REVIEW ARTICLE

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Amlodipine: A Review of Analytical Methods

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Abstracts: Amlodipine is a long-acting calcium channel blocker (dihydropyridine (DHP) class) used as an anti-hypertensive and in the treatment of angina. Like other calcium channel blockers, amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle . The clinical and pharmaceutical analysis of this drug requires effective analytical procedures for quality control and pharmacodynamic and pharmacokinetic studies as well as stability study. an extensive survey of the literature published in various analytical and pharmaceutical chemistry related journals has been conducted and the instrumental analytical methods which were developed and used for determination of amlodipine as single or combination with other drugs in bulk drugs, formulations and biological fluids have been reviewed. this review covers the time period from 1998 to 2011 during which 42 analytical methods including spectrophotometric methods like uv and derivative; visible which is based on formation of metal complexation, ion pair formation, charge-transfer complexation, IR spectroscopy, diffuse reflectance spectroscopy, spectrofluorometric methods and chromatographic method including HPLC, HPTLC, LC-MSMS and miscellaneous method like differential-pulse voltammetry, potentiometric method were reported. The application of these methods for the determination of amlodipine in pharmaceutical formulations and biological samples has also been discussed.

INTRODUCTION

Hypertensive is a growing public health problem, affecting million people worldwide according to the World Health Organization. There are numbers of newer Antihypertensive Drugs and their formulations are approved by FDA.These drugs may be either new entities or partial structural modification of the existing one.

The antihypertensive are a class of drugs that are used to treat hypertension (high blood pressure).[1] evidence suggests that reduction of the blood pressure by 5 mmhg can decrease the risk of stroke by 34%, of ischemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease.[2] there are many classes of antihypertensive, which lower blood pressure by different means; among the most important and most widely used are the thiazide diuretics, the ace inhibitors, the calcium channel blockers, the beta blockers, and the angiotensin ii receptor antagonists[3]

Classes of Antihypertensive Drugs [4]

- **Diuretics**
  - Loop diuretics: (eg. furosemide)
  - Thiazide diuretics: (eg. hydrochlorothiazide)
  - Thiazide-like diuretics:
  - Potassium-sparing diuretics: (eg. spironolactone)
- **Adrenergic receptor antagonists**
  - Beta blockers (atenolol, metoprolol, nadolol, oxprenolol, pindolol)
  - Alpha blockers (doxazosin,phentolamine, indoramin, phenoxybenzamine)
  - Mixed Alpha + Beta blockers (bucindolol,carvedilol,labetalol)
- **Calcium Channel Blockers**
  - dihydropyridines: (amlodipine,felodipine,isradipine)
  - non-dihydropyridines: (diltiazem,verapamil)
- **Renin Inhibitors**

Renin comes one level higher than Angiotensin Converting Enzyme (ACE) in the Renin-Angiotensin System. Inhibitors of renin can therefore effectively reduce hyptertension.

- **ACE Inhibitors** (captopril, enalapril, fosinopril)
- **Angiotensin II Receptor Antagonists** (candesartan,eprosartan,irbesartan)
- **Aldosterone Antagonists** (eplerenone,spironolactone)
- **Vasodilators**
  - **Alpha-2 agonists** (Clonidine,Guanabenz,Methyldopa)

Amlodipine [5-10]

Amlodipine is a long-acting calcium channel blocker used alone or in combination with other medications to treat high blood pressure and chest pain (angina). It lowers blood pressure by relaxing the blood vessels so the heart does not have to pump as hard. It controls chest pain by increasing the supply of blood to the heart. If taken regularly, amlodipine controls chest pain, but it does not stop chest pain once it starts. Your doctor may prescribe a different medication to take when you have chest pain.

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and non dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

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Table 1: Summary of analytical Methods of Amlodipine

S. NO	drug	method	description	detection at	linearity range	REF. NO.
1	Amlodipine besylate	HPLC IP(2007)	**stationary phase::** 3.9 mm x 15 cm column with packing of octy-decylsilane silica gel **mobile phase:** acetonitrile: methanol : phosphate buffer (15:35:50 v/v/v) **flow rate:** 1 ml/min **retention time:** 7 min.	237 nm.	-	11
2	Amlodipine besylate	HPLC BP(2007)	**stationary phase::** 3.9 mm x 15 cm column with packing of octy-decylsityl silica gel **mobile phase:** acetonitrile: methanol : phosphate buffer (15:35:50 v/v/v) **flow rate:** 1 ml/min **retention time:** 7 min.	237 nm.		12
3	Amlodipine besylate	spectrophotometric	-	540 nm.	100-600 µg/ml	13
4	Amlodipine in human plasma	HPLC	**stationary phase:** nucleosil $c_8$column mobile phase: 0.01 m sodium dihydrogen phosphate buffer and acetonitrile (63:37, v/v) adjusted to ph 3.5 flow rate:1.5 ml/ min	239 nm.	0.5-16 ng ml^{-1}	14
5	Amlodipine besylate in tablets.	spectrofluorometric		excitation: 375nm emission : 480nm	0.35-1.8 µg/ml	15
6	Amlodipine in pharmaceutical formulations	differential-pulse voltammetry	electrode: glassy carbon. LOD: 0.0072 mg ml(-1) LOQ: 0.022 mg ml(-1)	-	0.04 mg ml(-1)	16
7	Amlodipine in pharmaceutical dosage form	liquid chromatography and UV spectrophotometric method	**stationary phase::** RP C18 column **mobile phase:** 0.1% (v/v) ortho-phosphoric acid (ph 3.0) -acetonitrile (60 + 40, v/v) flowrate:ml/min	238 nm	10-30 microg/ml	17
8	Amlodipine in serum	LC/MS/MS method	limit of quantitation (loq): 0.014 ng ml^{-1}	-	0.014-7.2 ng ml^{-1}	18
9	Amlodipine besylate in human plasma by electrospray ionizationand its stability studies	LC-MS/MS method	**stationary phase: :** c18 analytical column **mobile phase**: 10mm ammonium formate/ methanol/acetonitrile (30/50/20, v/v/v) flow rate: 1.0 m		0.3-15.0 ng/ml,	19
10	Amlodipine besylate in tablets	Colorimetric method	acid-dye bromophenol blue at ph 3.2 a coloured ion-pair complexionis form and extracted in chloroform	414 nm	6-30 µg/ml	20
11	amlodipine besylate	Spectrophotometric method	five different dyes; methylene blue (mb), acid blue 74 (ab), acid red 73 (ar), amaranth dye (am) and acid orange 7 (ao)	λmax 663, 609, 511, 520, and 484 nm resp.	1.0-24, 0.9-22, 1.2-26, 0.9-12.8 and 1.0-14 µg ml-1, respectively.	21
12	Amlodipine besylate in drug formulations	Spectrophotometric methods (using 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone and ascorbic acid.)	charge transfer complexation with 2,3-dichloro 5,6-dicyano 1,4-benzoquinone interaction of drug with ascorbic acid in *n*,*n*-dimethylformamide medium	580 nm 530 nm. respectively	1–125 and 10–140 µg ml^{-1}respectively	22

13	Amlodipine containing pharmaceuticals	IR Spectroscopy and HPLC methods	**Stationary phase :**c18 (5µm, 250x4,6 mm) column **mobil phase**: water-methanol-phosphat buffer (36:64:1) (ph: 3 ±0,1) flow-rate of 0,7 ml.min-1.	absorption bands at 693 and 913 cm-1 In HPLC detected 275 nm	concentration range of 0,6 - 2,5 % w/w in kbr. **HPLC:** 4-12 µg.ml-1	23
14	Amlodipine besylate in bulk drug and their dosage forms	spectrophotometric method(using hydrotropic agent)	-	365 nm. And 240 nm	50 to 250 µg.ml-1	24
15	Amlodipine besylate in human urine and pharmaceuticals	Voltammetric method	-	-	5.0×10^{-9} to 1.0×10^{-6} mol L^{-1}	25
16	Atorvastatin calcium and amlodipine besylate in tablets	spectrophotometric (simultaneous equations) method		245 nm and 363 nm.	atorvastatin calcium: 0-40 µg/ml amlodipine besylate:0-20 µg/ml	26
17	Amlodipine besylate and atorvastatin calcium in tablet dosage forms	spectrophotometric methods	limit of quantitation (µg/ml) 0.086 0.163 amlo and atorva restectively	238.8 nm and 246 nm.	0.5-30 µg/ml	27
18	Atorvastatin, amlodipine, ramipril and benazepril in human plasma	LC-MS/MS **method**	**stationary pahse**:c8 **mobile phase:** 0.1% formic acid–acetonitrile (15:85, v/v) flow rate : 1 ml/min		0.26–210 ng/ml for ato; 0.05–20.5 ng/ml for aml; 0.25–208 ng/ml for ram and 0.74–607 ng/ml for ben	28
19	Amlodipine besylate(ab) and benazepril hydrochloride(bh) in tablets	HPTLC method	**stationary phase:** 60f254 silica gel **mobile phase** : ethyl acetate : methanol:chloroform:toluene(1.25:2:1.5:1) v/v r_f of ab: 0.45 r_f of bh: 0.76	254nm.	AB: 2-10 MCG/MCL BH: 4-20 MCG/MCL	29
20	Amlodipine and benazepril hydrochloride from their combination drug product	stability indicating RP-HPLC method	**Stationary phase** zorbax sb c18, 5 µm, 250 mm × 4.6 mm i.d, **mobil phase**: phosphate buffer : acetonitrile of 65:35 (v/v) ph 7.0	240 nm	6–14 µg/ml for am and 12–28 µg/ml for bh.	30
21	Atenolol and amlodipine besylate	UV-spectrophotometric	third order derivative [**dl** (n) = 2]	361 nm	-	31
22	Atenolol and amlodipine in pharmaceutical-dosage form	HPLC method	**Stationary phase:**shim-pack clc, ods (c18), 4.6 mm × 25 cm & 0.5 µm, **mobil phase**: ammonium acetate buffer (ph 4.5 ± 0.05): acetonitrile: methanol (35:30:35 v/v). flow rate of 1.5ml/min,	237 nm		32
23	Amlodipine and metoprolol	RP-HPLC	**stationary phase:** kromasil c18 (250 x 4.6 mm, 5 µm) column **mobile phase:** 0.02 m phosphate buffer solution: acetonitrile (70:30v/v, ph 3.0). **flow rate:** 1 ml/min **retention time:** 2.57 min for amlodipine and 4.49 for metoprolol	221 nm.	-	33
24	Amlodipine besylate and olmesartan medoxomil from tablet	RP-HPLC method	**stationary phase** :hiq sii c18 column -10 (4.5 mm x 250 mm). **mobile phase** :acn: water (60:40). flow rate: 1.0 ml/min.	248 nm	5-35 mg ml·	34

25	Amlodipine besylate and olmesartan medoximil in tablet dosage form	first derivative zero crossing method.	the limit of quantification was 0.18 and 0.43 µg/ml for amlodipine and olmesartan	259 nm for amloand 237 nm for olm	5 - 30 µg/ml for amlo and 5 – 30 µg ml-1 for olm	35
26	Amlodipine besilate and olmesartan medoxomil in pharmaceutical dosage form	RP HPLC, area under curve method and simultaneous equation method	as the mobile phase **Stationary phase** kromasil c18 (4.6 mm i.d.×250 mm) column **mobil phase**: 05m potassuim dihydrogen phosphate buffer:acetonitrile (50:50 v/v)wavelength of flow rate was 1.0 ml/min.	237.5 nm and 255.5 nm 242.5-232.5 nm and 260.5-250.5 nm HPLC:238 nm	For uv method: 10-50 µg/ml and 10-50 µg/ml, for both For HPLC mthod: 4-20 µg/ml and 10-50 µg/ml for amlodipine besilate and olmesartan medoxomil, respectively.	36
27	Amlodipine besylate and lisinopril in tablet dosage forms	spectrophotometric methods		: 360.0 nm and 248.0 nm 300.0 nm (as an iso-absorptive point) and 360.0 nm.	5-40 µg/ml.	37
28	Amlodipine Besylate and lisinopril dihydrate as a.p.i. and in tablet dosage forms	modified form of simultaneous equation method using derivative uv-spectrophotometry	**limit of quantification,** mg **ml-1** 0.694 0.751 amlodipine besylate and lisinopril dihydrate respectively	256 nm and 216 nm	range of 10.0 to 70.0 mg/ml and 4.0 to 40.0 mg/ml for amlo and lisinop respe.	38
29	Valsartan and amlodipine in capsule formulation.	stability indicating RP- HPLC method	**stationary phase** :c-18 column (kromasil, 250 x 4.6 mm) **mobile phase**:acetonitrile: phosphate buffer (0.02m, ph 3.0), (56:44 v/v)flow rate of 1.0 ml/min quantitation (µg/ml) 0.089 and 0.054 amlo and val Respectively	234 nm.	1-40 µg/ml 10-80 µg/ml amlo and val	39
30	Amlodipine besylate, valsartan and hydrochlorothiazide in bulk and in pharmaceutical formulation.	RP - HPLC method	**Stationary phase:** c18 column. **mobile phase** (acetonitrile: methanol: 50 mm phosphate buffer adjusted to ph 3 with orthophosphoric acid) 20: 50: 30% v/ v flow rate of 1.0 ml min-1	-	0.5 – 5 g ml-1µg ml-1 for valsartan and 1 – 10 µamlodipine besylate, 4 - 40 for hydrochlorothiazide	40
31	Amlodipine and valsartan	spectrophotometric method	quantification limits of amlodipine and valsartan were 10–80 ug/ml and 20–180 ug/ml respe	360.5 nm	10–80 ug/ml 20–180 ug/mlfor amlo and val respectively.	41
32	Hydrochlorothiazide, amlodipine besylate and valsartan in pharmaceutical products	single RP-HPLC method	**Stationary phase:**c18 column 150 x 4.6 mm, **mobil phase**: potassium dihydrogen phosphate and acetonitrileflow rate was 1.00 ml/ min	237nm.	5-75 ppm.	42
33	Nebivolol and amlodipine in combined dosage forms	HPTLC method	**stationary phase**: 60f254 silica gel **mobile phase :** chloroform-methanol-toluene-ammonia (8+ 1.8+ 1+ 0.3, v/v/v/v/) retardation factor (rf) values of 0.27 for aml and 0.51 for neb	273 nm.	400-1000 ng/spot and 200 – 800 ng/spot for nebivolol and amlodipine, respectively	43
35	Nebivolol and amlodipine in combined dosage form	derivative spectrophotometry	-	226.5 nm and 245 nm	10-70 _g/ml for both	45

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36	Nebivolol hydrochloride and amlodipine besylate in combined tablet dosage form	Q-analysis method	-	268nm and 282nm	-	46
37	Amlodipine besylate and bisoprolol fumarate in pharmaceutical preparations	spectrophotometric method **(**simultaneous equation method**)**	loq were found to be 4.31, 13.07 for amlo and 1.45, 4.42 for biso respectively.	222 nm and 365 nm	of 5-100 µg/ml for both	47
38	Perindopril erbumine and amlodipine besylate	spectrophotometric method (absorption factor method)	-	215 nm and 237 n	4-12 µg/ml 5-15 µg/ml perindopril and amlodipine respectively	48
39	Telmisartan and amlodipine besylate in bulk and tablets	TLC-densitometry method	**Stationary phase**:silica gel 60f-254 **Mobile phase:** tetrahydrofuran: dichloroethane: methanol: ammonia solution (6.0:2.0:1.0:0.4 v/v).	326 nm	1,200-7,200 ng for telmisartan and 400-1,400 ng for amlodipine besylate	49
40	Amlodipine and nifedipine in pharmaceutical preparations	kinetic spectrophotometric method	reduction of iron(iii) by the studied drugs	690 nm and 740 nm aml and nif, respectively	1.0-20.0 and 3.0-19.0 µg ml-1 for aml and nif,	50
41	Amlodipine besylate and hydrochlorothiazide in combined tablet dosage form	simultaneous equation, absorption ratio and first order derivative spectroscopy methods		maxima: 238.5 nm and 271 nm isobestic point 257.5 nm zcp's.225 and 271 nm	1-20 ug/ml for amlo and 2.2-50 ug/ml for hcl	51
42	Losartan potassium, amlodipine besilate and hydrochlorothiazide	spectrophotometric (chemometric method)			8–40, 1–5 and 3–15 mg ml–1 for losartan potassium, amlodipine besilate and hydrochlorothiazide, respectively.	52

Adverse Effects

- Very often: peripheral edema in 8.3% of users, fatigue in 4.5% of users
- Often: dizziness; palpitations; muscle-, stomach- or headache; dyspepsia; nausea - in 1 in 100 users
- Sometimes: blood disorders, development of breasts in men (gynecomastia), impotence, depression, insomnia, tachycardia, gingival enlargement - in 1 in 1,000 users,
- Rarely: erratic behavior, hepatitis, jaundice - in 1 in 10,000 users
- Very rarely: hyperglycemia, tremor, Stevens–Johnson syndrome - in 1 in 100,000 user

The progress of analytical chemistry in the scope of instrumentalisation of the methods of chemical analysis is reflected in the use thereof in pharmacopoeia monographs as well as in the standards adopted by manufacturers. a constant place is occupied by chromatographic methods [high-performance liquid chromatography (HPLC), thin layer chromatography (TLC), and gas chromatography (GC)]. Unification of the equipment used necessitates preparation of a very accurate and detailed description of conditions for carrying out the analysis. Other meaningful methods having a big meaning are also ultraviolet–visible (UV–VIS) and infrared (IR) spectrophotometry, atomic absorption spectrophotometry (AAS), nuclear magnetic resonance (NMR), mass spectrometry (MS) or spectrofluorometry. among the analytical methods used for determining amlodipine are also voltamperometric methods.

Introduction of new methods, enabling carrying out determinations with maximum accuracy, contributes to increased interest in analytical methods as such. They should enable to simultaneously determine the individual components in multicomponent preparations and in biological material. Range of guidelines, standardizing requirements concerning the quality of drugs, has been

issued. Fulfillment confirms them the appropriate quality of the product and of the analytical method used. These are numerical parameters that validate reliability of the results and enable comparing efficiency of the methods used. The process that is used to determine the above parameters is the so-called method validation (harmonised tripartite guideline, 1996).

Development and validation of analytical methods are of basic importance to optimize the analysis of amlodipine in the pharmaceutical industry and to guarantee quality of the commercialized product. several techniques like HPLC [11,12,14,23], LC [18,19], voltammetric methods [25], differential-pulse voltammetry[16], spectrofluorometric[15]. Colorimetric method [20, 22], spectrophotometric method [17, 21, 24] have been used for the determination of amlodipine. Chromatographic methods have been extensively used and recommended. However, these methods generally require complex and expensive equipment, provision for use and disposal of solvents, labour-intensive sample preparation procedures and personal skills in chromatographic techniques.

Chromatographic methods like HPLC, LC-MS, GC-MS, and UPLC are commonly used for the quantitative and qualitative analysis of raw materials, drug substances, drug products and compounds in biological fluids. The components monitored include chiral or achiral drug, process impurities, residual solvents, excipients such as preservatives, degradation products, extractables and leachable from container and closure or manufacturing process, pesticide in drug product from plant origin, and metabolites.

Spectrophotometric and spectrofluorometric methods for the determination of drugs can be used in laboratories where modern and expensive apparatuses such as that required for GLC or HPLC are not available. However, spectrophotometric and spectrofluorometric methods are versatile and economical particularly for developing countries. spectrophotometric and spectrofluorometric methods have several advantages such as being easy, less expensive and less time consuming compared with most of the other methods. spectrophotometric and spectrofluorometric methods are simple and rapid; so these methods can be successfully used for pharmaceutical analysis, involving quality control of commercialized product and pharmacodynamic studies.

There was no review published covering all different analytical method used for the determination of amlodipine. The high importance of amlodipine in hypertantion prompted us to review the most important recent analytical methods for their analysis in pure forms, in different pharmaceutical dosage forms and in biological fluids reported so far in the literature. because of the large number of references that appeared as individual methods or as part of clinical and pharmacological studies, it is possible to make reference only to the most important papers. The present review comprises references covering the period from 1998 to 201.

Analytical Method Including Spectroscopy and Chromatographic Method for Determination of Amlodipine

The official method of determination of amlodipine was HPLC method in indian pharmcopoeia and british pharmacopoeia [11, 12]

Determination of Amlodipine in Dosage form and Biological Fluid

Two simple and sensitive spectrophotometric method [13] have been developed and validated for determination of amlodipine besylate (AML) in tablets. acid dye is use for visible method and color intensity is measured at 540 nm. The calibration graphs were linear [correlation coefficient (r) > 0.999] in the studied concentration range of 100-600 microg/mL. The relative standard deviation values for intraday and interday precision studies were less than 2%, and the accuracy was greater than 98%.

A rapid, simple and sensitive high-performance liquid chromatography (HPLC) method [14] has been developed for quantification of amlodipine in plasma. The detectable limit of 0.2 ng ml^{-1}. The method involves simple, one-step extraction procedure and analytical recovery was about 97%. The separation was performed on an analytical 125 × 4.6 mm i.d. Nucleosil C_8 column. The wavelength was set at 239 nm. The mobile phase was a mixture of 0.01 M sodium dihydrogen phosphate buffer and acetonitrile (63:37, v/v) adjusted to pH 3.5 at a flow rate of 1.5 ml min^{-1}. The calibration curve was linear over the concentration range 0.5–16 ng ml^{-1}. The coefficients of variation for inter-day and intra-day assay were found to be less than 10%.

Two simple and sensitive spectrofluorometric method [15] have been developed and validated for determination of amlodipine besylate (AML) in tablets. The first method was based on the condensation reaction of AML with ninhydrin and phenylacetaldehyde in buffered medium (pH 7.0) resulting in formation of a green fluorescent product, which exhibits excitation and emission maxima at 375 and 480 nm, respectively. The second method was based on the reaction of AML with 7-chloro-4-nitro-2, 1, 3-benzoxadiazole (NBD-Cl) in a buffered medium (pH 8.6) resulting in formation of a highly fluorescent product, which was measured fluorometrically at 535 nm (lambda (ex), 480 nm). The factors affecting the reactions were studied and optimized. Under the optimum reaction conditions, linear relationships with good correlation coefficients (0.9949-0.9997) were found between the fluorescence intensity and the concentrations of AML in the concentration range of 0.35-1.8 and 0.55-3.0 microg ml(-1) for ninhydrin and NBD-Cl methods, respectively. The limits of assays detection were 0.09 and 0.16 microg ml (-1) for the first and second method, respectively. The precisions of the methods were satisfactory; the relative standard deviations were ranged from 1.69 to 1.98%. The proposed methods were successfully applied to the analysis of AML in pure and pharmaceutical dosage forms with good accuracy; the recovery percentages ranged from 100.4-100.8+/-1.70-2.32%. The results were compared favorably with those of the reported method.

A differential-pulse voltammetric method [16] was developed for the determination of amlodipine based on the oxidation of the dihydropyridine group on the surface

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of glassy carbon electrode under stationary and rotating conditions. The experiments were conducted in a supporting electrolyte consisting of 0.2 M KCl, 0.1 M phosphate buffer, and 10% (v/v) methanol during investigation of initial potential and pH effects. No adsorption effect was observed on using an initial potential of 0 mV and the supporting electrolyte solution at pH 5.5 under both stationary and rotating conditions. The factor affecting the voltammetric current was diffusional in the range of 200-1000 rpm for rotating, and 2-40 mV s-1 for stationary conditions up to a concentration of 0.04 mg mL-1 amlodipine. The limit of detection (LOD) and the limit of quantitative (LOQ) for the rotating and stationary techniques were found to be 0.004 and 0.0072 mg mL-1 (for S/N = 3.3) and LOQ 0.012 and 0.022 mg mL-1 (for S/N = 10), respectively. The proposed method was applied to the tablets containing amlodipine and according to the statistical evaluations acceptable results were obtained at the 95% probability level.

A liquid chromatography (LC) method and an ultraviolet (UV) spectrophotometric method [17] were developed and validated for quantitative determination of amlodipine in tablets and compounded capsules. The isocratic LC analyses were performed on an RP18 column using a mobile phase composed of 0.1% (v/v) ortho-phosphoric acid (pH 3.0) -acetonitrile (60 + 40, v/v) at a flow rate of 1.0 mL/min. The UV spectrophotometric method was performed at 238 nm. The analytical methods were validated according to International Conference on Harmonization Guidelines. The calibration graphs were linear [correlation coefficient (r) > 0.999] in the studied concentration range of 10-30 microg/mL for LC and 10-35 microg/mL for UV spectrophotometry. The relative standard deviation values for intraday and interday precision studies were less than 2%, and the accuracy was greater than 98% for both methods. The specificity of the LC method was proved using forced degradation. Statistical analyses showed no significant difference between the results obtained by the 2 methods. The proposed methods are precise and accurate and can be applied directly and easily to the oral pharmaceutical preparations of amlodipine.

A sensitive and specific liquid chromatographic method [18] coupled with tandem mass spectrometry was developed for the quantification of amlodipine in human and rat serum, which is a dihydropyridine derivative with calcium antagonist activity. An atmospheric pressure chemical ionization interface was used as the ion source and the analysis was performed in the selected reactive monitoring (SRM) mode. Deuterated amlodipine was used as the internal standard, and serum samples were treated with diethyl ether extraction prior to analysis. Serum levels in the range 0.014–7.2 ng ml^{-1} were measured accurately by this method, and the lower limit of quantitation (LOQ) was 0.014 ng ml^{-1} using 1 ml of human serum. The accuracy was within 7% of the expected values. The intra-assay precision was less than 3% and the inter-assay precision was less than 6%. The method was applied to a pharmacokinetic study of amlodipine in rats, in which the measurable range was 0.14–72 ng ml^{-1} using 0.1 ml of serum because of a limitation on the sample volume.

A sensitive and specific high-performance liquid chromatography [19] combined with electrospray ionization (ESI) tandem mass spectrometry (LC-MS/MS) method, operating in the positive ionization mode, for quantifying of amlodipine in human plasma using tizanidine as internal standard (I.S.) was developed and validated. The analyte and I.S. were extracted by simple one step liquid/liquid extraction with a mixture of diethylether/dichloromethane (70/30, v/v). The chromatographic separation was performed on a C18 analytical column under isocratic conditions using a mixture of 10mM ammonium formate/ methanol/ acetonitrile (30/50/20, v/v/v) as mobile phase at a flow rate of 1.0 mL/min. Total chromatographic run time was 5.0 min. Detection was performed on a API 2000 QTRAP quadrupole linear ion trap mass spectrometer via turbo ion spray ionization. Quantitation was performed using multiple reaction monitoring (MRM) mode to study parent product ion transitions of *m/z* 409.4 -238.1 for amlodipine and *m/z* 254.2 -44.1 for I.S., respectively. The validation and stability studies were performed according to the Thai FDA guidance for assessment of bioequivalence study in Thailand. The results were within the accepted criteria as stated in the aforementioned guidance. Linearity in plasma was obtained over the concentration range 0.3-15.0 ng/mL, with a coefficient of determination (*r*2) of 0.9993. Lower limit of quantification (LLOQ) was identifiable and reproducible at 0.3 ng/mL. The within- and between-run precision values were below 10% and the accuracy was ranged from 94.87 to 102.44% at all three quality controls samples levels. The analyte was found to be stable in plasma samples under three freeze-thaw cycles, long-term storage (3 months at -20oC), short-term storage (4 hours at room temperature), post-preparative and stock-solution stability. The robust and rapid LC-MS/MS method has been successfully applied for routine assay to support bioequivalence or pharmacokinetics studies of as a single oral dose (10 mg tablet) to Thai healthy volunteers. amlodipine administered tablet.

Amlodipine besylate [20] is a commonly used antyhipertensive drug acting as calcium antagonist. In this study, a coloured ion-pair complex formation reaction among amlodipine and acid-dye bromophenol blue at pH 3.2 was used for the colorimetric determination of the drug. The complex formed was extracted into chloroform and the maximum absorbance of the solution was measured at 414 nm against blank. The calibration curve calculated obeys Beer's law over the concentration range of 6-30 µg/ml and the regression equation was A=0.055C-0.018 (r=0.9997).The recovery of the drug from a commercial tablet was 100.7 % of the label claim with a relative standard deviation of 1.24 %. The results were compared with those of the spectrophotometric method currently used by the manufacturer of the tablets and no significant difference was found.

A simple, rapid, accurate, precise and sensitive spectrophotometric method [21] for the determination of

amlodipine besylate (ADB) in bulk sample and in dosage forms is described. The method is based on oxidation of the drug by potassium permanganate in acidic medium and determine the unreacted oxidant by measuring the decrease in absorbance for five different dyes; methylene blue (MB), acid blue 74 (AB), acid red 73 (AR), amaranth dye (AM) and acid orange 7 (AO) at a suitable λmax 663, 609, 511, 520, and 484 nm, respectively. Regression analysis of Beer's law plots showed good correlation in the concentration ranges 1.0- 24, 0.9-22, 1.2-26, 0.9-12.8 and 1.0-14 µg ml-1, respectively. The apparent molar absorptivity, Sandell sensitivity, detection and quantitation limits were calculated. For more accurate results, Ringbom optimum concentration ranges were 1.2-22.4, 1.1-20, 1.4-24.5, 1.0-12.3 and 1.3-13.2 µg ml-1, respectively. Statistical treatment of the results reflects that the proposed procedures are precise, accurate and easily applicable for the determination of amlodipine besylate in pure form and in pharmaceutical preparations.

Two simple and sensitive spectrophotometric methods[22] have been proposed for the determination of amlodipine besylate either in pure form or in pharmaceutical formulations. The first method is based on the charge transfer complexation reaction of the drug with 2,3-dichloro 5,6-dicyano 1,4-benzoquinone (DDQ) to give coloured product having maximum absorbance at 580 nm. The second procedure depends on the measurement of purple red colour produced by the interaction of drug with ascorbic acid in N,N-dimethylformamide medium (DMF) which absorbed maximally at 530 nm. Under the optimized experimental conditions, Beer's law was obeyed in the concentration ranges of 1-125 and 10-140 microg ml (-1) with DDQ and ascorbic acid, respectively. Both the methods were applied successfully for the analysis of amlodipine besylate in dosage forms. Results of analyses were validated statistically and through recovery studies

IR spectroscopic [23] method (KBr disc technique) was used and disulfiram (DSM) as internal standard. The specific absorption bands at 693 and 913 cm-1 were chosen for AMP and DSM respectively. Beer's law was obeyed in the concentration range of 0, 6 - 2, 5 % w/w in KBr. At 693 cm-1 and regression equation was found to be y = 0,653x + 0,022 (r2 = 0, 9972). The mean recovery and relative standard deviation (RSD) were found 103, 1 % and 1, 92 % for IR spectroscopic method respectively. In HPLC method, good chromatographic separation was achieved using a Luna C18 (5µm, 250x4,6 mm) column and mobil phase consisting of water-methanol-phosphat buffer (36:64:1) (pH: 3 ±0,1) while at a flow-rate of 0,7 ml.min-1. Mefrusid (MFD, internal standard) and AMP were detected 275 nm and were eluted 7, 2 and 11,5 min. respectively. Linearity range for AMP was 4-12 µg.mL-1. The regression equation was found to be *y* = 0,846x - 0,013 (r2 = 0, 9950). The mean recovery and RSD were found 100, 5 % and 1, 35 % respectively

A novel, safe, accurate and sensitive spectrophotometric method [24] was developed using 2 mol L-1 sodium acetate solution as hydrotropic solubilizing agent for the quantitative determination of poorly water-soluble drug amlodipine besylate in tablet dosage form. There was more than 75 fold enhancement in the solubility of amlodipine besylate in 2 mol L-1 sodium acetate solution as compared to solubility in distilled water. Amlodipine besylate shows maximum absorbance at 365 nm. Sodium acetate did not show any absorbance above 240 nm and thus no interference in the estimation of drug was seen. The sample follows the Beer's law in the concentration range of 50 to 250 µg.mL-1 (r2= 0.9998) with mean recovery ranging from 97.84 to 100.16%. Proposed method is new, simple, economic, safe, rapid, accurate and reproducible. The developed method was validated according to ICH guidelines and found to be in good accordance with the prescribed values.

Electrochemical [25]determination of amlodipine besylate (ADB) using single and multi-walled carbon nanotubes modified edge plane pyrolytic graphite electrodes (SWNT/EPPGE and MWNT/EPPGE) is described by using cyclic and square wave voltammetries at physiological pH 7.2. An increased peak current with a shift of peak potential to less positive value was observed using carbon nanotubes modified EPPGE as compared to bare electrode. The effect of pH, scan rate and analyte concentration has been examined. Under the optimum conditions the peak current was linear to the concentration of amlodipine in the range 5.0×10^{-9} to 1.0×10^{-6} mol L^{-1} for SWNT/EPPGE and the detection limit was found to be 1.0×10^{-9} mol L^{-1} whereas, for MWNT/EPPGE the detection limit was found to be 5.0×10^{-9} mol L^{-1}. The method was successfully used to determine the content of amlodipine in the pharmaceutical preparations and human urine samples of angina patients undergoing treatment with amlodipine. A comparison of electrocatalytic activities of SWNT and MWNT modified electrodes indicated that SWNT modified EPPGE is ~ 1.8 times more sensitive in comparison to MWNT/EPPGE. Biological relevance of the developed method has been described by the determination of amlodipine in human body fluids. Amlodipine can be determined without any interference from common urine metabolites such as uric acid, ascorbic acid and xanthine.

Determination of Amlodipine and Atorvastatin in Dosage form and Biological Fluid

Two simple, accurate and precise methods [26] for simultaneous estimation of atorvastatin calcium and amlodipine besylate in combined dosage form have been described. First method employs formation and solving of simultaneous equations using 245 nm and 363 nm as two analytical wavelengths. Second is dual wavelength method, which uses the difference of absorbance value at 259.9 nm and 354 nm for estimation of atorvastatin calcium and absorbance at 363 nm for amlodipine besylate. Fifty percent methanol was used as solvent, in which atorvastatin calcium and amlodipine besylate shows linearity in the range of 0-40 µg/ml and 0-20 µg/ml, respectively. Standard deviation was <1.5 in the assay of tablets. Methods were validated as per ICH norms and accuracy, precision, repeatability and robustness was found to be within the acceptable limit.

A simple, accurate, precise and reproducible UV spectrophotometric method [27] was developed for simultaneous estimation of Amlodipine besylate (AMD) and Atorvastatin calcium (ATR) in tablet dosage form have been developed. First method is simultaneous equation method; in this method 361nm and 246 nm were selected to measure the absorbance of drugs at both wavelengths. The second method is Q-value analysis based on measurement of absorptivity at 238.8 nm (as an iso-absorptive point) and 246 nm. AMD and ATR at their respective maximum wavelength 361 nm and 246 nm and at isoabsorptive point 238.8 nm shows linearity in a concentration range of 0.5-30 µg/mL. Recovery studies range from >99.82% for AMD and >98.09% for ATR in case of simultaneous equation method and >100% for AMD and >98.45% for ATR in case of Q-analysis method confirming the accuracy of the proposed method. The proposed methods are recommended for routine analysis since it is rapid, simple, accurate and also sensitive and specific (no heating and no organic solvent extraction is required).

A rapid, simple, sensitive and specific LC-MS/MS method [28] has been developed and validated for the simultaneous estimation of atorvastatin (ATO), amlodipine (AML), ramipril (RAM) and benazepril (BEN) using nevirapine as an internal standard (IS). The API-4000 LC-MS/MS was operated under the multiple-reaction monitoring mode using electrospray ionization. Analytes and IS were extracted from plasma by simple liquid–liquid extraction technique using ethyl acetate. The reconstituted samples were chromatographed on C_{18} column by pumping 0.1% formic acid–acetonitrile (15:85, v/v) at a flow rate of 1 mL/min. A detailed validation of the method was performed as per the FDA guidelines and the standard curves were found to be linear in the range of 0.26–210 ng/mL for ATO; 0.05–20.5 ng/mL for AML; 0.25–208 ng/mL for RAM and 0.74–607 ng/mL for BEN with mean correlation coefficient of ≥0.99 for each analyte. The intra-day and inter-day precision and accuracy results were well with in the acceptable limits. A run time of 2.5 min for each sample made it possible to analyze more than 400 human plasma samples per day. The developed assay method was successfully applied to a pharmacokinetic study in human male volunteers.

Determination of Amlodipine and Benazepril Hydrochloride in Dosage form and Biological Fluid

A simple, accurate, precise and reproducible HPTLC method [29] was developed for simultaneous estimation of Amlodipine besylate (AMD) and benazepril hydrochloride (BH) in tablet dosage. stationary phase was 60f254 silica gel and mobile phase was used ethyl acetate: methanol: chloroform: toluene (1.25:2:1.5:1) v/v/v/v. validation of the method was performed as per the FDA guidelines and the standard curves were found to be linear in the range of 2–10 ug/uL for AML; 4-20 ug/uL for BH with mean correlation coefficient of ≥0.99 for each analyte. The intra-day and inter-day precision and accuracy results were well with in the acceptable limits.

A stability indicating reversed-phase HPLC method [30] has been developed and subsequently validated for simultaneous estimation of amlodipine (AM) present as amlodipine besylate (AB), and benazepril hydrochloride (BH) from their combination product. The proposed RP-HPLC method utilizes a Zorbax SB C18, 5 µm, 250 mm × 4.6 mm i.d. column, mobile phase consisting of phosphate buffer and acetonitrile in the proportion of 65:35 (v/v) with apparent pH adjusted to 7.0, and UV detection at 240 nm using a photodiode array detector. AB, BH, and their combination drug product were exposed to thermal, photolytic, hydrolytic, and oxidative stress conditions, and the stressed samples were analysed by the proposed method. Peak homogeneity data of AM and BH peaks obtained using photodiode array detector, in the stressed sample chromatograms, demonstrated the specificity of the method for their estimation in presence of degradants. The described method was linear over a range of 6–14 µg/ml for AM and 12–28 µg/ml for BH. The mean recoveries were 99.91 and 100.53% for AM and BH, respectively. *F*-test and *t*-test at 95% confidence level were used to check the intermediate precision data obtained under different experimental setups; the calculated value was found to be less than critical value

Determination of Amlodipine and Atenolol in Dosage Form

Simple, accurate, and precise UV-Spectrophotometric method [31] was developed for the estimation of atenolol and amlodipine besylate in tablets. The standard stock solutions of atenolol and amlodipine besylate as well as mixed standard solution were diluted appropriately. The absorption spectra of the resultant solutions of atenolol and mixed standard solution were obtained by scanning between 264 to 308 nm against solvent blank. The spectra thus obtained was derivatised to obtain third order derivative [Dl (N) = 2] spectra. A tangent was drawn through the two satellite minima (DL 278.5 nm and DH ~286 nm). An altitude was drawn through this tangent to the inverted maxima termed as DB (~282 nm). The peak height was measured in mm and plotted against respective concentrations. The absorbances of the resultant solutions of amlodipine besylate as well as mixed standard solutions were read at 361 nm. A graph of concentration versus peak height in mm for atenolol was constructed. The E1cm value was calculated for amlodipine besylate at 361 nm. Atenolol was estimated in tablets by interpolation on the calibration curve. The concentration of amlodipine besylate in tablets was determined by E1cm. The proposed analytical method was found to be accurate, precise, and reproducible

A simple, rapid and precise method [32] is developed for the quantitative simultaneous determination of atenolol and amlodipine in a combined pharmaceutical-dosage form. The method is based on High Performance Liquid Chromatography (HPLC) on a reversed-phase column, shim-pack CLC, ODS (C18), 4.6 mm × 25 cm & 0.5 µm, using a mobile phase of ammonium acetate buffer (the pH was adjusted to 4.5 ± 0.05 with glacial acetic acid), acetonitrile and methanol (35:30:35 v/v). The buffer used in the mobile phase contains ammonium acetate in double-distilled water. The chromatographic conditions are- flow rate of

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1.5ml/min, column temperature at 40°C and detector wavelength of 237 nm. Both the drugs were well resolved on the stationary phase and the retention times were around 1.5 minute for atenolol and 3.4 minute for amlodipine. The method was validated and shown to be linear for atenolol and amlodipine. The correlation coefficients for atenolol and amlodipine are 0.999963 and 0.999979, respectively. The relative standard deviations for six replicate measurements in two sets of each drug in the tablets is always less than 2% and mean % error of active recovery not more than ± 1.5%. The method was validated for precision and accuracy. The proposed method was successfully applied to the pharmaceutical dosage forms containing the above-mentioned drug combination without any interference by the excipients.

Determination of Amlodipine and Metoprolol in Dosage Form

A reverse phase high performance liquid chromatography (RP-HPLC) method [33] for the simultaneous estimation of amlodipine and metoprolol in marketed formulation is developed. The determination was carried out on a Kromasil C18 (250 x 4.6 mm, 5 µm) column using a mobile phase of 0.02 M phosphate buffer solution: acetonitrile (70:30v/v, pH 3.0). The flow rate was 1.0ml/min with detection at 221 nm. The retention time for amlodipine was 2.57 min and for metoprolol 4.49 min. Amlodipine and metoprolol showed a linear response in the concentration range of 10-110 µg/ml. The correlation co-efficient (' *r* ' value) for amlodipine and metoprolol was 0.9991 and 0.9992, respectively. The results of analysis have been validated statistically and by recovery studies. The percentage recoveries obtained for amlodipine and metoprolol ranges from 100.04 to 100.57%.

Determination of Amlodipine and Olmesartan in Dosage Form

The present work describes RP-HPLC method [34] for simultaneous estimation of Amlodipine Besylate (AML) and Olmesartan Medoxomil (OLM) from tablet. Best resolution of two drugs was achieved with the mobile phase having composition of acetonitrile and water in the ratio 60:40. The linearity response of the HPLC system for both OLM and AML was obtained over the range of 5-35 µg ml-1. Optimum retention time with greater resolution of the two drugs and internal standard eluting within six minutes was achieved with a flow rate of 1 ml min-1. After recording the spectra of the two drugs and internal standard, 248 nm was selected as suitable wavelength for estimation. The result of analysis showed excellent recoveries for both the drugs ranging from 99.75 % to 100.62 % for OLM and 98.91 % to 102.05 % for AML. This suggested the good accuracy of the method. The results of analysis of tablet indicated that no interference due to common tablet excipients was observed with the developed method.

A simple, accurate and precise spectroscopic method [35] was developed for simultaneous determination of Amlodipine besylate and Olmesartan medoximil in tablets using first derivative zero crossing method. Amlodipine showed zero crossing point at 237 nm while olmesartan showed zero crossing at 259 nm. The dA/d_ was measured at 259 nm for amlodipine and 237 nm for olmesartan and calibration curves were plotted as dA/d_ versus concentration, respectively. The method was found to be linear from 5 - 30 µg/mL for amlodipine (r2 _ 0.9999) at 259 nm and 5 – 30 µg mL-1 for olmesartan (r2 _ 0.9998) at 237 nm. The within day and between day variations showed coefficient of variation (CV %) values less than 1.5% for both drugs. The limit of detection was 0.06 and 0.14 µg/mL for amlodipine and olmesartan, respectively. The limit of quantification was 0.18 and 0.43 µg/mL for amlodipine and olmesartan, respectively. The method was successfully applied for simultaneous determination both drug in tablet dosage form.

Two UV Spectrophotometric and [36]one reverse phase high performance liquid chromatography methods have been developed for the simultaneous estimation of amlodipine besilate and olmesartan medoxomil in tablet dosage form. First UV spectrophotometric method was a determination using the simultaneous equation method at 237.5 nm and 255.5 nm over the concentration range 10-50 µg/ml and 10-50 µg/ml, for amlodipine besilate and olmesartan medoxomil with accuracy 100.09%, and 100.22% respectively. Second UV spectrophotometric method was a determination using the area under curve method at 242.5-232.5 nm and 260.5-250.5 nm over the concentration range of 10-50 µg/ml and 10-50 µg/ml, for amlodipine besilate and olmesartan medoxomil with accuracy 100.10%, and 100.48%, respectively. In reverse phase high performance liquid chromatography analysis carried out using 0.05M potassuim dihydrogen phosphate buffer: acetonitrile (50:50 v/v) as the mobile phase and Kromasil C18 (4.6 mm i.d. ×250 mm) column as the stationery phase with detection wavelength of 238 nm. Flow rate was 1.0 ml/min. Retention time for amlodipine besilate and olmesartan medoxomil were 3.69 and 5.36 min, respectively. Linearity was obtained in the concentration range of 4-20 µg/ml and 10-50 µg/ml for amlodipine besilate and olmesartan medoxomil, respectively. Proposed methods can be used for the estimation of amlodipine besilate and olmesartan medoxomil in tablet dosage form provided all the validation parameters are met.

Determination of Amlodipine and Lisinopril in Dosage Form

Two simple [37], accurate, precise, reproducible, requiring no prior separation and economical procedures for simultaneous estimation of Amlodipine besylate (AML) and Lisinopril (LIS) in tablet dosage form have been developed. First method is simultaneous equation method; in this method 360.0 nm and 248.0 nm were selected to measure the absorbance of drugs at both wavelengths. The second method is Q-value analysis based on measurement of absorptivity at 300.0 nm (as an iso-absorptive point) and 360.0 nm. AMD and LIS at maximum wavelength of AML, 360.0 nm and at isoabsorptive point 300.0 nm shows linearity in a concentration range of 5- 40 µg/mL. Recovery studies range from >99.82% for AMD and >98.09% for LIS in case of simultaneous equation method and >100% for

AMD and >98.45% for LIS in case of Q-analysis method confirming the accuracy of the proposed method. The proposed methods are recommended for routine analysis since it is rapid, simple, accurate and also sensitive and specific (no heating and no organic solvent extraction is required).

A new second derivative UV-Spectrophotometric method [38] has been described for the simultaneous assay of Amlodipine Besylate and Lisinopril Dihydrate in bulk drug and in tablet dosage forms using double distilled water as the solvent. The method is based on simultaneous equation or Vierodt's method. The lmax values for Amlodipine Besylate and Lisinopril Dihydrate in the solvent medium were found to be 256 nm and 216 nm respectively. The systems obey Beer's law in the range of 10.0 to 70.0 mg/ml and 4.0 to 40.0 mg/ml with correlation coefficient of 0.9994 and 0.9996 for Amlodipine Besylate and Lisinopril Dihydrate respectively. Repeatability, Interday and intraday precision were found to be 0.134, 0.280, 0.349 and 0.205, 0.530, 0.569 respectively. No interference was observed from common tablet adjuvants. t –test and F-test have been applied for the recovery studies of the method. The method was successfully applied to the assay of Amlodipine Besylate and Lisinopril Dihydrate in tablet formulations.

Determination of Amlodipine and Valsartan in Dosage Form

Present work describes a precise, accurate and reproducible Reverse phase High Performance Liquid Chromatographic (RP-HPLC) method [39] for simultaneous estimation of Amlodipine besylate (AMLB) and Valsartan (VAT) on RP C-18 Column (Kromasil, 250 x 4.6 mm) using acetonitrile: phosphate buffer (0.02M, pH 3.0), (56:44 v/v) as mobile phase at a flow rate of 1.0 ml/min and the detection wavelength was 234 nm. The retention time for AMLB and VAT was found to be 3.07 and 6.20 min, respectively. The method was also applied for the determination of AMLB and VAT in the presence of their degradation products formed under variety of stress conditions. Proposed method was validated for precision, accuracy, linearity range, robustness and ruggedness.

A reverse phase high performance liquid chromatographic method [40] has been developed for the simultaneous estimation of amlodipine besylate, valsartan and hydrochlorothiazide in pharmaceutical formulation using RP - C18 column. The mobile phase (acetonitrile: methanol: 50 mM phosphate buffer adjusted to pH 3 with orthophosphoric acid) was pumped at a flow rate of 1.0 mL min-1 in the ratio of 20: 50: 30% v/ v and the eluents were monitored at 239 nm. Linearity was obtained in the concentration g mL-1 forμg mL-1 for amlodipine besylate, 4 - 40 μrange of 0.5 – 5 g mL-1 for hydrochlorothiazide. The method wasμvalsartan and 1 – 10 statistically validated and RSD was found to be less than 2% indicating high degree of accuracy and precision of the proposed HPLC method. Due to its simplicity, rapidness, high precision and accuracy, the proposed HPLC method can be applied for determining amlodipine besylate, valsartan and hydrochlorothiazide in bulk and in pharmaceutical dosage form

A spectrophotometric method [41] was developed for simultaneous determination of amlodipine (Aml) and valsartan (Val) without previous separation. In this method amlodipine in methanolic solution was determined using zero order UV spectrophotometry by measuring its absorbency at 360.5 nm without any interference from valsartan. Valsartan spectrum in zero order is totally overlapped with that of amlodipine. First, second and third derivative could not resolve the overlapped peaks. The first derivative of the ratio spectra technique was applied for the measurement of valsartan. The ratio spectrum was obtained by dividing the absorption spectrum of the mixture by that of amlodipine, so that the concentration of valsartan could be determined from the first derivative of the ratio spectrum at 290 nm. Quantification limits of amlodipine and valsartan were 10–80 ug/ml and 20–180 ug/ml respectively. The method was successfully applied for the quantitative determination of both drugs in bulk powder and pharmaceutical formulation.

A simple and accurate RP-HPLC method[42] has been developed for the simultaneous estimation of Hydrochlorothiazide, Amlodipine besylate and Valsartan by using C18 column 150 x 4.6 mm, 5μm with a simple gradient elution(0-4min, sol-A:80-55; 4-8min- sol-A:55-40; 8-11min- sol-A:40-30; 11-13min- sol-A:30-80 and 13-16min- sol-A:80-80). Mobile phase comprising of sol- A (pH 3.00±0.05 of 0.01M Potassium dihydrogen phosphate) and sol-B (Acetonitrile). Flow rate was 1.00 ml per min and the detection was monitored out by UV detector at 237nm. The retention times for Hydrochlorothiazide, Amlodipine besylate and Valsartan were found 4.5, 6.0 and 10.6 minutes. The proposed method has permitted the quantification of Hydrochlorothiazide, Amlodipine besylate and Valsartan over linearity in the range of 5-75 μg per ml and applicable for bulk and all type of pharmaceutical dosage forms.

Determination of Amlodipine and Nebivolol in Dosage Form

The manuscript describes validated High-Performance Thin-Layer Chromatography [43] (HPTLC) method for the estimation of Nebivolol (NEB) and Amlodipine (AML) in combined dosage form. The HPTLC separation was achieved on an aluminium-backed layer of silica gel 60F254 using chloroform-methanol-toluene-ammonia (8+ 1.8+ 1+ 0.3, v/v/v/v/) as mobile phase. Quantitation was achieved with UV detection at 273 nm over the concentration range 400-1000 ng/spot and 200 – 800 ng/spot for Nebivolol and Amlodipine, respectively with mean recovery of 100.3 ± 0.76 and 100.5 ± 0.92 % for Nebivolol and Amlodipine by HPTLC method. These method were found to be Simple, sensitive, accurate, precise, reproducible, and economical can be applicable for the simultaneous determination of Nebivolol and Amlodipine in combined dosage form.

sensitive, selective, precise and [44]stability indicating high-performance thin-layer chromatographic method of analysis of Amlodipine besylate and Nebivolol

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hydrochloride both as a bulk drug and in formulations containing these two in combination was developed and validated. The method employed TLC aluminum plates precoated with silica gel 60F254 as the stationary phase. The solvent system consisted of Ethyl acetate: Methanol: Dilute ammonia (8.5:1:1, v/v/v). This system was found to give compact spots for Amlodipine besylate (Rf 0.40± 0.01) and Nebivolol hydrochloride (Rf 0.60 ± 0.02). Amlodipine besylate and Nebivolol hydrochloride were individually subjected to stress degradation conditions like oxidation, dry heat treatment, photo degradation and hydrolysis under different pH. The peaks of products formed during stress degradation studies were well resolved from the bulk drug peak with significantly different *Rf* values. Densitometric analysis of Amlodipine besylate and Nebivolol hydrochloride was carried out at 240 and 280 nm respectively. The linear regression analysis data showed good linear relationship in the concentration range 500–2000 ng spot -1 for both Amlodipine besylate and Nebivolol hydrochloride. The method was validated for linearity, accuracy, specificity, LOD, LOQ, precision and robustness. The limits of quantitation for Amlodipine besylate and Nebivolol hydrochloride were found to be 313 and 277 ng spot -1 respectively. The statistical analysis proved that the method is repeatable and selective for the estimation of the said drugs. As the method could effectively detect the drugs in the presence of their degradation products, it can be employed as a stability indicating one.

Simple and accurate method [45] to determine Nebivolol and Amlodipine, in tablet dosage form, was developed and validated using Derivative Spectrophotometry. Derivative spectrophotometric method was based on the determination of both the drugs at their respective zero crossing point (ZCP). The first-order derivative spectra were obtained at N = 1 (scaling factor), __ = 2.0 nm, and determination was performed at 226.5 nm (ZCP of Amlodipine) for Nebivolol and 245 nm (ZCP of Nebivolol) for Amlodipine over the concentration range of 10-70 _g/mL for both drugs with mean recovery of 100.2 ± 1.25 % and 100.1 ± 1.38 % for Nebivolol and Amlodipine, respectively. Method was validated, and the results were compared statistically. They were found to be simple, sensitive, accurate, precise, reproducible and economical. The method was successfully applied for the determination of Nebivolol and Amlodipine in tablet dosage form without any interference from common excipients.

A simple, accurate, precise, rapid and economical spectrophotometric method [46] for simultaneous estimation of Nebivolol hydrochloride and Amlodipine besylate in combined tablet dosage form has been developed utilizing Q-analysis method or Absorbance ratio method. In this method, absorbance is measured at two wavelengths, one being the iso-absorptive point 268nm (λ1) and the other being λmax of one of the sample components 282nm (λ2). Both the drugs obey Beer's law in the concentration ranges employed for this method. Result of the method was validated statistically as well as by recovery studies. Proposed method for simultaneous estimation of NH and AB in combined sample solutions was found to be simple, accurate and reproducible. Once the equations are determined, analysis required only the measurement of the absorbances of the sample solution at the two wavelengths selected, followed by a few simple calculations. It is a novel method that can be employed for routine analysis in quality control or R & D laboratory.

Determination of Amlodipine and Bisoprolol in Dosage Form

Simple spectrophotometric method [47] has been developed for simultaneous estimation of amlodipine besylate and bisoprolol fumarate in combined dosage form. The method employed simultaneous equation method for analysis using 10% methanol as a solvent. The two wavelengths 222 nm and 365 nm were selected for estimation of bisoprolol fumarate and amlodipine besylate respectively. Linearity was observed in the concentration range of 5-100 µg/ml for both the drugs amlodipine besylate and bisoprolol fumarate. The recovery studies ascertained the accuracy of the proposed method and the results were validated as per ICH guidelines. The method can be employed for estimation of pharmaceutical formulations with no interference from any other excipients and diluents.

Determination of Amlodipine and Perindopril in Dosage Form

In this study, [48] Absorption factor method have been developed and validated for the simultaneous determination of perindopril erbumine and amlodipine besylate in their combined pharmaceutical formulation dosage form. Absorption factor method was performed for perindopril erbumine and amlodipine besylate at wavelength maxima 215 nm and 237 nm respectively. Amlodipine besylate was show liner at 237 nm but Amlodipine besylate also showed absorbance at 215nm and give interference in determination of Perindopril erbumine. Quantitative estimation of Perindopril erbumine was carried out by subtracting interference of Amlodipine besylate using experimentally calculated absorption factor. Result of analysis was validated by statistically. The result of the studies showed that the proposed Spectroscopic method is simple, rapid, precise and accurate, which can be used for the routine determination of Perindopril erbumine and Amlodipine besylate in bulk and in its pharmaceutical formulation.

Determination of Amlodipine and Telmisartan in Dosage Form

A rapid, simple, and selective high performance thin layer chromatographic method[49] was developed and validated for simultaneous estimation of telmisartan and amlodipine besylate in pharmaceutical dosage forms. The method employed TLC aluminium plates precoated with silica gel 60F-254 as the stationary phase. The solvent system comprised: tetrahydrofuran: dichloroethane: methanol: ammonia solution (6.0:2.0:1.0:0.4 v/v). This system was found to give compact spots for both telmisartan (Rf value

of 0.22 ± 0.02) and amlodipine besylate (Rf value of 0.45 ± 0.02). Spectrodensitometric scanning-integration was performed at a wavelength of 326 nm. The polynomial regression data for the calibration plots showed good linear relationship with r2 = 0.9993 in the concentration range of 1,200-7,200 ng for telmisartan and 400-1,400 ng for amlodipine besylate with r2 = 0.9996. The method was validated for precision, accuracy, ruggedness, and recovery. The minimum detectable amounts were found to be 149.41 ng and 53.07 ng for telmisartan and amlodipine besylate, respectively. The limits of quantitation were found to be 452.78 ng for telmisartan and 160.83 ng for amlodipine besylate. Statistical analysis proves that the method is reproducible and selective for the simultaneous estimation of telmisartan and amlodipine besylate.

Determination of Amlodipine and Nifedipine in Dosage Form

A simple, accurate, sensitive and economical procedure [50] for the estimation of amlodipine besylate and nifedipine, both in pure and dosage forms, has been developed. The method is based on the reduction of iron(III) by the studied drugs and subsequent interaction of iron(II) with ferricyanide to form Prussian blue. The reaction develops through a slow kinetics and completes in about 10 min. Both initial slope and fixed time methods were used to derive calibration graphs. The resulted calibration equations were linear in the concentration ranges of 1.0-20.0 and 3.0-19.0 µg ml-1 for AML and NIF, and the detection limits were 0.10 and 0.19 µg ml-1, respectively. Seven replicate analyses of solutions containing three different levels of each drug resulted in very low relative error of prediction (less than 1.6%) and relative standard deviation (less than 4%) confirming accuracy and precision of the proposed method. The proposed method was applied to the determination of these drugs in pharmaceutical formulations and excellent recoveries were obtained.

Determination of Amlodipine and Hydrochlorothiazide in Dosage Form

Three sensitive, precise, accurate and simple UV spectrophotometric methods [51] have been developed for simultaneous estimation of Amlodipine (AMLO) and hydrochlorothiazide (HCT) in tablet dosage forms. Method A involved simultaneous equation method. The two wavelengths 238.5 nm (λmax of AMLO) and 271 nm (λmax of HCT) were selected for the formation of Simultaneous equations. Whereas method B involved formation of Qabsorbance equation at isobestic point (257.5 nm). Method C is First order Derivative Spectroscopy method in which derivative amplitudes were measured at selected wavelengths (238.5 nm for HCT and 271 nm for AMLO). Linearity was observed in the concentration range of 1-10, 1-20,1-20 mcg/ml for AMLO and 2.5-25, 2.5-50, 2.5-50 mcg/ml for HCT by method A, B and C respectively. The proposed methods have been applied successfully to the analysis of cited drugs in pharmaceutical formulations. Recovery study was performed to confirm the accuracy of the methods. The methods were validated as per ICH guidelines.

40-In the present work, four different spectrophotometric methods [52] for simultaneous estimation of losartan potassium, amlodipine besilate and hydrochlorothiazide in raw materials and in formulations are described. Overlapped data was quantitatively resolved by using chemometric methods, classical least squares (CLS), multiple linear regression (MLR), principal component regression (PCR) and partial least squares (PLS). Calibrations were constructed using the absorption data matrix corresponding to the concentration data matrix, with measurements in the range of 230.5-350.4 nm (Δλ = 0.1 nm) in their zero order spectra. The linearity range was found to be 8-40, 1-5 and 3-15 µg mL-1 for losartan potassium, amlodipine besilate and hydrochlorothiazide, respectively. The validity of the proposed methods was successfully assessed for analyses of drugs in the various prepared physical mixtures and in tablet formulations.

CONCLUSION

The presented review highlights on various analytical methods published on amlodipine and combination with other drug with comparison in terms of sensitivity, accuracy, precision, advantages and disadvantages.LC-MS-MS methods were found to be most sensitive for amlodipine. Various analytical methods like spectrophotometry, chromatography and in combinations are presented in under Table 1. There is no doubt on the fact that these spectroscopic methods mentioned in the above texts are rapid and far more economical than chromatographic methods but their destructive nature and lack of sensitivity is huge disadvantage for the estimation in biological fluids and impurities estimationn which is possible by chromatography method. In this way various analytical methods for the estimation of these amlodipine in bulk or in various matrixes like blood, serum, plasma, alone or in combination with other drugs is discussed. The presented information is useful for the researchers especially those involved in the formulation development and quality control of amlodipine and combination with other drug.

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Abbreviations

HPLC, high-performance liquid chromatography; RP-HPLC, reversed phase high-performance liquid chromatography; LC, liquid chromatography;TLC, thin layer chromatography; GC, gas chromatography; IR, infrared; MS, mass spectrometry; MEKC, micellar electrokinetic capillary chromatography; UV, ultraviolet; λ, wavelength; ABS, absorbance; LOD, limit of detection; LOQ, limit of quantitation; mol l^{-1}, concentration; SD, standard deviation; RSD, relative standard deviation

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