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REVIEW

ANALYSIS OF HYPOTENSIVE COMPOUNDS OCCURRING IN COMPLEX AGENTS

MARIUSZ STOLARCZYK*, ANNA MAŚLANKA, ANNA APOLA and JAN KRZEK

Jagiellonian University,Collegium Medicum, Department of Inorganic and Analytical Chemistry, Medyczna 9, 30-688 Kraków, Poland

Abstract: This is a review of analytical methods, such as spectrophotometry, derivative spectrophotometry and various chromatographic (gas chromatography – GC, high-performance liquid chromatography – HPLC, thin-layer chromatography – TLC, high-performance thin-layer chromatography – HPTLC, liquid chromatography-tandem mass spectrometry – LC-MS, microchip electrophoresis – MCE, capillary electrophoresis – CE) and electroanalytical methods (differential pulse polarography – DPP, cathodic stripping voltammetry – CSV, anodic stripping voltammetry – ASV, differential pulse voltammetry – DPV, cyclic voltammetry – CV, stripping voltammetry – SV, square wave voltammetry – SWV, square wave polarography – SWP) that are used in the analysis of hypotensive complex agents. This review is based on representative publications that were published between 1995 and 2009.

Keywords: hypotensive drugs, analysis, reviev, spectrophotometry, chromatography, electroanalytical methods

Hypertension is one of the most serious diseases of the XXI century concerning about 20–30% of the world population of adults. A significant increase in the number of sick people is a result of the lifestyle (stress and improper feeding habits). Development in the diagnostic techniques and better consciousness of population together resulted in an increase of disease detection at the beginning stages. Early detection and proper pharmacotherapy of hypertension could decrease the risk of stroke, left-ventricular hypertrophy, cerebral hemorrhage, cerebral vessel disease or peripheral artery disease (1, 2). Diuretics, particularly thiazides and thiazide-like, loop diuretics and potassium sparing diuretics are applied in the hypertension treatment. From treatment perspective, complexes consisting of the selective and nonselective β-adrenergic receptor antagonists and α-adrenergic receptor antagonists, vasodilators, calcium channel blockers, ACE inhibitors (from angiotensin-converting enzyme) and angiotensin receptor antagonists play significant role.

Combined treatment proved to be more successful than monotherapy during pharmacotherapy studies of hypertension. Successful drug combinations made from different pharmacological group consist of:

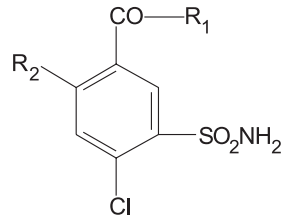
- diuretic agent + β blocker (hydrochlorothiazide and metoprolol);
- diuretic agent + ACE inhibitors or angiotensin receptor antagonists (hydrochlorothiazide and enalapril, hydrochlorothiazide and valsartan, hydrochlorothiazide and candesartan);
- diuretic agent + calcium channel blocker (hydrochlorothiazide and amlodipine);
- diuretic agent + diuretic agent with different way of action (hydrochlorothiazide and triamterene, hydrochlorothiazide and spironolactone, furosemide and spironolactone, furosemide and triamterene).

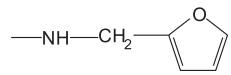
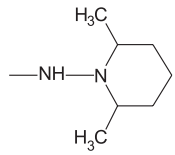
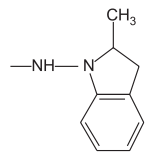
Usage of combined treatment by application of complex agents results in better hypotensive efficiency of applied drugs. This improved efficiency is achieved by synergic properties of different compounds. Hypotensive drugs were divided based on their chemical structure (3) as follows:

* Corresponding author: e-mail: mstolar@cm-uj.krakow.pl

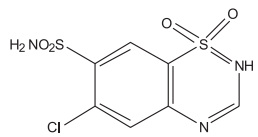
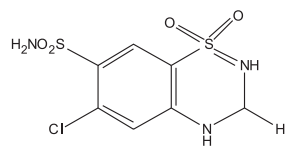
Diuretics

a) 4-Chloro-3-sulfamylbenzoic acid derivatives

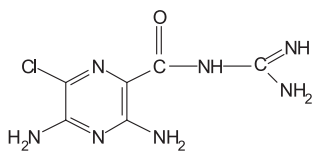
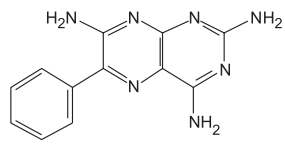


Compounds	R_1	R_2
Furosemide 4-Chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid		
Clopamide 4-Chloro-*N*-(2,6-dimethyl-1-piperidyl)-3-sulfamoyl-benzamide		
Indapamide 4-Chloro-N-(2-methyl-2,3-dihydroindol-1-yl)- 3-sulfamoyl-benzamide		

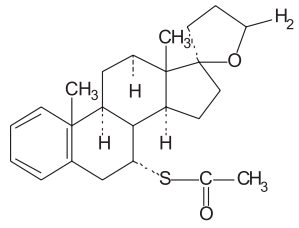
b) Benzothiadiazine derivatives

Chlorothiazide 6-Chloro-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide	
Hydrochlorothiazide 6-Chloro-1,1-dioxo-2*H*-1,2,4-benzothiadiazine-7-sulfonamide	

c) Cyclic amidines

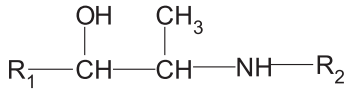
Amiloride 3,5-Diamino-6-chloro-*N*-(diaminomethylene) pyrazine-2-carboxamide	
Triamterene 6-Phenylpteridine-2,4,7-triamine	

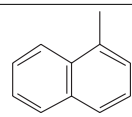
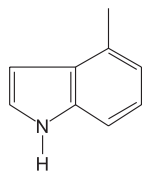
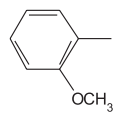
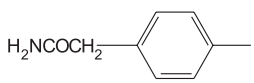
d) Drugs with different chemical structures

Spironolactone 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone	

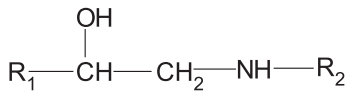
β-Blockers

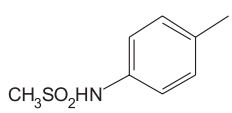
a) 1-Aryl-2-alkylamine-1-propanol derivatives



Compounds	R_1	R_2
Propranolol (*RS*)-1-(isopropylamino)-3-(1-naphthyloxy)propan-2-ol		
Pindolol (*RS*)-1-(1*H*-indol-4-yloxy)-3-(isopropylamino)propan-2-ol		
Metoprolol (*RS*)-1-(isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol		
Atenolol (*RS*)-2-{4-[2-hydroxy-3-(propan-2-ylamino)propoxy]phenyl}acetamide		

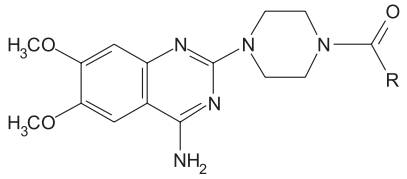
b) 1-Aryl-2-alkylaminoethanol derivatives

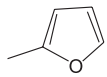
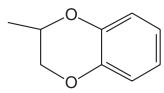


Compounds	R_1	R_2
Sotalol (*RS*)-*N*-{4-[1-hydroxy-2-(propan-2-ylamino)ethyl]phenyl}methanesulfonamide		

α-Blockers

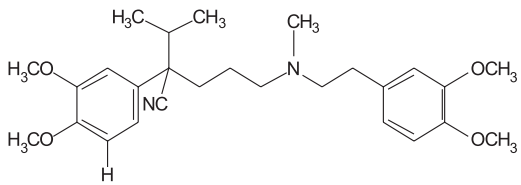
a) Quinazoline derivatives



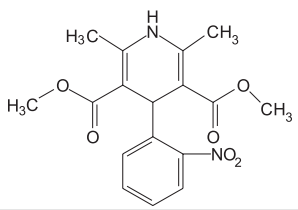
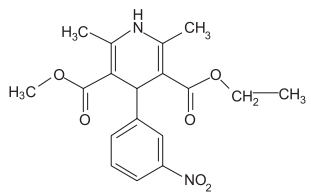
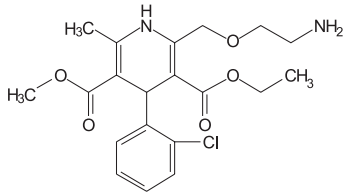
Compounds	R
Prazosin 2-[4-(2-Furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine	
Doxazosin (*RS*)-2-{4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-piperazin-1-yl}-6,7-dimethoxyquinazolin-4-amine	

Calcium channels blockers

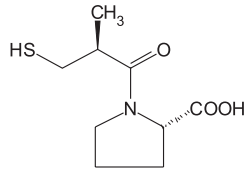
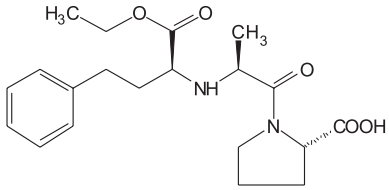
a) Phenylalkylamine derivatives

Verapamil (*RS*)-2-(3,4-dimethoxyphenyl)-5-[[2-(3,4-dimethoxyphenyl)ethyl]-(methyl)amino]-2-isopropylpentanenitrile	

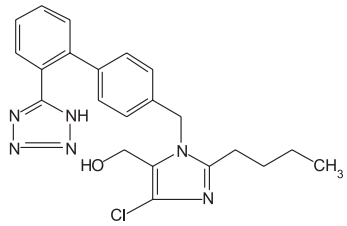
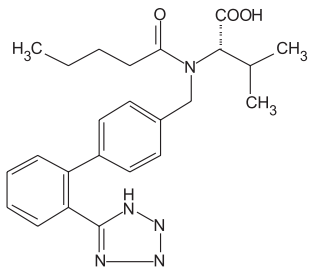
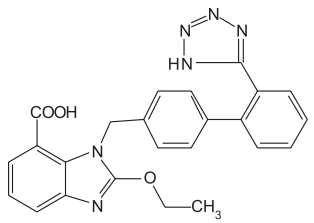
b) 1,4-Dihydropyridine derivatives

Nifedipine 3,5-Dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	
Nitrendipine Ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	
Amlodipine (*RS*)-3-ethyl-5-methyl-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate	

Angiotensin-converting enzyme inhibitors (I-ACE)

Captopril (2*S*)-1-[(2*S*)-2-methyl-3-sulfanylpropanoyl] pyrrolidine-2-carboxylic acid	
Enalapril (2*S*)-1-[(2*S*)-2-{[(2*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino} propanoyl]-pyrrolidine-2-carboxylic acid	

Angiotensin II receptor antagonists

Losartan (2-Butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl)biphenyl -4-yl]methyl}-1*H*-imidazol-5-yl)methanol	
Valsartan (*S*)-3-methyl-2-[*N*-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl) phenyl]phenyl}methyl) pentanamido]butanoic acid	
Candesartan 2-Ethoxy-1-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl] phenyl}methyl)-1*H*-1,3-benzodiazole-6-carboxylic acid	

Diversity of chemical structures present in a group of hypotensive drugs encourage for searching new methods useful in their quantitative analysis. The most commonly described in the literature are spectrophotometric methods using zero-order spectrum or derivative spectrum curve, as well as chromatographic (GC, HPLC, TLC, HPTLC, CE) and electroanalytical methods.

Spectrophotometric method (5–8)

Derivative spectrophotometry originates from the classic spectrophotometry. It was developed by differentiation of formula, which is a mathematical illustration of Lambert- Beer law, and assumption of stability of falling radiation intensity I_o in the whole studied wavelength [eq. 1]:

$$\frac{d^n A}{d\lambda^n} = \frac{d^n \varepsilon}{d\lambda^n} bc = {}^nDx,\lambda \qquad [1]$$

where: n – derivative order, λ – wavelength, ${}^nD_{x,\lambda}$ – derivative value of absorption spectrum of substance X.

Value of corresponding derivative depends on direct proportion of a concentration of studied solution and thickness of the layer [eq. 1].

In the studied radiation range of the phase, spectrum derivative of components is equal to total value of individual components [eq. 2]:

$${}^nD_{1+\ldots K} = {}^nD_1 + {}^nD_2 + \ldots + {}^nD_K \qquad [2]$$

Equation [2] shows that the derivative of n order of a mixture composed of K components at a given wavelenght, is equal to the sum of derivative values of n order of K components.

In derivative spectrophotometry, the specific feature is the dependence of derivative value on peak half-intensity width. Thus, the derivative values increase when peak half-intensity width decreases [eq. 3]:

$${}^nD_A > {}^nD_B \; gdy \; L_A < L_B \qquad [3]$$

where: L is a peak width in half of its height.

Due to application of derivative spectrophotometry, the folloving operations are possible:

- determination of trace components without their previous release from matrix;
- simultaneous determination of a few components of the mixture;
- elimination of background, sample opacity, spectra of disturbing substance with small run complexity, (with broad or flat bands);
- usage even very small bands causing inflexion on absorption curve or changes of slope angle;
- determination of precise values λ_{max}, and also points of inflexion;
- determination of organic compounds based on derivative of specified order.

Derivative spectrophotometry was used by G. Ragno et al., to analyze amlodipine and product of its photodegradation in pharmaceutical preparations (9). The process of photodegradation was carried out at various ranges of radiation. In the first case, the sample was exposed to sunlight from 9.00 AM to 5.00 PM in summer months (June–July). In the second case, the sample was exposed to UV radiation (280–360 nm, 30 W from 30 cm distance). Spectrum records of zero order, its transformation into third derivative and the wavelengths determination allow for quantitative analysis of amlodipine (D3 λ = 243 nm) and its degradation product (D3 λ = 229 nm and λ = 243 nm). The results obtained and their statistical estimation demonstrate the possibility of spectrophometric method application for such analyses. Spectrophotometric method was also used for the analysis of complex formulations containing various substances of hypotensive action in its composition. Cilazapril and hydrochlorothiazide were determined quantitatively by spectrophotometric zero-order method (10), after earlier establishment of chemometric algorithm that allows for quantitative interpretation of absorption spectra. Similar procedure was undertaken to determine amiloride in the presence of hydrochlorothiazide (11). The first-order method was applied for determination of benazepril and hydrochlorothiazide (12). Application of this method allows for determination of these active substances in a range 14.80–33.80 $\mu g \cdot mL^{-1}$ for benazepril and 18.50–42.20 $\mu g \cdot mL^{-1}$ for hydrochlorothiazide, in spite of significant interference of particular components on zero-order spectra. Commercially available Cibadrex 10/12.5 and Cibadrex 20/25 were subjected for analysis. In both cases, accuracy in determination was in the range of 99.3–99.9%.

Interferences from active substances were eliminated by applying derivative spectrophotometry for determination of candesartan and hydrochlorothiazide (13), ibersartan and hydrochlorothiazide in CoAprowel 150/12.5 (14), hydrochlorothiazide and losartan in Losazid and Neo Lotan Plus (15). Two other active substances from the group of hypotensive drugs, perindopril and indapamide, were determined in Preterax by using derivative spectrophotometry and LC method, as a reference one (16). The obtained results showed that spectrophometric method can be applied as a competitive method to chromatographic techniques. Statistically estimated parameters in both methods were similar. Method accuracy ($X_{mean} \pm SD$) with application of derivative spectrophotometry was 99.1 ± 1.5% for perindopril and 98.5 ± 1.9% for indapamide. For the LC method, these values were 98.4 ± 0.74% and 99.1 ± 1.28%, respectively.

Derivative spectrophotometry was also applied for the analysis of metoprolol formulation. Rathiopharm composition contains 100.0 mg/tablet of metoprolol formulation and 12.5 mg/tablet of hydrochlorothiazide (17). At chosen wavelengths λ = 317 nm for hydrochlorothiazide and 281 nm for metoprolol, there is a possibility of determination of active formulation components under conditions of differential spectrophotometry for metoprolol.

Application of the third derivative of absorption spectrum allows for complete elimination of the impact of hydrochlorothiazide on quantitative determination of metoprolol at the chosen wavelength. Hydrochlorothiazide content was determined by using zero-order spectrum.

Conversion of zero-order spectra into curves of the first derivatives allowed for determination of amiloride and furosemide (18) at λ = 241.4 nm and λ = 343.6 nm, in the range from 6.9×10^{-8} to 1.6×10^{-4} M (amiloride) and from 6.9×10^{-8} to 0.8×10^{-4} M (furosemide), and atenolol at λ = 276.0 nm and nifedipine at λ = 340.0 nm (19). Derivative spectrophotometry (D1 and D2) was successfully used for a mixture of furosemide and spironolactone (Lasilacton formulation containing 20 mg of furosemide and 50 mg of spironolactone in a pill) (20). Results of the determination with their statistical estimation confirmed the possibility of using derivative spectrophotometry for determination of those substances in complex pharmaceutical formulations.

Derivative spectrophotometry was used as a quantitative method for determination of enalapril and valsartan in the presence of hydrochlorothiazide (21), or hydrochlorothiazide in the presence of triamterene (22), in complex pharmaceutical formulations. Determinations were done by the first derivative method in a range 200–400 nm, assuming for analytical wavelengths values of λ_{225} for enalapril and λ_{278} for hydrochlorothiazide in determination of active substances in Enap HL formulation. The concentration range was between 4.1 $mg \cdot mL^{-1}$ and 20.5 $mg \cdot mL^{-1}$ for enalapril, and 5.2 $mg \cdot mL^{-1}$ to 26.0 $mg \cdot mL^{-1}$ for hydrochlorothiazide. For determination of valsartan in the presence of hydrochlorothiazide in the formulation of Co-Diovan, the second derivative was used at established wavelengths: λ_{261} for valsartan and λ_{284} for hydrochlorothiazide, and the concentration range was 6.45 $mg \cdot mL^{-1}$ to 32.25 $mg \cdot mL^{-1}$ for valsartan and 0.96 $mg \cdot mL^{-1}$ to 4.8 $mg \cdot mL^{-1}$ for hydrochlorothiazide.

Hydrochlorothiazide and triamterene were determined in Diureticum Verla formulation, by the first and also the second derivative. The ranges studied were between 1.25 $mg \cdot mL^{-1}$ and 6.25 $mg \cdot mL^{-1}$ for hydrochlorothiazide and from 2.4 $mg \cdot mL^{-1}$ to 12.0 $mg \cdot mL^{-1}$ for triamterene. For quantitative determination, the following wavelengths were chosen $\lambda_{255.7}$ and $\lambda_{240.9}$ in the case of first derivative or $\lambda_{278.2}$ and $\lambda_{283.2}$ in the case of second derivative. The results reported by authors were very accurate and precise, confirmed by presented statistical parameters.

Chromatographic methods

Chromatographic methods are widely used in the analysis of hypotensive drugs. These methods are characterized by very high precision and possibility of determination even several active substances simultaneously in analytical procedure. On the other hand, time-consuming sample preparation is often required. Repeatable, especially in case of simultaneous analysis of active substances in biological material, sample preparation must be followed by extraction to stationary phase and then by elution, so the time of analysis is extended.

HPLC and GC were applied for determination of compound with hypotensive action in pharmaceutical preparations (23–26). The HPLC method was also used to determine the concentration of hypotensive drugs in systemic fluids. Solid phase extraction of active pharmaceutical ingredients preceded their separation (27–32). Application of a proper extraction method enabled determination even a dozen or so compounds with good accuracy and precision. In addition, development of good analytical methods allowed to apply HPLC assay for determination of both pharmaceutical active ingredients and their metabolites (28, 33–35) as well as degradation products occurring during stress studies (36). Such studies enable to understand metabolic pathways of studied compounds and their behavior in the body. Moreover, these studies gave the possibility to determine degradation products of studied compounds *in vitro*.

A possibility of identification and separation of enantiomers is an important topic closely connected with drug metabolism, bioavailability, formulation and storage, and the efficacy of any therapy. For some drugs, pharmacological activity depends on the presence of some forms of the same pharmaceutical active ingredient, which differ in its spatial configuration.

Separation and identification of enantiomers was possible using chiral selectors in mobile or stationary phase or after stereoselective derivatization, as well as through modification of extraction methods, mobile phases and system of detection (37, 38). In HPLC, the separation of enantiomers was carried out by usage of chiral stationary phases or derivatization agents, such as triethylborane with ethyl acetate, pentafluoropropionic anhydride, and trifluoroacetic anhydride.

In TLC, the separation of enantiomers were done on carriers coated with chiral stationary phases or on nonchiral phases coated by selector like cellulose and its derivatives (39–41). Densitometry was

Table 1. Chromatographic methods used in the analysis of hypotensive compounds.

Compounds	Methods	Analyzed material	Conditions of separation			Reference
			solid phase	mobile phase	detection	
Althiazide, Amiloride, Bendroflumethiazide Benzthiazide, Bumetanide, Canrenone, Chlortalidone, Clopamide, Dichlorphenamide, Ethacrynic acid, Furosemide, Hydroflumethiazide,Indapamide, Piretanide, Polythiazide ,Spironolactone, Triamterene, Trichlormethiazide and Xipamide	HPLC	human urine	Hypersil (150 mm × 3.0 mm, i.d. 5 μm) C_{18} column	Sodium dodecyl sulfate – 4% tetrahydrofuran	UV	(42)
Acetazolamide, Bendrofluazide, Bumetanide, Canrenoic acid, Chlorothiazide, Chlorthalidone Clopamide, Epitizide, Etacrynic acid, Furosemide, Hydrochlorothiazide, Indapamide, Mefruside, Piretanide, Spironolactone,Torasemide, Triamterene	HPLC	human urine	Lichrospher 100 RP-18, Octadecylsilyl encapped (5 μm) column	Water – triethylamine – phosphoric acid – acetonitrile	diode array detector (DAD)	(43)
Moexeipril, Hydrochlorothiazide	HPLC	pharmaceuticals	Luna C18 column (250 mm × 4.6 mm i.d, 5 μm)	acetonitrile – phosphate buffer	UV	(44)
Captopril, Hydrochlorothiazide	HPLC	human plasma	Diamonsil (150 mm × 4.0 mm i.d., 5 μm) C_{18} column	acetonitrile – trifluoroacetic acid-water	UV	(45)
Enalapril, Lisinopril, Benazepril, Quinalapril, Ramipril	HPLC	pharmaceuticals	Hypersil ODS (150 mm × 4.5 mm i.d.)	sodium heptasulfonate – acetonitrile – tetrahydrofuran	UV	(46)
Metoprolol, Amlodipine	HPLC	pharmaceuticals	Hypersil BDS cyano (250 mm × 4.6 mm i.d., 5mm)	triethylamine – acetonitrile	photodiode array detector (PDA)	(22)
Eprosartan, Telmisartan, Irbesartan, Valsartan	HPLC	human urine	Waters Atlantis dC18 (100 mm × x 3.9 mm i.d., 3 μm)	trifluoroacetic acid	diode array detector (DAD)	(27)
Losartan, Irbesartan, Valsartan, Candesartan	HPLC	human urine	mBondapak C_{18} column;	acetonitrile – acetate buffer	UV	(47)
Losartan, Hydrochlorothiazide	HPLC	pharmaceuticals	Erbasil (125 mm x 4.0mm i.d., 5 μm)	acetonitrile – phosphate buffer	UV	(24)
Hydrochlorothiazide	HPLC	human plasma and urine	Ultra Phenyl column (100 mm × 3.2 mm, 3 μm)	acetonitrile – ammonium acetate	tandem MS detector	(48)
Hydrochlorothiazide	HPLC	human serum	column LiChroCard (125 mm × 4.0 mm i.d., 5 μm)	acetonitrile – phosphate buffer	electrochemical	(49)
Atenolol, Sotalol, Diacetolol, Carteolol, Nadolol, Pindolol, Acebutolol, Metoprolol, Celiprolol, Oxprenolol, Labetalol, Propranolol , Teratrolol, Betaxolol	HPLC	human plasma	Thermo-Hypersil C18, (250 mm × 4.6 mm i.d., 5 μm)	acetonitrile – phosphate buffer	photodiode array detector (PDA)	(28)

Table 1. cont.

Compounds	Methods	Analyzed material	Conditions of separation			Reference
			solid phase	mobile phase	detection	
Vepamil, Norverapamil	LC-MS/MS	rat plasma	Chiralpak AD	*n*-hexane – isopropanol – ethanol – diethylamine	tandem MS detector	(29)
Atenolol, Sotalol, Metoprolol, Bisoprolol, Propranolol, Carvedilol, Diltiazem, Amlodipine, Verapamil, Losartan, Irbesartan, Valsartan, Telmisartan	HPLC -MS	human blood	Waters Atlantis dC18 (150 mm × 2.1 mm. i.d., 3.0 µm)	ammonium formate – formic acid – acetonitrile	MS detector	(25)
Losartan	HPTLC	pharmaceuticals	HPTLC plates	acetonitrile – methanol – 0.1% acetic acid	densitometric	(36)
Losartan, Hydrochlorothiazide	HPLC	pharmaceutical	RP-YMC pack ODS A A-132 C18 (15 cm × 6.0 mm i.d., 5.0 µm)	0.01 M sodium dihydrogen phosphate – methanol – acetonitrile	UV	(26)
Amiloride, Triamterene, Bendroflumethiazide , Bumetanide	MCE	pharmaceuticals human urine	fused-silica capillary 50 µm i.d. × 375 µm (BGB Analytik Vertrieb, Germany) total length 60 cm	electrophoretic buffer	HeCd laser deep UV laser mercury lamp	(50)
Enalapril, Lisinopril, Quinalapril, Fosinopril, Cilazapril, Ramipril, Hydrochlorothiazide	CE	pharmaceuticals	fused-silica capillary 52 cm total length × 75 µm i.d.	sodium phosphate buffer	UV	(51)
Candesartan, Eprosartan, Irbesartan, Losartan, Telmisartan, Valsartan, Hydrochlorothiazide	CE	pharmaceuticals	fused-silica capillary 85 cm total length × 50 µm i.d.	sodium phosphate buffer	UV	(52)
Candesartan, Hydrochlorothiazide	HPTLC	pharmaceuticals	silica gel 60 GF_{254} plates	acetone – chloroform – ethyl acetate – methanol	densitometric	(53)
Hydrochlorthiazide, Valsartan, Candesartan, Enelapril	TLC	pharmaceuticals	TLC F_{254} plates	ethyl acetate – tetrahydrufuran – acetic acid; butan-1-ol – glacial acetic acid – water	densitometric	(54)
Quinalapril, Hydrochlorothiazide	HPTLC	pharmaceuticals	silica gel 60 F_{254}, HPTLC plates	ethyl acetate-acetone – acetic acid	densitometric	(55)
Valsartan, Hydrochlorothiazide	HPTLC	pharmaceuticals	silica gel G 60 F_{254} HPTLC plates	chloroform – ethyl acetate – acetic acid	densitometric	(56)
Losartan, Atenolol, Hydrochlorothiazide	HPTLC	pharmaceuticals	silica gel plates	toluene – methanol – triethylamine	densitometric	(57)
Benazepril, Captopril, Cilazapril, Enalapril	TLC	pharmaceuticals	normal or reversed-phase plates	ethyl acetate – acetone – acetic acid – water	UV	(58)
Atenolol, Propranolol, Bisoprolol, Metoprolol, Carvedilol	RP-HPLC	pharmaceuticals	C18 column (250 mm× 4.6 mm i.d., 5 µm)	trifluoroacetic acid – acetonitrile	Diode array detector (DAD)	(59)

Table 1. cont.

Compounds	Methods	Analyzed material	Conditions of separation			Reference
			solid phase	mobile phase	detection	
Acebutolol, Alprenolol, Bufuralol, Bisoprolol, Celiprolol, Carazolol, Indenolol, Metoprolol, Oxprenolol Propranolol	HPLC	pharmaceuticals	Chiral column CelluCoat (250 mm × 4.6 mm, 5.0 µm silica particle)	*n*-heptane – ethanol - diethylamine	UV	(30)
Sotalol, Atenolol, Pindolol, Nadolol, Timolol, Metoprolol, Acebutolol, Bunolol, Carazolol, Celiprolol, Oxprenolol, Labetalol, Bisoprolol, Propranolol, Alprenolol, Betaxolol,Carvedilol	HPLC-MS/MS	animal tissues	Acquity UPLCTM BEH C18 column (50 mm×2.1 mm; particle size, 1.7 µm).	water – acetonitrile; water – methanol; water with 0.1% formic acid – methanol; water with 0.1% formic acid – acetonitrile.	tandem MS detector	(31)
Amiloride, Chlorothiazide, Clopamide, Furosemide, Hydrochlorothiazide, Indapamide, Triamterene, Atenolol, Alprenolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Nadolol, Oxprenolol, Pindolol, Propanolol, Sotalol, Timolol	HPLC-MS/MS	human urine	Waters Atlantis T3TM column (100 mm × 2.1 mm i.d., 3 mm particle size)	ammonium formate (pH 3.5) – acetonitrile	tandem MS detector	(60)
	UPLC-MS/MS		Waters AcquityTM BEH Shield RP18 column (100 mm × 2.1 mm i.d.; 1.7 µm particle size)	formic acid in water – methanol	tandem MS detector	(60)
Chlorothiazide, Amiloride, Clopamide, Furosemide, Hydrochlorothiazide, Indapamide, Spironolactone, Triamterene	HPLC-MS/MS	human urine	Sunfire C18 column 50 mm × 2.1mm, 3.5 µm	water – methanol – ammonium acetate – acetic acid	tandem MS detector	(32)
Telmisartan, Losartan, Valsartan	HPLC	human urine	Chromolith RP-18e monolithic column	phosphate buffer – acetonitrile – methanol	fluorescence detector	(61)

Table 2. Electroanalytical methods used in the analysis of hypotensive drugs.

Compounds	Analyzed material	Methods	Working electrode	Reference
Amiloride, Hydrochlorothiazide	pharmaceuticals	DPP	DME	(74)
Atenolol, Propranolol	gastric juce	DPP	DME	(79)
Furosemide, Pretanide	pharmaceuticals, human urine	DPV, SWV	GCE	(70)
Indapamide	human serum	DPV ASV	CPE, GCE CPE	(83) (84)
Doxazosin	pharmaceuticals, human urine	DPP CSV DPP, SWP	DME CPE HMDE	(85) (86) (71)
Ramipril	pharmaceuticals, biological fluids	CV, DPP	DME, Pt	(64)
Amlodipine	pharmaceuticals, biological fluids	CV, SWV DPV	GCE GCE	(65) (87)
Prazosin	pharmaceuticals	DPP DPP	CPE DME	(80) (81)
Nifedipine, Nimodipine	hman urine and serum	SV	CPE	(88)
Nifedipine	pharmaceuticals, human serum and plasma	SWV SV	HMDE HMDE	(72) (67)
Quinalapril	pharmaceuticals	SWV	HMDE	(73)
Captopril	pharmaceuticals	SWV DPP, SWV	HMDE CGMDE	(74) (75)
Cilazapril, Quinapril, Ramipril	pharmaceuticals	SWV	HMDE	(89)
Bisoprolol	pharmaceuticals	DPV	GCE	(90)
Spironolactone	human urine	SWV	HMDE	(76)
Furosemide	human urine	DPV	HMDE	(91)
Hydrochlorothiazide	pharmaceuticals, human urine	CV	GCE	(66)
Verapamil	pharmaceuticals, human serum, urine	DPV SV	GCE HMDE	(92) (68)
Nitrendipine, Nisoldypine	phrmaceuticals	DPV	GCE	(82)
Valsartan	pharmaceuticals	SV	HMDE	(69)

used mostly as a detection technique in planar methods. Table 1 shows examples of chromatographic analysis of samples present in complex agents.

Electroanalytical methods (62)

The most commonly used analytical methods for the determination of hypotensive compounds are electroanalytical methods (63) such as:

- cyclic voltammetry (CV);
- linear sweep voltammetry (LSV);
- stripping voltammetry (SV);
  - anodic stripping voltammetry (ASV);
  - catodic stripping voltammetry (CSV);
- square wave polarography (SWP), voltammetry (SWV);
- differential pulse polarography (DPP), voltammetry (DPV);

Cyclic voltammetry was used for the analysis of ramipril (64), amlodipine (65), and hydrochlorothiazide (66). Stripping voltammetry was applied for determination of nifedipine (67), verapamil

(68) and valsartan (69), whereas square wave polarography, voltammetry were used for furosemide (70), doxazosin (71), amlodipine (65), nifedipine (72), quinalapril (73), captopril (74, 75), spironolactone (76) and candesartan (77). The hanging mercury drop electrode (HMDE) or controlled growth mercury drop microelectrode (CGMDE) were mostly used as working electrodes. Differential pulse polarography/voltammetry with modified carbon electrode (GCE or CPE), mercury electrode (DME or HMDE) were applied for analysis of amiloride and hydrochlorothiazide (78), atenolol and propranolol (79), furosemide and pretanide (70), prazosin (80, 81), nitrendipine and nisoldipine (82).

It should be emphasized that electrochemical methods need suitably prepared analyte and selection of electrolyte as well as appropriate type of electrode. HMDE, CGMDE, DME, CPE, GCE and metallic electrodes made from noble metals, most frequently from platinum (Pt), gold (Au) and silver (Ag), are used as working electrodes in the described techniques. All mentioned electroanalytical methods are characterized by high detectability, limit of determination, high sensitivity, and a possibility of usage of different basic electrolytes in order to obtain clear and well-developed signals, and possibility of reduction of the influence of template's compounds on the result of assay. Selected examples of the analysis of drug components are presented in Table 2.

CONCLUSIONS

Diversity in the chemical structures of hypotensive drugs enables application of different methods of quantitative and qualitative analysis of individual components in pharmaceutical formulations. In the cited literature, separation applications such as chromatography methods and capillary electrophoresis are used for the quantitative analysis of formulations containing several active substances. Authors of the cited publications employed different stationary and mobile phases and diverse detection methods in order to obtain the best resolution of analyzed substances.

Separation methods, and in some cases derivative spectrophotometry, were used in the analysis of the complex agents by using different solvents and derivative curves D_1, D_2 or D_3.

Electrochemical methods, due to their character, are mostly used for the analysis of single substances. Electrochemical analysis of the complex agents was usually preceded by their preliminary separation through extraction preceded and then the obtained eluent was processed by proper analytical method.

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