International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319-6718, ISSN (Print): 2319- 670X
www.ijpsi.org Volume 11 Issue 3 || May. –June. 2022 || PP. 18-26

Amlodipine: A Review of Characteristics, Properties, Analytical Methods and Impact in the Green Chemistry

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Abstract: *Hypertension is considered a public health problem. The initial treatment consists of improving the lifestyle and making changes in the diet. When the changes are not enough, the use of medication becomes necessary. Amlodipine is a calcium channel blocker medication used to treat high blood pressure and coronary artery disease.The objective is to survey the characteristics and properties of Amlodipine, as well as hold a discussion on the existing analytical methods to green chemistry and their impacts for both the operator and the environment. For the survey, data searches were conducted by scientific papers in the literature as well as in official compendium. The characteristics and properties are shown, also, methods using liquid chromatography techniques, titration, absorption spectrophotometry in the ultraviolet and the infrared region. Most of the methods presented are not green chemistry oriented. It is necessary the awareness of everyone involved in the optimization of the methods applied through the implementation of green chemistry to determine the Amlodipine.*

Keywords*: Analytical Methods, Hypertension, Green Chemistry, Amlodipine*

Date of Submission: 15-06-2022 Date of acceptance: 30-06-2022

I. Introduction:

Hypertension has been identified by WHO [1] as one of the most significant risk factors for morbidity and mortality worldwide and is responsible for the deaths of approximately nine million people annually [1]. In the UK, the National Institute for Health and Care Excellence (NICE) [2] defines high blood pressure (BP), also known as hypertension, as a clinic blood pressure of 140/90 mmHg or higher confirmed by a subsequent ambulatory blood pressure monitoring daytime average (or home blood pressure monitoring average) of 135/ 85 mmHg or higher.

High blood pressure does not just develop in older adults. Over 2.1 million people under 45 years old had high blood pressure in England in 2015 [3]. This is important because treating hypertension results in significant reductions in risk of subsequent cardiovascular disease [4, 5]. Despite strong evidence for such treatment, studies suggest that many people remain sub-optimally controlled [6]. New approaches, including new technologies, are therefore needed to improve screening, detection and control of raised blood pressure in the community.

High blood pressure is largely asymptomatic, especially in the early stages, leading to its description as a 'silent killer' [1].

There are mainly two objectives under treatment of Hypertension:

Primary objective

1. To quantify the mortality and morbidity effects from different first- line anti- hypertensive drug classes: thiazides (low dose and high dose), beta- blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, and alpha- blockers, compared to placebo or no treatment.

Secondary objectives

1. To quantify the blood pressure lowering effect of antihypertensive treatment when different drug classes are used as the first- line drug.
2. To quantify the rate of withdrawal due to adverse drug effects of different first- line antihypertensive class drugs, compared to placebo or no treatment.[7]

The first-generation calcium channel blockers (diltiazem, nifedipine, and verapamil), which are short-duration agents with half-lives of 1.5 to 7 hours, are administered every 6 to 8 hours. They are associated with wide swings in plasma levels and consequently in blood pressure and heart rate (Figure) [8]. In contrast, long-acting calcium channel blockers have half-lives of 35 to 45 hours, which allows once-daily administration. Such agents include amlodipine, nifedipine gastrointestinal therapeutic system, and extended-release verapamil.

All calcium channel blockers lower arterial pressure by reducing peripheral vascular resistance. They are effectivein reducing both systolic and diastolic blood pressure [9,10]. Their efficacy as antianginal agents is

due to their effects on myocardial oxygen supply and demand [11]. All calcium channel blockers improve myocardial oxygen supply by vasodilating the coronary arteries. In addition, nondihydropyridines reduce heart rate and myocardial contractility, thus decreasing oxygen demand [11,12]. Multiple studies have confirmed the antianginal properties of calcium channel blockers [12–15].

Calcium channel blockers are also used to treat coronary spasm associated with variant (Prinzmetal's) angina [13,14]. They may be used as first-line agents for the prevention of spasm associated with the use of a radial artery graft for coronary artery bypass grafting [16,17]. Because of their negative chronotropic and dromotropic properties, nondihydropyridines have been used successfully in the treatment of supraventricular arrhythmias [18]. Additionally, verapamil has been found to improve coronary vasomotor response to physical stress in patients with hypertrophic obstructive cardiomyopathy [19,20].

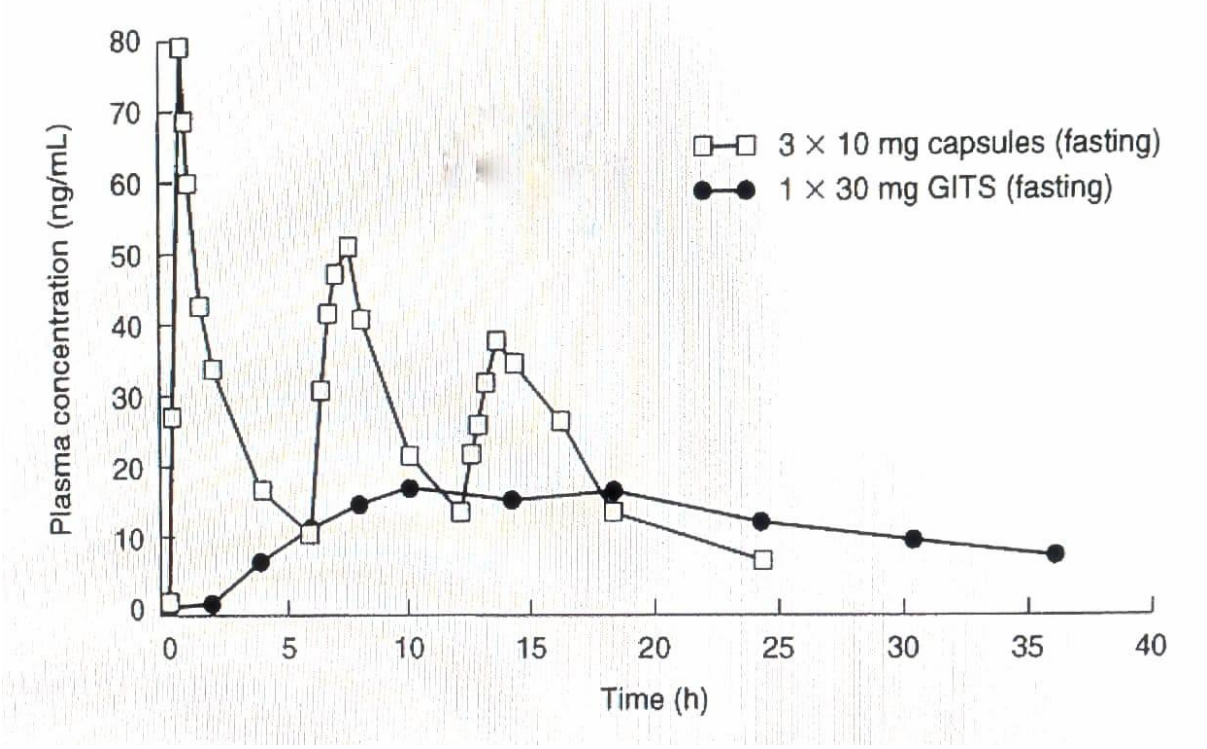

Figure [1]:Short-acting calcium channel blockers (empty squares) are associated with wide swings in plasma levels, whereas long-acting agents (filled circles) are associated with more sustained plasma concentrations. GITS = gastrointestinal therapeutic system. Reprinted from Epstein M. The calcium antagonist controversy: the emerging importance of drug formulation as a determinant of risk. Am J Cardiol. 1997; 79:9-19, Copyright 1997, with permission from Excerpta Medica Inc.

Amlodipine:

Amlodipine is a synthetic dihydropyridine and a calcium channel blocker with antihypertensive and antianginal properties. Amlodipine inhibits the influx of extracellular calcium ions into myocardial and peripheral vascular smooth muscle cells, thereby preventing vascular and myocardial contraction. This results in a dilatation of the main coronary and systemic arteries, decreased myocardial contractility, increased blood flow and oxygen delivery to the myocardial tissue, and decreased total peripheral resistance. This agent may also modulate multi-drug resistance (MDR) activity through inhibition of the p-glycoprotein efflux pump.[21]

Amlodipine besylate is a second generation calcium channel blocker that is used in the therapy of hypertension and angina pectoris. Amlodipine has been linked to a low rate of serum enzyme elevations during therapy and to rare instances of clinically apparent acute liver injury.[22]

Amlodipine is a fully substituted dialkyl 1,4-dihydropyridine-3,5-dicarboxylate derivative, which is used for the treatment of hypertension, chronic stable angina and confirmed or suspected vasospastic angina. It has a role as an antihypertensive agent, a calcium channel blocker and a vasodilator agent. It is a dihydropyridine, a member of monochlorobenzenes, an ethyl ester, a methyl ester and a primary amino compound.[23]

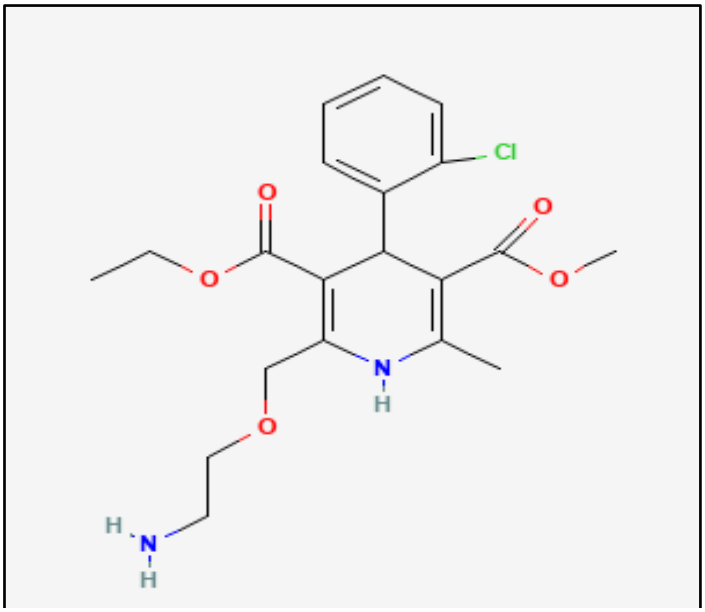

Figure [2]: Chemical Structure of Amlodipine [24]

Action Mechanism:

Mechanism of Action on Blood Pressure:

Amlodipine is considered a peripheral arterial vasodilator that exerts its action directly on vascular smooth muscle to lead to a reduction in peripheral vascular resistance, causing a decrease in blood pressure. Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the influx of calcium ions into both vascular smooth muscle and cardiac muscle. Experimental studies imply that amlodipine binds to both dihydropyridine and nondihydropyridines binding sites, located on cell membranes. The contraction of cardiac muscle and vascular smooth muscle are dependent on the movement of extracellular calcium ions into these cells by specific ion channels. Amlodipine blocks calcium ion influx across cell membranes with selectivity. A stronger effect of amlodipine is exerted on vascular smooth muscle cells than on cardiac muscle cells. Direct actions of amlodipine on vascular smooth muscle result in reduced blood pressure. [25]

Mechanism of Action in Angina:

The exact mechanism by which amlodipine relieves the symptoms of angina have not been fully elucidated to this date, however, the mechanism of action is likely twofold:

Amlodipine has a dilating effect on peripheral arterioles, reducing the total peripheral resistance (afterload) against which the cardiac muscle functions. Since the heart rate remains stable during amlodipine administration, the reduced work of the heart reduces both myocardial energy use and oxygen requirements. [25]

Dilatation of the main coronary arteries and coronary arterioles, both in healthy and ischemic areas, is another possible mechanism of amlodipine reduction of blood pressure. The dilatation causes an increase in myocardial oxygen delivery in patients experiencing coronary artery spasm (Prinzmetal's or variant angina) and reduces coronary vasoconstriction caused by smoking. [25]

Pharmacokinetics:

Amlodipine is a dihydropyridine calcium antagonist drug with distinctive pharmacokinetic characteristics which appear to be attributable to a high degree of ionisation. Following oral administration, bioavailability is 60 to 65% and plasma concentrations rise gradually to peak 6 to 8h after administration. Amlodipine is extensively metabolised in the liver (but there is no significant presystemic or first-pass metabolism) and is slowly cleared with a terminal elimination half-life of 40 to 50h. Volume of distribution is large (21 L/kg) and there is a high degree of protein binding (98%). There is some evidence that age, severe hepatic impairment and severe renal impairment influence the pharmacokinetic profile leading to higher plasma concentrations and longer half-lives. There is no evidence of pharmacokinetic drug interactions. Amlodipine shows linear dose-related pharmacokinetic characteristics and, at steady-state, there are relatively small fluctuations in plasma concentrations across a dosage interval. Thus, although structurally related to other dihydropyridine derivatives, amlodipine displays significantly different pharmacokinetic characteristics and is suitable for administration in a single daily dose.[26]

Physicochemical Properties:

Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1.[27] It is slightly soluble in water and sparingly soluble in ethanol. Amlodipine chemically identified as Amlodipine benzenesulfonate Amlodipine besilate, Amlodipine besylate. Its molecular formula is$C_{26}H_{31}ClN_2O_8S$. and its CAS number is111470-99-6.Amlodipine has a molecular mass of 567.1g/mol, whereas Amlodipine Besylate has a mass of 566.14g/mol.[28] It is slightly soluble in water and sparingly soluble in ethanol.[29] The melting point ranges from 199-201°C,[30] its LogP is2.22and pKa 19.12 (strongest acidic), 9.45(strongest basic).[31]

Analytical Methods:

The analytical methods for Amlodipine evaluation were researched in the literature through scientific articles, as well as in official compendium. Table [1] shows the analytical methods described in the literature for the determination of Amlodipine.

Table [1]: Analytical Methods described in the Literature for the Determination of Amlodipine

Method	Conditions	Matrices	Reference
HPLC	Analytical 125 × 4.6 mm i.d. Nucleosil C_8 column wavelength=239nm Mobile Phase=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}.	Human Plasma	[32]
HPLC	Perfectsil Target ODS-3, 5 microm, 250 mm x 4.6 mm i.d. column using a mobile phase consisting of acetonitrile-0.025 M NaH_2PO_4 buffer (pH 4.5) (55:45, v/v) at a flow rate of 1 ml/min and UV detection at 237 nm	Tablets	[33]
HPLC	4-chloro-7-nitrobenzofurazan (NBD-Cl) and reverse-phase chromatography on C18 column Mobile Phase=sodium phosphate buffer (pH 2.5) containing 1 ml/l triethylamine and methanol at flow rate of 2.8 ml/min	Human Serum	[34]
HPLC	Hypersil BDS cyano (250 mm × 4.6 mm, 5m) column using PDA detectormobile phase consisting of buffer (aqueous triethylamine pH 3) and acetonitrile in the ratio of 85:15 (v/v) at a flow rate of 1.0 mL/min was used	Pharmaceutical Dosage Form	[35]
HPLC	The mobile phase was mixture of 25 mM ammonium acetate adjusted to pH 5.0 and methanol (65: 35) at 0.8 ml/min. The stationary phase was Luna C18-2 column (3 µ, 50×4.6 mm ID). UV detection was performed at 230 nm. Retention time was 1.45 min and 3.91 min for bisoprolol and amlodipine, respectively.	Tablets	[36]
HPLC	RP-C18 chromatographic column, Phenomenex Kinetex (150 mm × 4.6 mm i.d) and a mobile phase consisting of acetonitrile-phosphate buffer (0.05 M) with pH 2.8 in the proportion of (40/60, v/v) at a flow rate 0.8 mL/min and the wavelength detection was 227 nm. The retention time for HCT, AML and VAls was 2.26, 3.16 and 11.19 min; respectively.	Dosage Form and Spiked Human Plasma	[37]
Improved HPLC	Phenomenex C18 analytical column (15064.6 mm id, 5 µm) connected with a Phenomenex C18 guard cartridge (463 mm id, 5 µm).methanol – acetonitrile – 15 mM K2HPO4 buffer (pH 5.33) (10:42.08:47.92, v/v/v) as the mobile phase and 1.12 mL/min as the flow rate.	Pharmaceutical Formulations	[38]
HPLC UV	0.025 M phosphate buffer (pH 3.7):acetonitrile (57:43 v/v) as the mobile phase and Kromasil C18 (4.6 mm i. d×250 mm) column as stationary phase with detection wavelength of 232 nm linearity was obtained in the concentration range of 2-14, 20-140 and 5-40 µg/ml first UV spectrophotometric method detection at 236.5, 254 and 271 nmsecond UV method detection at 231.5-241.5, 249-259 and 266-276 nm	Tablets	[39]
RP-HPLC	KromasilC18 (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	Tablet Formulation	[40]
RP-HPLC	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	Tablet	[41]
RP-HPLC	phenomenex Gemini C-18, 5 µm column having 250×4.6 mm i.d. in isocratic mode, with mobile phase containing 0.02 M potassium dihydrogen phosphate:acetonitrile:methanol (30:10:60, v/v/v) adjusted to pH 4 using ortho phosphoric acid was used. The flow rate was 1.0 ml/min and effluents were monitored at 240 nm	Pharmaceutical Formulations	[42]
RP-HPLC	Phenomenex Gemini C-18, 5 µm column having 250×4.6 mm i.d. in isocratic mode, with mobile phase containing 0.02 M potassium dihydrogen phosphate:acetonitrile:methanol (30:10:60, v/v/v) adjusted to pH 4 using ortho phosphoric acid was used. The flow rate was 1.0 ml/min and effluents were monitored at 240 nm	Capsule Formulation	[43]
RP-HPLC	Stationary Phase-RP-C18 column (150x4.6 mm I.D.; particle size 5	Tablet Dosage Form	[44]

	µm)The mobile phase used was a mixture of acetonitrile and 0.03M phosphate buffer pH 2.9 (55:45% v/v). The detection of atorvastatin and amlodipine was carried out on dual γ absorbance detector at 240 nm and 362 nm, respectively		
RP-HPLC	Lichrospher® 100 C18, 5 mm, 250 mm4.0 mm i.d. column, at ambient temperature, optimum mobile phase consisted of acetonitrile and 50 mM potassium dihydrogen phosphate buffer (60: 40, v/v), apparent pH adjusted to 30.1 with 10% phosphoric acid solution, effluent flow rate monitored at 1.0 ml/min, and UV detection at 254 nm.	Tablet Dosage Form	[45]
RP-HPLC	A phenomenex Luna C-18, 5 µm column having 250 × 4.6 mm i.d. in isocratic mode, with mobile phase containing methanol: acetonitrile: 50 mM KH_2PO_4 (20:50:30; pH 3.5) was used. The flow rate was 1.0 ml/min and effluent were monitored at 240 nm. The retention time of atorvastatin calcium and amlodipine besylate was 7.6 min and 3.2 min respectively.	Tablet Dosage Form	[46]
RP-HPLC	Eclipse XDB C-8 (150 mm X 4.6 mm), 5mm. The mobile phase constituted of Buffer: Acetonitrile (65:35) and pH adjusted to 2.6 with dilute Ortho- Phosphoric Acid was delivered at the flow rate 1.0 mL/min. Detection was performed at 210 nm. Separation was completed within 8 min. Calibration curves were linear with correlation coefficient between 0.99 to 1.0 over a concentration range of 8 to 60 mg/mL of Perindopril Erbumine and 10 to 75 mg/mL of Amlodipine Besylate.	Combined Dosage Form	[47]
RP-HPLC	Isocratic separation using sodium phosphate buffer (pH 5.6): acetonitrile: methanol in a ratio 30:55:15 (v/v) as the mobile phase on a Zorbax C18 (150 mm) reverse-phase (RP)-HPLC column. The analysis was performed at 25°C, using a flow rate of 1.2 mL/minute.	Pure and Formulation using an Experimental Design	[48]
RP-HPLC	The Column used was Spherisorb C_8(5µ),250 mm × 3.9 mm id. The mobile phase, phosphate buffer (pH 5.5): Acetonitrile (50:50), was used at a flow rate of 1 ml/min with an operating pressure of 3000 psi. Bondapak C_{18}/Corasil was used as guard column.	Formulations	[49]
HPLC and HPTLC	Merck HPTLC aluminium sheets of silica gel 60 F254 using n-butanol: acetic acid: water (5:1:0.1, v/v/v) as the mobile phase. The second method was based on the HPLC separation of the two drugs on the RP-PerfectSil-100 ODS3–C18 column from MZ-Analyse Technik GmbH, Germany and acetonitrile/0.03M ammonium acetate buffer (pH ¼ 3) in a ratio of 55:45 as the mobile phase.	Bulk drug and formulation	[50]
HPLC	A C18 column (ODS 2, 10 µm, 200 x 4.6 mm) and a mobile phase of phosphate buffer (pH 3.6, 0.01 mol L-1): acetonitrile: methanol (46:44:10 v/v/v) mixture were used for separation and quantification. Analyses were run at a flow-rate of 1 mL min-1 and at ambient temperature. The injection volume was 20 µL and the ultraviolet detector was set at 240 nm. Under these conditions, amlodipine and valsartan were eluted at 7.1 min and 3.4 min, respectively. Total run time was shorter than 9 min.	combined dosage forms and in vitro dissolution studies	[51]
HPLC and CE	Agilent Zorbax® ODS column (5 µm, 4.6 x 250 mm), flow rate of 1.0 mL min–1 and UV detection were performed at 254.0 nm. Mobile Phase used was acetonitrile/methanol/phosphate buffer pH = 3.0 (45:30:25, V/V/V); pH was adjusted to 2.5 ± 0.1 with orthophosphoric acid.	Tablets	[52]
RP-HPLC	RP C18 base deactivated silica column (250 3 4.6 mm, 5 mm) with a mobile phase consisting of triethylamine (pH 3.0) adjusted with orthophosphoric acid (A) and acetonitrile (B), with a timed gradient program of T/%B: 0/30, 7/70, 8/30, 10/30 with a flow rate of 1.4 mL/min. Ultraviolet detection was used at 236 nm. The retention times for OLME, AMLO and HCTZ were found to be 6.72, 4.28 and 2.30, respectively.	Tablet Dosage Form	[53]
RP-HPLC	Gemini C18 column and mobile phase gradient starting from 20 % acetonitrile and 80 % 10 mmol L–1 ammonium formate (V/V, pH 3.5 ± 0.2, by formic acid) to 70 % acetonitrile and 30 % 10 mmol L–1 ammonium formate, over 20 minutes, with a flow rate of 1 mL min–1.	Human Plasma	[54]
RP-HPLC	Inertsil ODS 3V (150 mm × 4.6 mm, 5 m) column using a 65:35 (v/v) mixture of 1% triethyl amine, pH adjusted to 3.0 with orthophosphoric acid and acetonitrile as mobile phase. The flow rate was 1.0 ml/min and the elution was monitored at 220 nm.	Determination of Genotoxic Alkyl Benzenesulfonates	[55]
HPLC and TLC	Separation by HPLC was achieved using a xTerra C18 column and methanol /acetonitrile /water/ 0.05% triethylamine in a ratio 40:20: 30:10 by volume as mobile phase, pH was adjusted to 3 ± 0.1 with o-phosphoric acid. The flow rate was 1.2 mL min^{-1}. The linearity range was 0.2 to 2 mg mL^{-1} for amlodipine besilate and 0.4 to 4 mg mL1 for Valsartan with a mean percentage recovery of 99.59±0.523% and 100.61±0.400% for amlodipine besilate and valsartan, respectively. The TLC method used silica gel 60 F254 plates; the optimized mobile phase was ethyl acetate/ methanol / ammonium hydroxide (55:45:5 by volume). Quantitatively, the spots were scanned densitometrically at 237 nm. The range was 0.5–4.0 mg spot1 for amlodipine besilate and 2.0–12.0 mg spot1 for valsartan.	Human Plasma	[56]
RP-HPLC	A Brownlee C-18, 5 µm column with a mobile phase containing 0.02 M potassium dihydrogen phosphate– methanol (30+70, v/v) total pH-adjusted to 3 using o-phosphoric acid was used. The flow rate was 1.0 mL min−1	Pharmaceutical Formulation	[57]

	and effluents were monitored at 242 nm. The retention times of amlodipine besylate and indapamide were 5.9 min and 3.6 min, respectively.		
RP-HPLC	Phenomenex luna 5m CN 100R, 250 × 4.60 mm 5-micron size column, ambient temperature with a low-pressure gradient mode with mobile phase containing acetonitrile, water and 0.4% of potassium dihydrogen phosphate buffer pH 2.7 adjusted with orthophosphoric acid (45:35:20). The flow rate was 1 mL min1 and eluent was monitored at 230 nm. The selected chromatographic conditions were found to effectively separate hydrochlorothiazide, amlodipine and losartan with retention time of 3.9, 4.9 and 5.8 min respectively.	Tablet Dosage Form	[58]
HPLC-MS-MS	C18 column using a gradient elution. The mobile phase consisted of 0.1% of formic acid in water and 0.1% of formic acid in acetonitrile and was pumped at a flow rate of 0.4 mL min^{-1}. Detection of analytes was achieved by tandem mass spectrometry with electrospray ionization (ESI) interface in positive ion mode. The calibration curves were linear over the range of 0.46–1,000 ng mL^{-1}.	Plasma of Hypertensive Patients	[59]
Stability indicating HPLC	C-18 column (250 mm × 4.6 mm, 5 µm)30:70 (v/v) solvent mixture of acetonitrile and 0.1 M ammonium acetate buffer (pH 5) as mobile phase. The flow rate of the mobile phase was 1.5 mL/min and all the detections were carried out at 240 nm using UV detector.	Pharmaceutical Formulations	[60]
HPLC	Nucleosil C18 column (250 mm × 4.6 mm, 5 mm) at 40 C. The mobile phase consisted of acetonitrile and 0.02 M monopotassium phosphate buffer (pH 2.2) in the ratio of 50:50 (v/v) was eluted at 1.0 ml/min. The eluent was monitored by the UV detector for fimasartan and amlodipine at 237 nm for 8 min, detection time.	Combination Tablets	[61]

Notes: MP: Mobile Phase, HPLC: High Performance Liquid Chromatography, HPLC–UV: High Performance Liquid Chromatography with Ultraviolet Detection, HPTLC: High Performance Thin Layer Chromatography.

The quantification of Amlodipine in biological samples is very important for conducting pharmacokinetic studies, bioavailability, bioequivalence and consequently for the therapeutic monitoring of this substance. In the analyzed literature, there is a predominance of determination by high-performance liquid chromatography (HPLC), but also determinations using liquid chromatography of ultra-efficiency, titration, ultraviolet absorption spectroscopy and diffuse infrared spectroscopy.

It is necessary to emphasize the absence of analytical methods in the literature and pharmacopoeias for tablet form or other pharmaceutical product, most of them are only for the raw material. This absence is dangerous and can trigger many public health problems. The most commercially available product of amlodipine is the tablets. Thus, the pharmaceutical industry must have analytical methods for evaluating the quality of the final product before release to the consumer market. If quality control does not exist or it is ineffective, products with a doubtful content will be found in the market. The consequence of this is patients without treatment improvement who will return to the health services, which will be overloaded.

Another question is the type of analytical method. The big pharmaceutical and chemical industries have money to invest in technology; however, the small and medium pharmaceutical and chemical industries or even independent or unrelated laboratories to large companies are not equipped with the latest technologies. Therefore, varied methods are needed with the purpose of the industry or laboratory choosing the most appropriate to their reality.

An end item that also impacts this multi-dimensional view is cost. The choice of type of analysis has a direct impact on the cost of this final product. So, it is important to know the impact of an analytical decision.

Impact of Analytical Decisions:

Among the methods studied, most of them do not fit the theory of green chemistry, being toxic waste generators, for example the organic solvents as acetonitrile and methanol. Buffer solutions are not toxic to the environment and the operator, but they can decrease the life of equipment and accessories, such as chromatographic columns and this impacts the cost of the analysis. The proposal is to try to change the solvent used by another less toxic or try to decrease the amount of solvent. However, the reality is that analysts and operators do not try to change processes or do not want to improve the process. They test directly, for example, methanol and acetonitrile automatically.

Drugs that are poorly soluble in water can be solubilized first in ethanol (for example) and diluted in water. This is very common in laboratories that work toward green chemistry. The solvent is still used, but it is a less toxic solvent (ethanol, for example) and in a smaller amount (since the water was used as diluent). This contemplates the solvent required for HPLC technology and the solubility of poorly soluble drugs. This is the thought.

During the development of the method considered green there is concern in the choice of solvents with low toxicity (for example, ethanol and water), as well as to use them in low concentrations in addition to the effort to work with reduced samples, through the miniaturization of the samples. If this is not possible, work

must be done through on recovery of toxic solvents, as these materials cannot be disposed of directly into the environment.

Decrease the process steps and the pre-treatment of the samples are also a part of the green chemistry, because these activities directly influence in the amount of reagents used, the time of analysis or reaction, the number of materials required and cost involved.The method of spectrophotometry in the infrared region is an option and a reality for analysis of pharmaceuticals. It can be used for both qualitative and quantitative analyses of raw materials and pharmaceuticals. It is known as a technique of excellence in pharmaceutical analysis. The method of spectrophotometry in the infrared region is also able to indicate the stability of the product to be analyzed by comparing the spectrum of the standard, being considered an indicative method of stability.

The choice of equipment should also be important, it is recommended to use those that require the least amount of solvent, less time for analysis, lower energy consumption, lower costs for the company and lower final product prices as for example the HPLC or capillary electrophoresis. In capillary electrophoresis, samples are used around nL and in HPLC it is used around µL. Each method has its advantages and disadvantages. The choice must not be by the most famous method or by the method that everyone is using, but the ideal one for your analysis or for what you want to study. HPLC or capillary electrophoresis? It depends on your objectives. What do you want to investigate at the moment?

These methods should be increasingly encouraged by their advantages and economic benefits. Thus, the universities become reference research centers in the area contributing to achievement of this objective.

II. Conclusion:

Amlodipine is the drug of choice for the treatment of hypertension, disease considered a worldwide epidemic. The wide use of this drug contributes to the development of studies that need carry out their analytical and bioanalytical quantification. The existing methods in the literature and official compendiums for quantification of amlodipine in raw material, pharmaceuticals and biological systems can still contemplate more the thought of green chemistry, whether in the choice of solvent, method, amount of sample, number of steps… The improvement of methods of analysis must be constant.

Conflict of interest:

The authors declare no conflicts of interest.

References:

[1]. Organisation WH. World Health Organization (2013), A global brief on hypertension. Report. 2013 April 2013. Contract No.: WHO/DCO/WHD/2013.2.

[2]. Excellence NIFC. <NICE CG 107 hypertension-in-pregnancy-diagnosis-and-management-pdf-35109334011877.pdf>. 2011

[3]. England Public Health. Health matters: combating high blood pressure. WWW.GOV.UK: Public Health England, 2017. Accessed March 2019.

[4]. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338: b1665.

[5]. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet.1990;335(8693):827–38.

[6]. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension treatment and control in five European countries, Canada and the United States. Hypertension. 2004;43(1):10–7.

[7]. Wright, James & Musini, Vijaya & Gill, Rupam. (2018). First-line drugs for hypertension. Cochrane Database of SystematicReviews.4.10.1002/14651858.CD001841.pub3.

[8]. Epstein M. The calcium antagonist controversy: the emerging importance of drug formulation as a determinant of risk.Am J Cardiol. 1997; 79:9–19.

[9]. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. N Engl J Med. 1993; 328:914–921.

[10]. Frishman WH, Brobyn R, Brown RD, et al. Amlodipine versus atenolol in essential hypertension. Am J Cardiol. 1994; 73:50A–54A.

[11]. Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Unstable angina pectoris. N Engl J Med. 2000; 342:101–114.

[12]. Frishman WH, Michaelson MD. Use of calcium antagonists in patients with ischemic heart disease and systemic hypertension. Am J Cardiol. 1997; 79:33–38.

[13]. Taylor SH. Usefulness of amlodipine for angina pectoris. Am J Cardiol. 1994; 73:28A–33A.

[14]. Mayer S, Hillis LD. Prinzmetal's variant angina. Clin Cardiol. 1998; 21:243–246.

[15]. Vandergoten P, Benit E, Dendale P. Prinzmetal's variant angina: three case reports and a review of the literature. Acta Cardiol. 1999; 54:71–76.

[16]. Kulkarni NM, Thomas MR. Severe spasm of a radial artery coronary bypass graft during coronary intervention. Catheter Cardiovasc Interv. 1999; 47:331–335.

[17]. Caputo M, Nicolini F, Franciosi G, Gallotti R. Coronary artery spasm after coronary artery bypass grafting. Eur J Cardiothorac Surg. 1999; 15:545–548.

[18]. Brill DM, Fozzard HA. Calcium channel blocking drugs. Part II: clinical applications. Compr Ther. 1985; 11:67–71.

[19]. Dimitrow PP, Krzanowski M, Nitankowski R, et al. The effect of verapamil on response of coronary vasomotion to handgrip exercise in symptomatic patients with hypertrophic cardiomyopathy.Cardiovasc Drugs Ther. 2001; 4:331–337.

[20]. Roberts R, Sigwart U. New concepts in hypertrophic cardiomyopathies, part II. Circulation. 2001; 104:2249–2252.

[21]. https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C61635

[22]. https://www.ncbi.nlm.nih.gov/books/n/livertox/Amlodipine/
[23]. http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:2668
[24]. https://pubchem.ncbi.nlm.nih.gov/compound/Amlodipine#section=2D-Structure
[25]. https://go.drugbank.com/drugs/DB00381
[26]. Meredith, Peter & Elliott, Henry. (1992). Clinical Pharmacokinetics of Amlodipine. Clinical pharmacokinetics. 22. 22-31. 10.2165/00003088-199222010-00003.
[27]. https://www.rxlist.com/norvasc-drug.htm
[28]. https://pubchem.ncbi.nlm.nih.gov/compound/Amlodipine-besylate
[29]. https://www.google.com/search?q=solubility+of+amlodipine+besylate&rlz=1C1CHBF_enIN923IN923&oq=solubility+of+amlo&aqs=chrome.1.0i512l2j69i57j0i512j0i22i30l2j69i60.6049j0j15&sourceid=chrome&ie=UTF-8
[30]. https://www.worldofchemicals.com/chemicals/chemical-properties/amlodipine-besylate.html
[31]. https://go.drugbank.com/salts/DBSALT001054
[32]. Zarghi, Afshin & Foroutan, Seyed & Shafaati, Alireza & Khoddam, A. (2005). Validated HPLC method for determination of amlodipine in human plasma and its application to pharmacokinetic studies. Farmaco (Società chimica italiana: 1989). 60. 789-92. 10.1016/j.farmac.2005.06.012.
[33]. Mohammadi, Ali & Rezanour, Nasrin & Ansari Dogaheh, Mehdi & Ghorbani-Bidkorbeh, Fatemeh & Hashem, M & Walker, Roderick. (2007). A stability-indicating high performance liquid chromatographic (HPLC) assay for the simultaneous determination of atorvastatin and amlodipine in commercial tablets. Journal of chromatography. B, Analytical technologies in the biomedical and life sciences. 846. 215-21. 10.1016/j.jchromb.2006.09.007.
[34]. Bahrami, Gh & Mirzaeei, Sh. (2004). Simple and rapid HPLC method for determination of amlodipine in human serum with fluorescence detection and its use in pharmacokinetic studies. Journal of pharmaceutical and biomedical analysis. 36. 163-8. 10.1016/j.jpba.2004.05.016.
[35]. Dongre, Vaijanath & Shah, Sweta & Karmuse, Pravin & Phadke, Manisha & Jadhav, Krishnat. (2008). Simultaneous determination of metoprolol succinate and amlodipine besylate in pharmaceutical dosage form by HPLC. Journal of pharmaceutical and biomedical analysis. 46. 583-6. 10.1016/j.jpba.2007.11.006.
[36]. Vora, D & Kadav, Arun. (2008). Development and Validation of a Simultaneous HPLC Method for Estimation of Bisoprolol Fumarate and Amlodipine Besylate from Tablets. Indian journal of pharmaceutical sciences. 70. 542-6. 10.4103/0250-474X.44616.
[37]. El-Gizawy, Samya & Abdelmageed, Osama & Omar, Mahmoud & Deryea, Sayed & Abdel-Megied, Ahmed. (2012). Development and Validation of HPLC Method for Simultaneous Determination of Amlodipine, Valsartan, Hydrochlorothiazide in Dosage Form and Spiked Human Plasma. American Journal of Analytical Chemistry. 2012. 10.4236/ajac.2012.36055.
[38]. Sivakumar, Thanikachalam & Manavalan, Rajappan & Muralidharan, Chandrasekaran & Kannappan, Valliappan. (2007). An improved HPLC method with the aid of a chemometric protocol: Simultaneous analysis of amlodipine and atorvastatin in pharmaceutical formulations. Journal of separation science. 30. 3143-53. 10.1002/jssc.200700148.
[39]. Wankhede, Sagar & Raka, K & Wadkar, S & Chitlange, Sohan. (2010). Spectrophotometric and HPLC Methods for Simultaneous Estimation of Amlodipine Besilate, Losartan Potassium and Hydrochlorothiazide in Tablets. Indian journal of pharmaceutical sciences. 72. 136-40. 10.4103/0250-474X.62239.
[40]. Chitlange, Sohan & Imran, Mohammed & Sakarkar, Dinesh. (2008). RP-HPLC method for simultaneous estimation of amlodipine and metoprolol in tablet formulation. Asian Journal of Pharmaceutics. 2. 10.4103/0973-8398.45037.
[41]. Naidu, Raghu & Kale, Udhav & Shingare, Murlidhar. (2005). Stability indicating RP-HPLC method for simultaneous determination of amlodipine and benzapril hydrochloride from their combination drug product. Journal of pharmaceutical and biomedical analysis. 39. 147-55. 10.1016/j.jpba.2005.04.001.
[42]. Shah, Dixit & Kashyap, Bhatt & Mehta, R.S. & Baldania, Sunil & Tejal, Gandhi. (2008). Stability Indicating RP-HPLC Estimation of Atorvastatin Calcium and Amlodipine Besylate in Pharmaceutical Formulations. Indian Journal of Pharmaceutical Sciences. 70. 10.4103/0250-474X.49117.
[43]. Chitlange, Sohan & Bagri, Kiran & Sakarkar, D. (2007). Stability Indicating RP-HPLC Method for Simultaneous Estimation of Valsartan and Amlodipine in Capsule Formulation. Asian J Res Chem. 1.
[44]. Rajeswari, K. & Sankar, Guntuku & Atmakuri, Lakshmana Rao & Seshagirirao, JVLN. (2006). RP-HPLC Method for the simultaneous determination of Atorvastatin and Amlodipine in tablet dosage form. Indian Journal of Pharmaceutical Sciences. 68. 10.4103/0250-474X.25738.
[45]. Chaudhari, Bharat & Patel, Natvarlal & Shah, Paresh. (2007). Stability Indicating RP-HPLC Method for Simultaneous Determination of Atorvastatin and Amlodipine from Their Combination Drug Products. Chemical & pharmaceutical bulletin. 55. 241-6. 10.1248/cpb.55.241.
[46]. Shah, Dixit & Kashyap, Bhatt & Shankar, M. & Mehta, R. & Tejal, Gandhi & Baldania, Sunil. (2006). RP-HPLC determination of atorvastatin calcium and amlodipine besylate combination in tablets. Indian Journal of Pharmaceutical Sciences. 68. 10.4103/0250-474X.31019.
[47]. Prajapati, Jignesh & Patel, Ajay & Patel, M & Prajapati, Nimesh & Prajapati, Rashmika. (2011). Analytical method development and validation of Amlodipine besylate and Perindopril erbumine in combine dosage form by RP-HPLC. International Journal of PharmTech Research. 3.
[48]. Attimarad, Mahesh & Venugopala, Katharigatta & SreeHarsha, Nagaraja & Al-Dhubiab, Bandar & Nair, Anroop. (2019). Validation of rapid RP-HPLC method for concurrent quantification of amlodipine and celecoxib in pure and formulation using an experimental design. Microchemical Journal. 152. 104365.10.1016/j.microc.2019.104365.
[49]. Sankar, S. & Nanjan, M.J. & Vasudevan, M. & Shaat, N. & Suresh, B. (1997). Simultaneous estimation of atenolol and amlodipine in formulations by reversed phase - HPLC. 59. 171-173.
[50]. Kamble, Asmita & Mahadik, Mahadeo & Khatal, Laxman & Dhaneshwar, Sunil. (2010). Validated HPLC and HPTLC Method for Simultaneous Quantitation of Amlodipine Besylate and Olmesartan Medoxomil in Bulk Drug and Formulation. Analytical Letters - ANAL LETT. 43. 251-258. 10.1080/00032710903325906.
[51]. Celebier, Mustafa & Kaynak, Mustafa & Altınöz, Sacide & Sahin, Selma. (2010). HPLC method development for the simultaneous analysis of Amlodipine and Valsartan in combined dosage forms and in vitro dissolution studies. Brazilian Journal of Pharmaceutical Sciences. 46. 761-768. 10.1590/S1984-82502010000400018.
[52]. Hassan, Said & Elzanfaly, Eman & El-Zeany, Salem & Salem, Maissa. (2016). Development and validation of HPLC and CE methods for simultaneous determination of amlodipine and atorvastatin in the presence of their acidic degradation products in tablets. Acta Pharmaceutica. 66. 10.1515/acph-2016-0040.
[53]. Jain, Pritam & Patel, M.K. & Gorle, A.P. & Chaudhari, Amar & Surana, Sanjay. (2012). Stability-Indicating Method for Simultaneous Estimation of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide by RP-HPLC in Tablet Dosage Form. Journal of chromatographic science. 50. 680-7. 10.1093/chromsci/bms067.

[54]. Sharma, Ritesh & Pancholi, Shyam. (2012). Simple RP-HPLC method for determination of triple drug combination of valsartan, amlodipine and hydrochlorothiazide in human plasma. Acta pharmaceutical (Zagreb, Croatia). 62. 45-58. 10.2478/v10007-012-0004-3.

[55]. Nanduri, Raman & Reddy, K & Prasad, A & Ramakrishna, Karipeddi. (2008). Development and validation of RP-HPLC method for the determination of genotoxic alkyl benzenesulfonates in amlodipine besylate. Journal of pharmaceutical and biomedical analysis. 48. 227-30. 10.1016/j.jpba.2008.05.021.

[56]. Ramadan, Nesrin & Mohamed, Heba & Moustafa, Azza. (2010). Rapid and Highly Sensitive HPLC and TLC Methods for Quantitation of Amlodipine Besilate and Valsartan in Bulk Powder and in Pharmaceutical Dosage Forms and in Human Plasma. Analytical Letters - ANAL LETT. 43. 570-581. 10.1080/00032710903406953.

[57]. Patel, Deval & Mehta, Falgun & Kashyap, Bhatt. (2012). Simultaneous Estimation of Amlodipine Besylate and Indapamide in a Pharmaceutical Formulation by a High-Performance Liquid Chromatographic (RP-HPLC) Method. Scientia pharmaceutical. 80. 581-90. 10.3797/scipharm.1203-07.

[58]. Tengli, Anandkumar & Gurupadayya, B.M. & Soni, Neeraj. (2013). Simultaneous estimation of hydrochlorothiazide, amlodipine, and losartan in tablet dosage form by RP-HPLC. International Journal of Chemical and Analytical Science. 4. 33–38. 10.1016/j.ijcas.2013.03.003.

[59]. Yu, Qi & Hu, Zhe-Yi & Zhu, Fan-Yuan & Zhu, Jin-Hui & Wan, Li-Li & Li, Yan & Guo, Cheng. (2011). HPLC–MS–MS for the Simultaneous Determination of Atorvastatin and Amlodipine in Plasma of Hypertensive Patients. Chromatographia. 73. 257-262. 10.1007/s10337-010-1883-4.

[60]. Ashfaq, Muhammad & Akhtar, Tazeem & Mustafa, Ghulam & Razzaq, Dr. Syed Naeem & Nazar, Muhammad. (2014). Simultaneous Estimation of Rosuvastatin and Amlodipine in Pharmaceutical Formulations Using Stability Indicating HPLC Method. Brazilian Journal of Pharmaceutical Science. 50. 629-638. 10.1590/S1984-82502014000300023.

[61]. Moon, Hyeon & Yousaf, Abid & Cho, Kwan & Yong, Chul & Kim, Jong & Choi, Han-Gon. (2014). Evaluation of stability and simultaneous determination of fimasartan and amlodipine by a HPLC method in combination tablets. Asian Journal of Pharmaceutical Sciences. 9. 10.1016/j.ajps.2014.04.002.

Jeet P. Shah, et. al. "Amlodipine: A Review of Characteristics, Properties, Analytical Methods and Impact in the Green Chemistry." *International Journal of Pharmaceutical Science Invention*, vol. 11(03), 2022, pp 18-26. Journal DOI- 10.35629/6718