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Study on Amlodipine and Its Analytical Methods

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Abstract. Amlodipine (Norvasc) reduces hypertension and atherosclerosis. Orally. Swelling, fatigue, stomachache, and nausea are symptoms. Heart attacks and low blood pressure may kill. Unknown pregnancy and nursing safety Liver disease and ageing diminish the dose. Amlodipine dilates arteries. extended-release dihydropyridine calcium channel blocker. In 1982, amlodipine was patented. It is classified as "essential medicine" by the WHO.This drug is generic. It will have approximately 69 million prescriptions in 2020. Amlodipine is widely used and investigated. These combination medications are not pharmacopoeia-analyzed. Analysts struggle to meet medication criteria while optimising analytical techniques. Multiple spectroscopic, chromatographic, and capillary electrophoresis studies have evaluated amlodipine and its formulation utilising UV, DF, electrochemical, and mass spectrometric (MS) detectors. This paper collects as many amlodipine analysis approaches as possible so researchers may pick the most relevant data for their methodology. International drug analysis procedures are uncommon. Researchers and companies will improve amlodipine and formulation analysis procedures. Amlodipine requires lab or industrial testing.

Keywords: Amlodipine, Formulation, Calcium channel blocker, Pharmacokinetics

INTRODUCTION:

Antihypertensive and antiatherosclerotic effects of amlodipine (Norvasc). Orally. Inflammation, exhaustion, nausea, and vomiting are some of the symptoms. The two leading causes of death in the United States are heart disease and hypertension[1]. There is a lack of data on the safety of the substance during pregnancy and breastfeeding. Aging and liver illness reduce effectiveness. Arteries are made wider by amlodipine. Dihydropyridine, a calcium channel blocker with extended release. The amlodipine patent was issued in 1982. It has been deemed "essential medication" by the World Health Organization. The medicine is available in generic form. Around 69 million prescriptions will be filled by 2020. There has been a lot of research and usage of amlodipine[2]. None of these multi-drug preparations have been evaluated by the pharmacopoeia. Optimizing analytical methods while still meeting pharmaceutical requirements is a challenge for analysts. Amlodipine and its formulation have been the subject of many spectroscopic, chromatographic, and capillary electrophoresis research using UV, DF, electrochemical, and mass spectroscopy detectors (MS). This publication compiles a wide variety of amlodipine analysis methods to provide researchers a wider range of options from which to choose. Testing and analysis methods for drugs on a global scale are unusual. In order to better understand how amlodipine works, scientists and pharmaceutical firms will do analytical research. Laboratory or production tests on amlodipine are necessary[3].

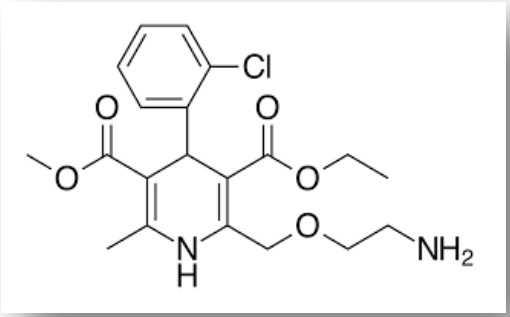

Fig. 1: Chemical Structure of Amlodipine

Mechanism of Action

Normally, contraction of vascular smooth muscle begins when calcium enters the cell via voltage-dependent L-type calcium channels. The calcium stimulates myosin light-chain kinase by binding to and activating calmodulin, an intracellular protein (MLCK). Myosin light chain

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kinase (MLCK) catalyses myosin light chain phosphorylation, a process that initiates muscle contraction and vasoconstriction. Ca2+ triggers calcium release from the sarcoplasmic reticulum, which further amplifies the contraction of vascular smooth muscle. A lower blood flow, more resistance in the blood vessels, and higher blood pressure are the results of this chain of events[4].

Amlodipine is able to do its job by preventing the initial inflow of calcium by blocking the voltage-dependent L-type calcium channels. Vascular smooth muscle contractility is reduced, smooth muscle relaxation is enhanced, and vasodilation is the outcome when intracellular calcium levels are lowered. Vascular endothelial function has also been enhanced in hypertensive individuals after treatment with amlodipine. By causing vasodilation and relaxation of smooth muscles, amlodipine is able to reduce hypertension[5].

As a result of its vasodilatory and antihypertensive effects, amlodipine may alleviate stable angina. Since the heart doesn't have to work as hard to pump blood into the systemic circulation, myocardial oxygen demand is reduced regardless of the intensity of the activity when afterload is reduced. As with Prinzmetal or variant angina, amlodipine reduces symptoms by preventing coronary spasms and relieving ischemia[6].

Color changes in the distal skin of the fingers, toes, nose, and earlobes are clinical manifestations of Raynaud phenomenon (RP), an exaggerated vascular reaction to cold temperature. Patients with Raynaud's phenomenon may benefit from amlodipine's short-term use as a therapy since it causes smooth muscle relaxation[7].

Diabetic nephropathy is often treated first with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)[8].

The antiproteinuric impact of amlodipine plus an ARBs/ACE-I +, however, has been proven in clinical studies for individuals with type 2 diabetic nephropathy to be stronger[9].
Although the Anglo-Scandinavian Outcomes Trial (ASCOT) found that a blood pressure regimen based on amlodipine reduced the long-term risk of stroke compared to atenolol, further study is needed[10].

Pharmacokinetics

Absorption: Amlodipine's absolute bioavailability is 64%-90%. Amlodipine's bioavailability is unaffected by foodbetween 6 and 12 hours is when plasma concentrations are at their highest. After 7 to 8 days of once-daily dosage, steady-state plasma levels are reached with amlodipine. Approximately 40-60% increased AUC is seen in patients with hepatic impairment due to reduced clearance of amlodipine[11].

Distribution: Amlodipine is highly bound to proteins in the plasma (93 percent)[12].

Metabolism: The liver plays a major role in converting amlodipine into inactive metabolites[13].

Excretion: Hepatic impairment lengthens the terminal elimination phase of amlodipine's biphasic plasma half-life, which is roughly 30-50 hours. The kidneys are responsible for most of the elimination process; 10% of the parent molecule and 60% of the metabolites are eliminated in the urine[14].

Administration

Amlodipine comes in tablet forms with dosages of 2.5 mg, 5 mg, and 10 mg, and is often used orally. Patients of any age who have trouble swallowing may have suspensions made from oral pills. Amlodipine has a half-life of 30-50 hours, making it the longest of all dihydropyridine drugs. Such a lengthy half-life allows for once-daily treatment, which is a great convenience for patients[15].

Recommended Dosages

Hypertension

Adults: Start with 5 mg once day and increase to 10 mg as needed.

Geriatric and Debilitated Patients: Reduce initial dose to 2.5 mg once daily; maximum dose of 10 mg per day

Adolescents and Children 6 years of age or older: Generally, once daily dosing in the range of 2.5–5 mg is safe, with a daily max of 5

Children 6 years of age or younger:0.05 to.2 mg/kg daily; 0.3 to.6 mg/kg daily maximum (up to 5 mg per day)

Acute Coronary Syndrome, Chronic Stable Angina, Prinzmetal Angina, Angiographically Confirmed Acute Coronary Syndrome, No History of Heart Failure, and an Ejection Fraction Greater Than or Equal to 40%

Adults: Five to ten milligrammes (mg) once day is the recommended starting dosage.
Elderly and debilitated patients: Initial dose 5 mg once daily; usual dose is 10 mg once daily
Amlodipine can be used as monotherapy or combination with several different medications to manage hypertension or CAD in patients. Common combinations include:

Amlodipine/atorvastatin: To lessen the likelihood of cardiovascular problems, people take atorvastatin, a lipid-lowering medication that works by inhibiting the production of cholesterol.
Amlodipine/aliskiren or amlodipine/ aliskiren/ hydrochlorothiazide: Direct renin inhibitors like aliskiren bind to renin and block it from activating the renin-angiotensin-aldosterone pathway, which is responsible for high blood pressure (RAAS). Thiazide diuretics, like hydrochlorothiazide, cause the body to eliminate excess fluid by increasing urine production. As a result, both combinations are effective in reducing blood pressure.
Amlodipine/ benazepril or amlodipine/ perindopril: Blocking the RAAS conversion of angiotensin I to angiotensin II is the goal of ACE-inhibitors like benazepril and perindopril.
Amlodipine/olmesartan or amlodipine/ telmisartan or amlodipine/ valsartan: Drugs like olmesartan, telmisartan, and valsartan, together known as angiotensin-II receptor blockers (ARBs), reduce RAAS activity by blocking angiotensin II receptors[16].

Use in Specific Patient Population
Patients with Hepatic Impairment: Due to the fact that amlodipine is largely processed by the liver and that the plasma elimination half-life is extended with reduced hepatic function, careful titration of the dosage is advised. Initial treatment for hypertension requires 2.5 mg once day, whereas treatment for angina requires 5 mg once daily. Vary the dose according to the patient's reaction[17].

Patients with Renal Impairment: Amlodipine pharmacokinetics are unaffected by moderate to severe renal impairment. Thus, there is no need to change the dosage for individuals with renal impairment[18].

Pregnancy Considerations: Pre-eclampsia, preterm delivery, intrauterine growth restriction (IUGR), and intrauterine mortality are several complications that may arise from untreated hypertension during pregnancy. Findings from the Chronic Hypertension and Pregnancy (CHAP) study suggest that targeting a blood pressure of less than 140/90 mm Hg in pregnant women with moderate chronic hypertension is linked with better pregnancy outcomes than reserving therapy for just severe hypertension. Based on these results, the ACOG and the SMFM recommend treating moderate chronic hypertension in pregnancy with antihypertensive medications to achieve a blood pressure (BP) of 140/90 mm Hg. Besides the commonly used calcium channel blockers, labetalol, nifedipine, and methyldopa are also recommended by the American College of Obstetricians and Gynecologists (ACOG). Although other antihypertensive drugs and untreated maternal hypertension are linked to an increased risk of foetal abnormalities, amlodipine intake during pregnancy does not seem to raise this risk. New research suggests that amlodipine may be used safely to treat hypertension in pregnant women[19].

Breastfeeding Considerations: Amlodipine is not detected in the plasma of babies who have been breastfed. There is no evidence that breastfed newborns are at risk when their mothers use amlodipine. In conclusion, amlodipine is safe for nursing moms to take[20].

Adverse Effects

Amlodipine's main side effects include peripheral edoema, heart failure, pulmonary edoema, flushing, dizziness, headache, drowsiness, skin rash, nausea, stomach discomfort, and constipation. Side effects such as swelling, dizziness, flushing, and heart palpitations were seen in a dose-dependent manner in clinical studies. At a dosage of 10 mg, for instance, 10.8 percent of people had edoema, 3.4% experienced dizziness, 2.6% experienced flushing, and 4.5% experienced palpitations. Headaches, weariness, nausea, and stomach discomfort all occurred in 7.3%, 4.5%, 2.9%, and 1.6% of people, respectively[21].

Rare cases of idiosyncratic drug-induced liver damage have been associated with calcium channel blockers like amlodipine. Amlodipine-induced liver damage often displays a mixed hepatocellular-cholestatic pattern. There should be full healing in 4-8 weeks following drug withdrawal. It has been observed that the risk of hypotension and acute renal damage is enhanced when amlodipine is given along with clarithromycin or erythromycin owing to impaired

metabolism by CYP3A4. There is an elevated risk for myopathy and rhabdomyolysis when amlodipine is administered along with high dosages of statins[22].

Amlodipine has been linked to peripheral edoema, so be aware of the possibility. When edoema is misdiagnosed as a different health problem and a diuretic is given to treat it, this is called a "prescribing cascade."[23]

Enhancing Healthcare Team Outcomes

Among the several available antihypertensive drugs, amlodipine stands out as a top choice for first treatment. Amlodipine's ability to reduce cardiovascular outcomes has also been shown to be quite significant (especially stroke). Amlodipine's half-life is the longest (between 30 and 50 hours), compared to that of nifedipine and other dihydropyridine family drugs. Having a half-life so long allows for once-daily dosage, which is convenient. Consequently, it is imperative that doctors, pharmacists, nurse practitioners, etc., know when amlodipine is appropriate and when it is not. Overdosing on the medicine may result in life-threatening hypotension, therefore it's best to start with a modest dosage and increase it gradually. Further, maintaining good blood pressure management requires continuous monitoring of patients[24].

Every member of the healthcare team should be involved in amlodipine treatment for optimal results. Treatment is often started by clinicians such general practitioners, naturopaths, and specialists. The pharmacist must inform the doctor about any possible medication interactions (e.g., simvastatin or erythromycin). A pharmacist's other responsibilities include confirming the proper dosage and informing the patient about any side effects. The nurse's role is to check on the patient's compliance and provide advice on how to take their medications. If there are any problems, the pharmacist and the nurse should notify the doctor. Emergency medical personnel and triage nurses dealing with a patient who has taken an overdose of amlodipine should prioritise blood flow stabilisation. An immediate consultation with a physician toxicologist should be sought after in the case of a significant overdose of amlodipine. Patients receiving vasopressor treatment in the MICU must be under the supervision of a physician specialising in critical care. By optimising effectiveness and limiting the risk of adverse medication responses, the interprofessional team approach may enhance patient outcomes associated to amlodipine treatment. An further study showed that long-term blood pressure management associated to antihypertensive treatment, including calcium channel blockers, may be achieved via Team based care (TBC) combining community pharmacists and nurses working interprofessionally with doctors[25].

Analytical methods for the analysis of amlodipine

Spectrophotometric Methods for amlodipine analysis in different matrices

A novel spectrophotometric approach for the measurement of amlodipine and nicardipine in their raw materials and pharmaceutical formulation was developed and validated by Derayea and co-authors. Maximum absorption was seen at 549 nm when the two medicines were treated with eosin Y to produce a binary complex. Temperature, pH, and surfactant concentration were all investigated and found to be optimal for the process. The standards were prepared by dissolving the drugs in ethanol and distilled water, respectively; then, one millilitre of standard was combined with half a millilitre of methyl cellulose surfactant (0.3 percent) and half a millilitre of Mcllvaine buffer; finally, one millilitre of eosin Y was added, and the mixture was incubated at room temperature for 10 minutes. Then, in a volumetric flask, the volume was adjusted to 10 ml. A UV/Vis spectrophotometer set to the wavelength of 549 nm was used for the study. Both amlodipine (5-60 g/ml) and nicardipine (10-60 g/ml) were found to be linearly analysed by the approach. Amlodipine and nicardipine have detection limits of 1.8 and 1.1 micrograms per millilitre, respectively. The LOQs for amlodipine and nicardipine were 6 g/ml and 5 g/ml, respectively. In terms of precision, accuracy, and specificity, the approach was tested and found to be adequate. The commercial formulation was applied to the procedure and compared to other methods. Recoveries ranged from 97.1% to 99.8%, with no appreciable variation from the reference procedures. The authors conclude that their approach should be employed in quality control laboratories since it is cost-effective and requires no specialised equipment or special reagents. They said their process was easy and didn't need any kind of extraction. In general, the disclosed approach is very sensitive and can identify even trace amounts of the substances of interest[26].

Analysis of amlodipine and its pyridine photodegradation product (AMLOX) in ethanol (95%) as solvent at two different wavelengths was

performed by Ragno and colleagues utilising third order derivative spectrophotometric techniques. They noticed that amlodipine and AMLOX spectra overlap significantly, so they examined the first through fourth derivatives and found that the third derivative provided the best results with the least amount of overlap. Since the pyridine derivative of amlodipine did not affect the results of the analysis, it could be read at 243 nm. Both 5-50 micrograms per millilitre and 0.2-5.0 micrograms per millilitre ranges of amlodipine and AMLOX were examined. Using this method, we determined that 0.15 g/ml was the LOD for AMLOX and that 0.45 g/ml was the LOQ. Because the derivative spectra are unaffected by background absorption caused by turbidity baseline, this approach may be employed directly for dissolved and diluted tablet without any further treatment. They arrived at the conclusion that this approach is straightforward and may be used for quality control in amlodipine pharmaceutical production[27].

Murat Uzturk and colleagues devised a spectrophotometric approach for detecting amlodipine besylate in plasma without the need for derivatization. Extractions were performed using a liquid-liquid technique, using a combination of 1-4 volume percent (v/v) ether and hexane in a buffer solution. Samples and standards were prepared using an ethanol-acetonitrile (30:70) solution, and the wavelength was set to 360 nm. Results showed a linear response between 2 and 17 ng/ml, with a limit of detection (LOD) and limit of quantitation (LOQ) of 1.5 and 2 ng/ml, respectively. The extraction process resulted in a recovery of 88.0% -98.4%. It was determined by the authors that their approach was quick, easy, and accurate, and that it could be used with no negative effects from the excipients[28].

The spectrophotometric technique for estimating amlodipine besylate in pharmaceutical dosages and weight was developed by Shyni Bernard and her colleagues. Although amlodipine is weakly soluble in water, the authors claim that they have circumvented the need for an organic solvent by instead using a 2 M urea solution as hydrotropic solubilizing. Urea did not affect the measurement at the working wavelength of 243 nm. In a linear range of 5-25 g/ml, the results indicated that the LOD and LOQ were 2 g/ml and 5 g/ml, respectively. Two commercial formulations of amlodipine were analysed using the devised approach, and the findings demonstrated a high degree of concordance between the measured and declared levels of the drug. The author concludes that the approach described here is suitable for regular analysis of amlodipine in pharmaceutical formulations and biological fluids since it is straightforward, accurate, quick, and cost-effective[29].

Two spectrophotometric techniques for the measurement of amlodipine besylate and losartan potassium in tablet form were devised and verified by Patil and colleagues. Two medicines, amlodipine besylate and losartan potassium, were dissolved in methanol, and their spectra indicated that their respective max values were 208 nm and 237.5 nm, with a single iso absorptive point at 242.5 nm. The findings from the spectra suggested that the simultaneous equation approach should have been the first to be developed. To do this, a simultaneous equation was created and solved using two analytical wavelengths, 208 nm and 237.5 nm, respectively, for both medicines. The absorbance was measured at 242.5 nm (the iso-absorptive point) and 237.5 nm using the Absorbance ratio or Q-analysis technique. To facilitate the calculation of drug concentrations, two separate equations were developed, one for each methodology. Both medicines had a linearity range of 2-20 ng/ml, indicating that the procedures were accurate. The methods were also applied to commercial tablets, yielding a recovery of 95–110 percent and a concordance between calculated and suggested values for two medications in commercial tablets. The author concludes that the two approaches are innovative in that they are quick, easy, do not need further extraction or heating, and use no organic solvents. They may be used in regular quality control analysis of Amlodipine besylate and losartan potassium[30].

Mishra's group also created two spectrophotometric techniques for a different amlodipine formulation. These techniques were used to calculate the tablet dosages of amlodipine besylate and nebivolol hydrochloride. After being dissolved in methanol, the medications' spectra were scanned, revealing that amlodipine and nebivolol, respectively, had maximal wavelengths of 238 and 360 nm. The results also demonstrated that there was no interference between the two medications at those wavelengths, hence 238 nm and 281 nm were chosen for amlodipine and nebivolol in the first approach, while 360 nm and 281 nm were used in the second method. In both

procedures, we were able to directly determine the amlodipine concentration from the measured absorbance, but the nebivolol concentration required the use of derived equations. Standard concentration ranges were evaluated, and the procedures were statistically verified. The recovery research used these two approaches to commercial pills and found that they were both reproducible and reliable. Finally, the author concludes that these two procedures are straightforward, reliable, sensitive, and exact. As a result, they are useful for determining both commercially available medication formulations at the same time. The author also found that the first approach was the most reliable[31].

CONCLUSION

The drug amlodipine has been the subject of much study and development due to its widespread medicinal use. The pharmacopoeia does not yet provide analytical procedures for these combination medicines. It becomes very challenging for the analyst to create and meet the drug's specifications in a way that optimises the analytical process. In the past, researchers have reported their findings after analysing amlodipine and its formulation using UV, diode array, fluorescence, electrochemical, and MS detectors, among others, utilising spectroscopic, chromatographic, and capillary electrophoresis techniques. We set out to provide as many existing approaches to amlodipine analysis as possible so that academics may pick and choose the most relevant ones from which to draw conclusions and formulate their own strategy. Unfortunately, there is still a dearth of analytical methods that meet the standards set out by the worldwide community for the testing of pharmaceuticals. To better analyse amlodipine and its formulation, scientists and companies are working on new techniques that should be available soon. More research and development in the area of amlodipine analysis is still welcome in either a laboratory or factory setting.

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