Column (25 cm × 4.6 mm)	Methanol	UV (254 nm)	(118)
Imidapril HCl	A Chiralpak WH column (25 cm × 4.6 mm i.d.)	3 mmol L-1-aq. $CuSO_4$/CAN (3:1)	UV (230 nm)	(119)

Drug(s)	Column	Mobile phase	Detection	Ref.
Enalapril and felodipine	A 5 µm Spherisorb C8 column (25 cm × 4.6 mm i.d.)	1 mmol L-1-KH_2PO_4 pH 2/ACN (13:7)	UV (215 nm)	(120)
Losartan potassium	(25 cm x 4.6 mm i.d.) Lichosorb10 RP-8 column Phenomenex	75% methanol/25% NaH_2PO_4 (10 m mol L-1, pH 8) and butylparben (1.25 mg⁄ml) as an internal standard	UV (230 nm)	(121)
Enalapril maleate, benazepril HCl, lisinopril dihydrate., and quinapril	Hypersil ODS column(250 mmx4.5mm i.d.	20 mmol L-1 sodium heptasulfonate (pH 2.5), ACN-THF (95/5 v/v)	UV 215nm	(122)
Enalapril maleate and HCT	10 µm Bondapak C18 column (30 cm × 3.9 mm i.d.)	0.025 mol L-1-orthophosphoric acid adjusted to pH 3 with triethylamine/ACN (21:4)	UV (226 nm)	(123)
Benazepril or cilazapril	10 µm LiChrosorb RP-18 column (25 cm × 4 mm i.d)	Phosphate buffer pH 2.4/ACN(7:3), using enalapril maleate in methanol as internal standard	UV (211 nm)	(124)
Amlodipine and enalapril maleate	C18 ODS Hypersil column (25 cm × 4.6 mm)	0.025 mol L-1-KH2PO4/ACN (3:2), paracetamol was used as the internal standard	UV (238 nm)	(125)
Cilazapril and its degradation product cilazaprilat	microBondapak C18 column	Methanol-5 mmol L-1 phosphoric acid (50:50, v/v)	Amperometric detection using a glassy carbon electrode at 1350 mV	(126)
Cilazapril	LiChrospher C8 (5 µm) column (25 cm × 4.6 mm i.d.)	of acetonitrile, methanol and phosphate buffer (pH 2.0) (60:10:30, v/v/v)	UV (212 nm)	(127)
Benazepril, its enantiomer, two diastereomers	A Kromasil C8 (5 µm) column (25 cm × 4.6 mm i.d.)	0.01-0.06 mol L-1-KH2PO4 buffer of pH 3-7 containing various proportions of an organic modifier	UV (240 nm)	(128)
(HCT) and lisinopril	5 µm R-LiChrosorb C18 column (20 cm × 4.6 mm i.d.)	H_2O (pH 3.8 with acetic acid)/ACN (4:1)	UV (213 nm)	(129)
Benazepril HCl and (HCT)	BDS C-18 micro-bore analytical column	A mixture of 0.025 mol L-1 sodium dihydrogen phosphate (pH 4.8) and ACN (55:45, v/v)	UV (250 nm)	(130)
Losartan potassium and (HCT)	Analytical (125x4.0 mm i.d. Erbasil , 5 µm) column and (20x4.6 mm i.d., 40 µm) guard column	A mixture of ACN and phosphate buffer (pH 4.0; 0.1 M) (35:65, v: v)	UV (230 nm)	(131)
Enalapril	A Supelco LC 18 (5 µm, 250x 4.6 mm i.d.) and a guard column (20x4.6 mm i.d.)	20 mmol L-1 phosphate buffer pH 2:ACN (60/ 40, v/v)	Photodiode array detector (215 nm)	(132)
HCT and Losartan potassium	10 µm µBondapak C18 column (30 cm × 3.9 mm i.d.)	Aqueous methanolic mobile phase (pH = 3)	UV (270 nm)	(133)
Trandolapril	LiChrosorb RP-18 column	ACN -0.067 mol L-1 phosphate buffer pH 2.7 (7:3, v/v), benazepril was used as an internal standard	UV (220 nm)	(134)

Drug(s)	Column	Mobile phase	Detection	Ref.
Ramipril and (HCT)	5 µm ODS Hypersil column (25 cm × 3.9 mm i.d.)	Aqueous 45% ACN containing 0.1% triethylamine, adjusted to pH 3.0	Photodiode array (210, 278 nm) for ramipril and HCT (210) for simultaneous determination	(135)
Enalaprilat	PH-resistant Shodex C18 column	H_2O –ACN orthophosphoric acid (85% W: V) (90:10:1, v: v: v) pH 2.8	UV (215 nm)	(136)
Enalapril maleate, enalaprilat, and lisinopril	Column packed with 5 mm Spherisorb Octyl (Waters)	20 mmol L-1 phosphate buffer at pH 2.0 and 7.0 containing various amounts of ACN at different temperatures	UV (215 nm)	(137)
Benazepril HCl, fosinopril sodium and ramipril, and (HCT)	LC-8 (125×4.0 mm i.d.; 5 µm)	20 mmol L-1 sodium heptanesulphonate (pH=2.5) and methanol (32:68 v/v)	UV detection	(138)
Fosinopril sodium and (HCT)	C18 column	Aqueous 40% methanol, pH 4 with orthophosphoric acid, sulfamethoxazole as an internal standard	UV detection	(139)
Benazepril HCl and (HCT)	ODS column	ACN and H_2O (35:65 v/v) pH 3.3	UV (240 nm)	(98)
Cilazapril and (HCT)	5 µm Lichrospher 100 RP-18c column (25 cm × 4 mm i.d)	Methanol-phosphate buffer	UV (254 nm)	(140)
Trandolapril and verapamil	LiChrosorb RP18 column	ACN-methanol-phosphate buffer of pH 2.7 (2:2:1)	UV (220 nm)	(141)
Losartan potassium and (HCT)	A reversed-phase column	0.01 N sodium dihydrogen phosphate: methanol: ACN (8:2:1 v/v/v) pH 5.5	UV (265.0 nm)	(142)
Losartan potassium and (HCT)	C18 reversed-phase column	A mixture of 10mmol L-1-KH2PO4/ACN (13:7) pH 3.1	UV (232 nm)	(143)
Ramipril and HCT (stability indicating method)	A supelcosil LC-8 column (5 microm), 15 cm x 4.6 mm i.d.	ACN: sodium perchlorate solution (0.1 M) pH 2.5±0.2 (46:54 v/v), clobazam as an internal standard	UV (210 nm)	(144)
Benazepril	BDS C-18 column (250×3.0mm i.d., 5 µm)	0.020 mol L-1 disodium hydrogen phosphate, pH 3.0 with phosphoric acid, and methanol (40:60, v/v)	UV (250 nm)	(145)
Lisinopril	A Supelcosil LC 5 column (250x4.6 mm i.d.) and a guard column (20x4.6 mm i.d.)	A mixture of 20 mmol L-1 phosphate buffer pH 7-CAN (90/10, v/v)	UV (215 nm)	(146)
Lisinopril, enalapril maleate, ramipril and perindopril tert-butylamine	A stainless steel cylinder (50mm × 7.5mm i.d.) was used as a reservoir for packing materials, and connected to a column (10mm × 4.6mm i.d.)	Ethanol and distilled–deionized H_2O (1:1)	UV(lisinopril, enalapril maleate ,ramipril and perindopril) at (262, 272, 265, 252 nm respectively)	(147)

Drug(s)	Column	Mobile phase	Detection	Ref.
Enalaprilat	A Supelco LC 18 (250x4.6 mm i.d., 5 µm) and a guard column (20x4.6 mm i.d.)	20 mmol L-1 phosphate buffer pH 7: ACN (90/10 v/v)	UV (215 nm)	(148)
Lisinopril; methyl paraben; propyl paraben	Platinum EPS C8 (250mm×4.6mm i.d.,5 µm), Mac-Mod Hydrobond AQ C8 (150 mm×4.6 mm i.d., 5µm) and a Hewlett-Packard RP-8 Licrosorb (200 mm×4.6 mm i.d., 10 µm)	Potassium phosphate buffer (30 mmol L-1, pH 2.2): ACN (91:9, v/v)	Diode array detector (215 nm)	(149)
Enalapril maleate and (HCT)	Waters Symmetry® C18 Column 5 µm 4.6 × 250 mm.	0.2 mol L-1 acetate buffer and ACN (v/v, 60:40) using losartan as internal standard.	Diode array detector (220, 230, 240, 250, and 260 nm)	(150)
Fosinopril sodium	X-Terra 50-mmx4.6-mm, 3.5-mum particle size column	Micro emulsion containing 0.9% w/w of cyclohexane, 2.2% w/w of sodium dodecyl sulphate (SDS), 8.0% w/w of n-butanol and 88.9% of aqueous 25 mM disodium phosphate, pH 2.8 with 85% orthophosphoric acid	UV (220 nm)	(151)
(HCT) and losartan potassium	4.6 mm i.d. × 250 mm, 5 µm particle, Waters Symmetry C18 reversed-phase column	Acetate buffer (0.2 M, pH 4.8)-ACN 60: 40(v/v),using enalapril maleate as internal standard (IS)	Photodiode array at (250, 255, 260, 265, and 270 nm)	(152)
Amlodipine besilate, and benazepril HCl (Stability indicating study)	a Zorbax SB C18, 5 microm, 250 mm x 4.6 mm i.d.	Phosphate buffer and ACN 65:35 (v/v), pH adjusted to 7.0	Photodiode array detector (240 nm)	(153)
Ramipril (stability in solvents at different pH)	A Nucleosil 100-S 5 microm C18, 250 mm x 4.6 mm i.d.	ACN: sodium perchlorate	UV (210 nm)	(154)
Losartan potassium, ramipril, and HCT	150 mm × 4.6 mm i.d., 5 µm particle, Cosmosil C18 column.	0.025 mol L-1 sodium perchlorate-ACN, 62: 38 (v/v), contains 0.1% hepta-nesulphonic acid, pH 2.85 with orthophosphoric acid	UV (215 nm)	(155)
Felodipine with either (+)-metoprolol Tartrate salt or ramipril	A reverse phase Hypersil BDS C18 3 µm (150 × 4.6) column.	Resolution of the two binary mixtures separately, accomplished by a mobile phase of 0.015 mol L-1 sodium dihydrogen phosphate monohydrate-methanol-ACN (40 : 30 : 30, v/v/v) at pH 6.5 for the determination of felodipine with metoprolol and at pH 2.5 for felodipine with ramipril	UV (230 nm) for felodipine & metoprolol (pH 6.5) And UV (210 nm) for felodipine & ramipril (pH 2.5)	(156)
Enalapril maleate and enalapril maleate tablet formulations	Hypersil ODS, 5 µm particles, 250mm×4mm i.d. column	Phosphate buffer (pH 2.0):ACN 58:42 (V/V)	UV (215 nm)	(157)

Drug(s)	Column	Mobile phase	Detection	Ref.
Candesartan cilexetil	Synergy Polar-RP (150mm×2 mm, 4µm) with a guard column (4mm×2 mm, same packing material)	Solvent A (0.1% formic acid (v/v) with 1 mmol L-1ammonium formate) and solvent B (ACN: 0.1% formic acid 95:5 (v/v) with 1 mmol L-1ammonium formate)	UV (254 nm)	(158)
(HCT) and candesartan cilexetil	Phenyl-2 column	25: 27: 0.2 mixture of 0.02 mol L-1 potassium dihydrogen phosphate, methanol, and triethylamine	UV (271 nm)	(159)
HCT, lisinopril, and their impurities	C18 column (4.6 mm × 20 mm), 3.5 µm particle size	A gradient 7: 93 (v/v) ACN-25 m mol L-1 potassium dihydrogen phosphate, pH 5, and 50: 50 (v/v) ACN-25 mmol L-1 potassium dihydrogen phosphate. Methylparaben as internal standard	UV (215 nm)	(160)
Lisinopril (stability indicating study)	Bondapak C18 reversed phase column	Phosphate buffer (pH = 5) - ACN - triethylamine (90: 10: 0.1) mixture	UV (209 nm)	(161)
Fosinopril sodium impurities	SunFire RP C18, 3.5 µm, 4.6×100 mm.	Methanol–10 m mol L-1 ammonium acetate buffer–glacial acetic acid (80:19.5:0.5 v/v/v)	Mass detector (220 nm)	(162)
Candesartan cilexetil	A250 mm × 4.6 mm, 5 µm particle, CN column	50:50 (v/v) mixture of phosphate buffer, pH 3.0, and CAN	UV(210 nm)	(163)
Lisinopril, aspirin and one each among atenolol/(HCT) and atorvastatin /simvastatin/pravastatin	RP (C-8) column	ACN: phosphate buffer (pH 2.3)	UV (210 nm)	(164)
(HCT) and losartan potassium	A monolithic C (18) column (25 mm x 4.6 mm i.d.)	10 mmol L-1potassium dihydrogen phosphate (pH 3.1)-ACN-methanol (65:33:2 v/v/v)	Diode array detector, UV at 226 nm	(165)
(HCT) and losartan potassium	Monolithic column, Chromolith Flash RP-18e column (25 mmx4.6 mm i.d.)	10 m mol L-1 potassium dihydrogen phosphate (pH 3.0):ACN: Methanol (60:30:10 v/v/v)	UV (226 nm)	(166)
Ramipril and moexipril HCl	A cyanoproyl column	40: 60 (v/v) aqueous 0.01 mol L-1 ammonium acetate buffer (pH 6)-methanol	UV (210 nm)	(167)
Telmisartan and ramipril	C18, 25-cm	Buffer-ACN (55: 45 v/v). The buffer 0.1 mol L-1 sodium perchlorate, pH 3.0 with trifluoroacetic acid	Photodiode array detector (215) nm	(168)
Enalapril maleate (forced degradation study)	C18 column	ACN and phosphate buffer (pH 3). ACN and H_2O, (pH 3) adjusted with formic acid	UV (210 nm) LC-MS	(169)
Amlodipine besilate and benazepril HCl	BEH C8 (100 mm x 2.1 mm, 1.7 µm)	Phosphate buffer pH 3.0 (0.01 mol L-1) and ACN:	photo diode array (237	(170)

Drug(s)	Column	Mobile phase	Detection	Ref.
		methanol 45:55	nm)	
Quinapril and (HCT)	RP-C18 Gemini (150×4.5 mm, 5 µm)	0.1% v/v triethylamine (pH 3.5), containing 1 mmol L-1 of hexane sulphonic acid: ACN (30:70% v/v)	photo diode array (220 nm)	(171)
Losartan potassium, atenolol, and (HCT)	Zorbax C-18, 50 mm x 4.6 mm, 1.8 µm)	(H_2O: ACN : triethylamine : orthophosphoric acid (60: 40 : 0.1 : 0.1, v/v)	UV (225 nm)	(172)
Tranexamic acid and losartan potassium		ACN: H_2O (50:50), pH 2.6 with phosphoric acid	UV (205 nm)	(173)
Losartan potassium	Octylsilane column (100 mm x 4.6 mm, 5 µm)	potassium phosphate buffer (pH 6.2; ACN (65:35, v/v)	UV (254 nm)	(174)
Candesartan cilexetil (Stress degradation)	Luna C-18 (150 mm×4.6mm 5 µm) column	ACN and potassium dihydrogen orthophosphate buffer (pH 2.8; 0.01M) in a gradient mode	LC-MS/TOF	(175)
Lisinopril and its RSS enantiomer	A Hypersil ODS2 column (4.6 × 250 mm, 5 µm)	20 mmol L-1 ammonium acetate buffer (pH 4.5) with glacial acetic acid and ACN (90 : 10, v/v)	Electrospray ionization/ Tandem mass spectrometry	(176)
Atorvastatin calcium, ramipril and aspirin	a Phenomenex Luna C18 (250 mm x 4.6 mm , 5 µm)	0.1%, orthophosphoric acid buffer: ACN : methanol (45 : 50 : 5 v/v/v), pH 3.3	Uv (210 nm)	(177)
Ramipril and telmisartan	A Genesis C18 (5 mum ,4.6x250 mm)	0.01 mol L-1 potassium dihydrogen phosphate buffer (pH 3.4) : methanol: ACN (15:15:70 v/v/v)	Uv (210 nm)	(178)
Enalapril and losartan	Kromasil C18 column (5 µm, 250 x 4.6 mm)	Methanol: H_2O: ACN (45:35:20% v/v)	UV (224 nm)	(61)

5.1.2.3. Gas chromatographic methods. Lisinopril was analyzed on a stainless-steel column (1.9 m × 4 mm i.d.) packed with 5% of OV-1 on Chromosorb WHP (100-120 mesh) and operated at 240°C, with N2 as carrier gas (22 ml/min) and dual FID[179]

5.1.2.4. Capillary electrophoretic methods. They are classified into:

(a) Capillary zone electrophoresis (CZE);
(b) Micellar electrokinetic capillary chromatography (MEKC).

(a) Capillary zone electrophoresis (CZE)

Capillary electrophoretic separation of eight ACEIs: enalapril, lisinopril, quinapril, fosinopril, perindopril, ramipril, benazepril and cilazapril by means of two phosphate buffers (each 100 mM) pH 7.0 and pH 6.25, respectively[180]. Cilazapril and its active metabolite cilazaprilat were analyzed using 60 mM borate buffer pH 9.5, using current of 82 mA and detection at 214 nm[181]. Simultaneous determination of (HCT) and several ACEIs was achieved by CZE using sodium phosphate buffer, pH 7.25, 100 mM), 20 kV as applied voltage and detection at 214 nm[182], quantification of enalapril, lisinopril, quinapril, fosinopril, perindopril and benazepril is applied by CZE using two phosphate buffers (each 100 mM) at pH 7.0 and 6.25, respectively[183]. Capillary electrophoresis was used to determine losartan and (HCT) by using mixture of 50 mM ammonium acetate pH 7, water, acetonitrile (1/1.5/7.5) as mobile phase[184]. (CZE) method was optimized for the separation of five ARBs (losartan, irbesartan, valsartan, telmisartan and eprosartan) and two of their metabolites (EXP 3174 and candesartan M1)using 50 mM potassium dihydrogen phosphate: boric acid (25:75 v/v) buffer at pH

5.5 in the presence of 5% methanol and application of 25 kV voltage[185].

Alkylulfonic additives were used for the determination of lisinopril, ramipril, benazepril, quinapril by CZE[186], the usefulness of alkylsulphonates as ion-pairing agents was also investigated to optimize a capillary electrophoretic separation method for eight ACEIs enalapril, lisinopril, quinapril, fosinopril, perindopril, ramipril, benazepril, and cilazapril[187].

Determination of quinapril and its combination with (HCT) was carried out by Prieto *et al.* using enalaprilat as internal standard at 25°C[188]. CZE was used to simultaneously separate (HCT) and six ARBs[189]. Stellwagen *et al*. found that the two isomeric forms of enalapril can be separated using capillary buffers having pH values in the dissociation ranges of the enalapril carboxyl group, pKa (cis) and pKa (trans) of 2.6 and 3.1, and of the Enalapril amine group, pK(cis) and pK(trans) of 5.9 and 5.6.[190]. The separation of the rotational cis-trans isomeric enalaprilat has been performed in an aqueous 20 mM borate buffer at pH 9.3.by CZE[191]. The separation of enalapril, its derivative Enalaprilat, the diuretics Xipamide and (HCT), was achieved by CZE at a potential of 30 kV, the detection carried out at 206 nm and 35°C, respectively[192]. (CZE) method was developed to achieve the separation and determination of trandolapril and verapamil using 10 mM phosphate buffer at pH 7.0, and a voltage of 15 kV[193].

(b) Micellar electrokinetic capillary chromatography (MEKC)

Determination of enalapril maleate (I) and its degradation products were determined using buffer solution of 80 mM-Na borate - 100 mM-Na dodecyl sulfate (pH 8.5) or 50mM-Na phosphate - 40mM-Na dodecyl sulfate (pH 8.25) at 20° to 25°C[194]. Thomas *et al*.[195], evaluated a mixed MEKC method for validated pharmaceutical quality control of enalapril maleate. MEKC was used to simultaneously separate (HCT) and six ARBs[187].

5.1.3. Electrochemical methods

Several electrochemical methods are reported for determination of ACEIs and ARBs. This section summarizes the most recent methods for their analysis.

5.1.3.1. Direct potentiometry using ion selective electrodes. Stefan *et al.*[196] developed an amperometric biosensor, based on L-amino acid oxidase for the analysis of the S-enantiomer of S-enalapril, and S-ramipril. Potentiometric enantioselective membrane electrode for S-enalapril assay was constructed and used in zero-current chronopotentiometry using a Ag/AgCl/0.1M-KCl reference electrode and glassy carbon counter-electrode[197]. Construction and use of an enantioselective membrane electrode based on graphite paste impregnated with chiral selector is described for determination of S-ramipril[198]. A coated-wire benazepril-selective electrode was constructed for determination of benazepril[199].

5.1.3.2. Voltammetry. Cyclic voltammetry (CV), direct current polarography (DCt), differential pulse polarography (DPP) and alternating current polarography (ACt) were used for the determination of ramipril[200]. Highly sensitive voltammetric method was developed for the determination of benazepril and ramipril after treatment with nitrous acid and measurement of the resulting cathodic current[201]. A sensitive adsorptive stripping voltammetric (ASV) method was applied for the measurement of cilazapril in 0.04 M Britton-Robinson buffer (pH 9.0) solution followed by differential pulse voltammetry (DPV)[202], Square wave voltammetry (SWV) was used for determination of cilazapril, quinapril and ramipril which are reduced at a hanging mercury drop electrode in the pH range 3.5-13 using Britton-Robinson buffers as supporting electrolyte and KCl as ionic medium[203]. Differential pulse anodic stripping voltammetric (DPASV) method is described for the determination of alendronate sodium, desferrioxamine mesylate and lisinopril, the method is based on the formation of labile drug-Cu (II) complex[204]. The electrochemical behavior of candesartan cilexetil and quinapril was investigated using different voltammetric techniques such as (DPV), (CV), (SWV) and chronoamperometry[205&206.] Square-wave adsorptive stripping voltammetric method was developed for the determination of candesartan cilexetil in bulk form and pharmaceutical formulations by complex formation with Cu (II)[207].

5.2. Analysis in biological fluids

5.2.1. Spectroscopic methods

5.2.1.1. Spectroflourometry. Determination of ramipril in plasma by use of 7-fluoro-4-nitrobenzo-2-oxo-1, 3-diazole (NBD-F) producing the corresponding fluorescent NBD-ramipril, measuring the fluorescence of solution at 530 nm after excitation at 465 nm[85].

5.2.1.2. Chemiluminescence methods. A chemiluminescent method using flow injection (FI) was used for determination of enalapril maleate and atenolol in both urine and serum, based on the sensitizing effect of these drugs on the Ce (IV)-sulfite reaction[94].

5.2.2. Chromatographic methods

5.2.2.1. High-performance liquid chromatographic methods. This technique is the most frequently applied technique for the determination of ACEIs & ARBs in biological fluids (blood, plasma, urine, cerebrospinal fluid, etc.), animal tissues, food, etc. Table 8 summarizes the recent HPLC reported methods for the analysis of ACEIs & ARBs in biological fluids, animal tissues, food, etc.

Table 8: The recent reported HPLC methods for the analysis of ACEIs & ARBs in biological fluids, animal tissues, food, etc.

Drug(s)	Column	Mobile phase	Detection	Ref.
Quinapril and quinaprilat	Spherisorb ODS-II column (12.5 cm × 4.6 mm, i.d., 5 µm)	H_2O - methanol - ACN (3:8:9)	Fluorimetric detection (at 360 and 440 nm)	(208)
Losartan and its metabolite	A cyano column	ACN and phosphate buffer at pH 2.5	UV (254 nm)	(209)
Lisinopril	Mu Bondapak c18 column	ACN (60 ml), methanol (10 ml) and tetrahydrofuran (10 ml) in 15 m mol L-1 phosphate buffer (920 ml) at pH 2.90, using enalaprilat as internal standard	UV (206 nm)	(210)
Quinapril and quinaprilat	C8 column (250 x 4.6 mm i.d, 5 µm)	0.01% triethylamine (pH adjusted to 2.00 with phosphoric acid)-ACN (45:55, v/v)	Radiochemical detection	(211)
Candesartan cilexetil	AM-312 (5 µm ODS, 150 x 6.0 mm i.d.)	Isocratic H_2O -ACN-trifluoroacetic acid (70 : 30 : 0.1, v/v/v)	Tandem mass spectrometry	(212)
Losartan and its major metabolite, EXP-3174	A Hypersil Phenyl (150 mmx3.2 mm i.d., 3 µm)	25 m mol L-1 potassium phosphate and ACN pH 2.2	Fluorescence Detector at 250 and 375 nm)	(213)
Enalapril	Spherisorb C8 column (200 mm x 4.6 mm, i.d., 5 µm)	Ethanol—H_2O --10% H3PO4--triethylamine (30:70:1.5:0.1)	UV (215 nm)	(214)
Imidapril and imidaprilat	A Symmetry C18 column (100x2.1 mm i.d., 3.5 µm)	ACN–0.05% (v/v) formic acid (1:3, v/v)	Electrospray ionization tandem mass spectrometry	(215)
Losartan and its major metabolite, EXP-3174	A reversed-phase C18 column	An isocratic consisting of [0.1% triethylamine-0.1% acetic acid (pH 7.1)]-ACN (65:35, v/v)	Electrospray ionization tandem mass spectrometry	(216)
Fosinopril and fosinoprilat	polymer-based C18 column (Asahipak ODP	Methanol and 10 m mol L-1 ammonium acetate, pH 5.5.	Electrospray tandem mass	(217)

Drug(s)	Column	Mobile phase	Detection	Ref.
	PVA-C18, 2x50 mm)		spectrometry	
Losartan, irbesartan, Valsartan, and candesartan cilexetil and its metabolite candesartan M1	A μBondapak C18 column.	Mixtures of ACN and 0.1 mol L-1 acetate buffer, pH 4	UV (254 nm)	(218)
Losartan and its active metabolite EXP3174	(250 x 2 mm i.d.) C18 reversed phase column preceded by a 4 x 4 mm guard column	0.01 mol L-1 ammonium phosphate: ACN: methanol (6:3:1) containing 0.02 % sodium azide and 0.04% TEA, pH 3.2	UV (254 nm)	(219)
Fosinoprilat	Luna C8 analytical column (2 x 50 mm,i.d. 3 μm)	Methanol and H_2O with 10 m mol L-1 ammonium acetate	Positive ion Electrospray tandem mass spectrometry	(220)
Cilazapril and cilazaprilat	MicroBondapak C18 column	Methanol-10 m mol L-1 phosphoric acid (50:50 v/v), enalapril maleate as internal standard	UV (206 nm)	(221)
Losartan potassium and HCT	a C18 reversed-phase column	10m mol L-1-KH2PO4/ACN (13:7) pH 3.1	UV (232 nm)	(143)
Losartan, irbesartan, valsartan, candesartan cilexetil and its metabolite candesartan MI	reversed-phase column, muBondapak C18	ACN-5 m mol L-1 acetate buffer, pH 4	Fluorimetric (At250 and 375 nm)	(222)
Quinapril and quinaprilat	C18 Symmetry column	Two mobile phases: tetrabutyl ammonium hydrogensulfate (10 mM , pH 7)-ACN (62:38, v/v) for quinapril, and (25:75, v/v) for quinaprilat	UV (215 nm)	(223)
Ramipril and ramiprilat	Inertsil Octyl column (50x2.1 mm, i.d, 5 μm)	ACN, methanol and 0.1% formic acid (4:4:5, v/v)	Tandem mass spectrometry	(224)
Candesartan cilexetil, and HCT	A Supelcosil C18 (15 cm × 4.6 mm, i.d. 5 μm)	10m mol L-1-potassium dihydrogen phosphate/methanol/ACN (2: 80: 18, v/v/v), pH 2.5	Photodiode array detector	(225)
Lisinopril	Kromasil C18 (250 × 3.2 mm, i.d. 5 μm)	50m mol L-1 ammonium formate buffer (pH 3)/ACN/methanol (72:7:21, v/v/v)	Tandem mass spectrometry	(226)
Losartan and EXP3174	Cyano column (50x2.1 mm, i.d.3 μm)	ACN: 0.2% formic acid (55:45, v/v)	Tandem mass spectrometry	(227)
Lisinopril	C18-column	Methanol and 0.02 mol L-1 phosphate buffer pH 3.2	Fluorimetric (at 383 and 477 nm)	(228)
Lisinopril	C8 analytical column	ACN/ H_2O (60:40, v/v) + 20 m mol L-1 acetic acid + 4.3 m mol L-1 of triethylamine	Electrospray ionization coupled to tandem mass	(229)

Drug(s)	Column	Mobile phase	Detection	Ref.
			spectrometry	
Enalapril and enalaprilat	A Zorbax Extend-C(18) column	Methanol– H_2O –formic acid (70:30:1, v/v/v)., daidzein as internal standard	Tandem mass spectrometry	(230)
Fosinoprilat	Bakerbond ENV (4.6 mm x 150 mm i.d, 5 µm)	1.0% (w/v) of di-isopropyl ether, 2.0% (w/v) of sodium dodecyl sulphate (SDS), 6.0% (w/v) of n-propanol and 91% (w/v) of aqueous 25 m mol L-1 di-sodium hydrogen phosphate, pH 2.8	UV (220 nm)	(231)
Imidapril HCl	XTerra MS C18 column (2.1 x 150 mm i.d., 3.5 µm)	ACN-0.1% formic acid (67:33, v/v) (pH 2.4), using ramipril as an internal standard	Tandem mass spectrometry	(232)
Benazepril HCl and benazeprilat	C18 silica (250mm×4.6 mm i.d; 5 µm)	ACN and 0.1% formic acid aqueous solution	Electrospray-mass spectrometry	(233)
Losartan	A Chromolith Performance (RP-18c, 100 x 4.6 mm)	Disodium hydrogen phosphate buffer-ACN (60:40 v/v) (pH 3.5)	UV (254 nm)	(234)
Lisinopril	YMC-Pack-Octyl analytical column (50 mm×4.0 mm i.d.)	Isocratic 75% MeOH, 25% 10m mol L-1 formic acid and 5mmol L-1 ammonium acetate in H_2O (v/v), using enalaprilat as internal standard	Tandem mass spectrometry	(235)
Candesartan, losartan, irbesartan, valsartan and telmisartan	Betasil C18 column (250 mm×4.6 mm i.d.; 5 µm)	ACN–5mmol L-1 NaAc buffer solution (pH 3.5) (40:60; v/v)	UV (250 nm) Fluorescence (at 250 and 380 nm)	(236)
Trandolapril	X-Terra C8 MS column (150 mm × 4.6 mm i.d., 5 µm)	Isocratic acetic acid 20 mmol L-1 and triethylamine 4.3 m mol L-1 /ACN (40:60 (v/v))	Tandem mass spectrometric	(237)
Benazepril, benazeprilat and HCT	A reversed-phase porous graphitized carbon (PGC) analytical column (2.1 x 125.0 mm i.d., 5 µm)	55% ACN in isocratic system of H_2O containing 0.3% v/v formic acid, using chlorthalidone as internal standard	Electrospray ionization mass spectrometry	(238)
Ramipril and ramiprilat	A Waters Atlantis C18 column (2.1 mm x 100 mm, 3 µm)	0.1% formic acid-methanol (25:75, v/v), using enalapril as an internal standard	Tandem mass spectrometry	(239)
Perindopril and perindoprilat	X Terra MS C8, (30 mm×2.1 mm, 3.5 µm)	0.1% (v/v) aqueous ammonia solution: methanol - 20:80 (v/v), using ramipril as internal standard	Tandem mass spectrometry	(240)
Trandolapril and trandolaprilat	a Chromolith RP-18 column (100mmx 4.6mm i.d, 5 µm)	Isocratic mixture of 10mmol L-1 ammonium acetate/methanol (1:99, v/v)	Electrospray ionization tandem mass spectrometry	(241)
Irbesartan	ODS-C-18 column (100 mm x 4.6 mm i.d., 5 µm)	0.01 mol L-1 potassium dihydrogen phosphate buffer (containing 0.07% triethylamine as peak modifier, pH 3.0) and ACN	Fluorescence detection (at 259 and 385 nm)	(242)

Drug(s)	Column	Mobile phase	Detection	Ref.
		(66:34, v/v)		
Cilazapril and cilazaprilat	YMC C8 reversed-phase chromatographic column	10 mmol L-1 ammonium formate buffer-methanol (10 : 90, v/v; pH 3.2), using enalapril as internal standard	Electrospray ionization tandem mass spectrometry	(243)
Lisinopril	Phenomenex Luna 5µ, C18 (2) column	10 mmol L-1 ammonium acetate buffer (pH 5.0)-methanol (70: 30, v/v, enalaprilat as internal standard	Tandem mass spectrometry	(244)
Captopril	Chromolith C18 column (50 mm×4.6 mm, 5 µm)	Methanol and H_2O (65:35, v/v) (pH 3.1)	Electrospray ionization mass spectrometry	(245)
Enalapril and enalaprilat	C18 column	Methanol-20 mmol L-1 ammonium acetate (53: 47, v/v) containing 0.15% trifluoroacetic acid (v/v), pH 3.0, using benazepril HCl as internal standard	Electrospray ionization mass spectrometry	(246)
Fosinopril and fosinoprilat	LiChrospher-C8 column (250 mm×4.6 mm I.D. 5 µm)	Eluent A and eluent B, methanol as eluent A and 10 mmol L−1 ammonium acetate aqueous was as eluent B(gradient elution) using zaleplon as internal standard	Tandem mass spectrometric	(247)
Benazepril and Benazeprilat	A Hypersil BDS C18 (300 mm×4.6 mm, 5 µm)	10 mmol L-1Phosphate buffer (pH 2.6) and ACN mixture, using riluzole as an internal standard	UV (237nm)	(248)
Metoprolol tartarate and ramipril	A C8 column, (50 mm×3 mm i.d., 3 µm)	Methanol: 10 mmol L-1 ammonium formate buffer (97:3, v/v)	Electrospray ionization tandem mass spectrometry	(249)
(HCT), quinapril and its metabolite quinaprilat	Hypurity C8 (100 mm×2.1 mm i.d., 5 µm)	0.5% (v/v) formic acid: ACN (25:75, v/v)	Tandem mass spectrometry	(250)
Ramipril and ramiprilat	a Diamonsil C18 column (150 mm × 4.6 mm i.d., 5 µm)	1% formic acid-ACN (25 : 75, v/v), using enalapril as the internal standard	Tandem mass spectrometry	(251)
Quinapril and quinaprilat	Acquity UPLC BEH C18 column)	ACN– H_2O –formic acid (70:30:0.1, v/v/v)	(UPLC-MS/MS)	(252)
Irbesartan	Zorbax Xclipse XDB C18 column (150 x 4.6 mm, i.d., 5 µm)	ACN: 0.1% formic acid (37:63, v/v)	Fluorescence at 250 and 370 nm	(253)
Losartan, telmisartan, and valsartan	Chromolith monolithic column (25 mm×4.6 mm)	5mmol L-1 phosphate buffer (pH 3.8)-ACN-methanol (65:20:15, v/v/v)	Fluorescence at 259 and 399 nm	(254)
(HCT), cilazapril and cilazaprilat	A Zorbax Eclipse XDB-C18 column	Methanol and 10 mmol L-1 phosphate buffer (pH 2.3) (gradient elution)	UV (206 nm)	(255)
Chlorthalidone, valsartan, valsartan-M1, fluvastatin	C18 Atlantis column (100 mm x 3.9 mm, 3 µm)	ACN and H_2O containing 0.01% of formic acid and 10 mmol L-1 of ammonium formate (pH 4.1)	UV and fluorimetric detectors	(256)
Ramipril and ramiprilat	Platinum C18 column (100 mm×4.6 mm, 3 µm)	Methanol/ H_2O (70:30, v/v) with 15mmol L-1 ammonium	LC–MS/MS	(257)

Drug(s)	Column	Mobile phase	Detection	Ref.
		formate		
Enalapril and enalaprilat	Ultimate XB-C(18) column (50 mm x 2.1 mm, i.d., 3 µm)	Methanol- H_2O -formic acid (62:38:0.2, v/v/v)	HPLC-MS/MS	(258)
Enalapril, and 19 other drugs.acenocoumarol, and spironolactone	RP-18 endcapped; (250x4 mm; 5µm) , equipped with guard column Li Chrosphere 100 RP-18 endcapped (4x4 mm; 5 µm)	ACN, methanol and 0.05% trifluoroacetic acid in H_2O using a gradient elution program	Diode array detector	(259)
Olmesartan and (HCT)	XTerra MS C18 column (2.1 mm×50 mm, 3.5 µm)	ACN/0.05% formic acid/methanol (60/36/4, v/v/v)	(HPLC-MS/MS)	(260)
Moexipril	C18 column	methanol and 0.1% formic acid buffer (85:15, v/v)	HPLC-MS/MS	(261)

5.2.2.2. Gas chromatographic methods. Benazepril, and its active metabolite, benazeprilat, were determined in plasma and urine was made by capillary gas chromatography - mass-selective detection after derivatization with diazomethane[262], determination of enalapril and its active metabolite enalaprilat in plasma and urine was developed by (GC/MS) through drevatization with diazomethane and trifluoroacetic anhydride, detection made by ion monitoring at m/z 288 (enalaprilat) and 302 (enalapril)[263]. Quinapril and its active metabolite, quinaprilat were determined in human plasma and urine by gas chromatography-negative-ion chemical ionization mass spectrometry[264]. (GC/MS) method was developed for the determination of three metabolites of imidapril, in plasma and urine by drevatization with pentafluorobenzyl bromide and heptafluoro-n-butyric acid anhydride[265]. Determination of the dioxopiperazine metabolites of quinapril in plasma and urine was performed by capillary column gas chromatography-electron-impact mass spectrometry with selected-ion monitoring, the method is applicable to pharmacokinetic studies[266].

Simultaneous determination of moexipril and its active metabolite, in human plasma was carried out by gas chromatography - negative-ion chemical ionization mass spectrometry[267], (GC-MS) screening procedure was developed for the detection of benazepril, enalapril, perindopril, quinapril, ramipril, trandolapril, their metabolites, or both and valsartan, in human urine samples, the compounds were separated by capillary GC and identified by computerized MS[268]. Lisinopril was determined in human plasma is made by gas chromatography/negative ion chemical ionization mass spectrometry, through solid phase extraction on C18 sorbent and derivatization to the pentafluorobenzyl diester trifluoroacetamide derivatives[269]. Benazepril and its active metabolite, benazeprilat, was determined in human plasma by capillary gas chromatography-mass-selective detection[270].

Ramipril and ramiprilat were determined in plasma and urine after alkylation with trimethylsilyldiazomethane solution[271].

5.2.2.3. Capillary electrophoretic methods. CZE method has been developed for the quantitation of cilazapril and its active metabolite cilazaprilat in urine using borate buffer at pH 9.5 current of only 23 mA[181], the enantioseparation of phenprocoumon (PhC) in capillary electrophoresis (CE) has been studied using various cyclodextrins and the method has been applied to the analysis of urine samples of patients under treatment with PhC in combination with other drugs such as ramipril, (HCT), and nifedipine[272], CZE system is optimized for the analysis of quinapril and its active metabolite quinaprilat in urine, using running electrolyte of a 60 mM borate buffer solution (pH 9.5)[188].

5.2.3. Electrochemical methods. Determination of ramipril in urine and plasma was made adopting the alternating current polarography technique by the development of

cathodic waves in Britton-Robinson buffers over the pH range 6-12[200]. Determination of benazepril in spiked human urine and plasma was carried out by treatment with nitrous acid, followed by measuring the cathodic current of the resulting nitroso derivatives[201].

6. Conclusion

This review presents analytical methods applied for the determination of ACEIs & ARBs. Among all of the published methods, liquid chromatography with UV-visible or MS-MS detection is the most popular technique used for both; analysis of pharmaceutical preparations and biological materials. It is applied not only for the determination of active components, purity and stability studies, but also for pharmacokinetic analysis. Other chromatographic methods, i.e. TLC, GC, are not so popular. Another technique used for mixture components separation is electrophoresis, in which after separation, the individual components can be analyzed in the buffer solution using a spectrophotometric or electrochemical detector. Modifications in the design of capillaries or the buffers used, combined with modern detection techniques allow for further development of these techniques and more and more widespread use thereof in the analysis. Spectrophotometric methods in UV-vis (classical and for consecutive derivatives) as well as fluorimetric are also quite common, being most frequently used for quantification or confirmation of substance identity. Despite wide availability of the equipment, their use is however still limited. Various voltamperometric techniques are becoming more and more popular especially because they allow obtaining correct results with great accuracy and sensitivity.

Automation of some stages in the analytical procedure as well as combining many methods increase the potential of analysis and detection of components and lead to the development of new methods, e.g. flow-injection analysis, and modification of those already used. The ultimate goal is to obtain results with more and more precision and accuracy and at increasingly lower concentration levels of the substances being determined. This also facilitates the course of analysis by reducing the impact of the matrix, without prior labor-consuming preparation of the samples (especially the biological ones).

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دراسة تحليليه للمركبات المثبطه والمضاده للانزيم المحول للانجيوتنسين

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تُستخدم مثبطات ومضادات الإنزيم المحول للأنجيوتنسين على نطاق واسع في علاج ارتفاع ضغط الدم ، وفشل القلب المزمن ، واحتشاء عضلة القلب ، واعتلال الكلية السكري ، لذلك هناك حاجة إلى طرق محددة وحساسة للتحديد النوعي والكمي لهذه الأدوية في أشكال الجرعات الصيدلانية وفي المواد البيولوجية. في السنوات القليلة الماضية ، لم تكن هناك مراجعات منشورة تغطي جميع الطرق التحليلية المختلفة المستخدمة لتحليل هذه الأدوية.

الهدف من هذا العمل هو مراجعة أهم الطرق الحديثة لتحليلها في صور نقية وفي أشكال جرعات دوائية مختلفة وفي السوائل البيولوجية نظرا للأهمية الكبيرة لهذه الفئة من الأدوية.

تتضمن هذه المراجعة جزأين: الجزء الأول يعرض الطرق المطبقة لتحليل هذه الادويه في المستحضرات الصيدلانية. الجزء الثاني مخصص للطرق المطبقه لقياسها في المواد البيولوجية (الدم والبلازما والبول).