CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://zenodo.org/records/12774204

https://www.iajps.com/volumes/volume11-july-2024/15-issue-07-july-24/

Available online at: http://www.iajps.com Review Article

A REVIEW ON SPECTROSCOPIC ANALYSIS OF AMLODIPINE

Amritha. A[*1], Dileep. C. Babu[*1], Varsha Suresh[*1], Mrs. Dhanya. S[2], Mr. Nishad V.M[3], Dr. R. Xavier Arulappa[4], Dr. Prasobh G.R[5]

[1]B Pharm students, Sree Krishna College of Pharmacy and Research Centre Parassala, Thiruvananthapuram, Kerala, India., [2]Assistant Professor, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India., [3]Associate Professor, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India., [4]Professor and HOD, Department of Pharmaceutical Chemistry, Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram, Kerala, India., [5]Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

Article Received: June 2024 Accepted: June 2024 Published: July 2024

Abstract:

Hypertension is one of the most common communicable diseases nowadays and is the leading cause of death worldwide, affecting 1.4 billion people. Treatment options include the widely used calcium channel blockers, among which amlodipine, a dihydropyridine, has low renal clearance and long half-life and duration of action, which allows it to sustain its anti-hypertensive effect for more than 24 h following a single dose. It has proven to reduce BP variability and successfully lower BP. A simple, sensitive, specific, and validated UV method has been developed for the quantitative determination of Amlodipine besylate in pure and tablet dosage form. UV methods are simple, rapid, and cost-effective. They are suitable for routine quality control analysis in pharmaceutical formulations. UV spectroscopy avoids the need for complex separation techniques.

Key Words: *Amlodipine, UV Spectroscopy, L type calcium channel blockers.*

Corresponding author:

Amritha.A – *amrithaanil255@gmail.com*
Dileep.C. BABU – *dileepcb.99@gmail.com*
Varsha Suresh – *varshasuresh3854@gmail.com*
B Pharm students, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

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Please cite this article in press Amritha.A et al ***Formulation And Evaluation Of Aloin Loaded Microspheres To Treat Diabetes.,*** *Indo Am. J. P. Sci, 2024; 11 (07).*

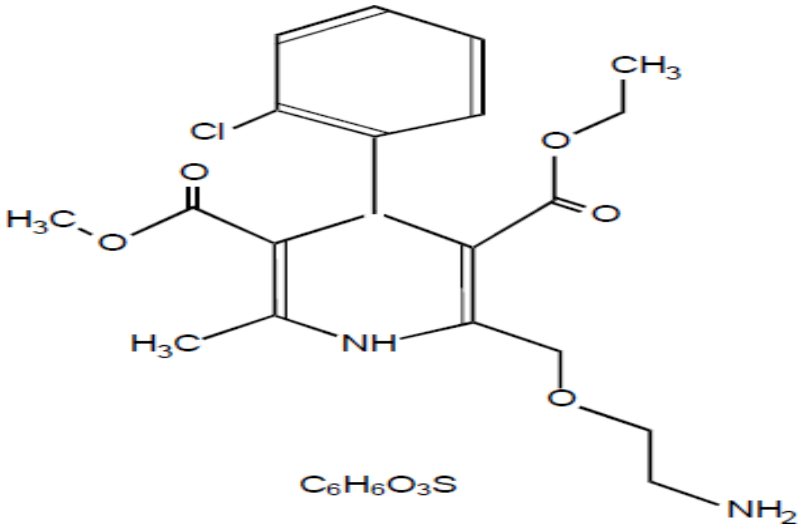
INTRODUCTION:

Amlodipine is a potent long-acting, lipophilic third generation dihydropyridine (DHP) calcium channel blocking agent (CCB) that exerts its action through inhibition of calcium influx into vascular smooth muscle cells and myocardial cells, which result in decreased peripheral vascular resistance (PVR). The drug has been widely used to treat high blood pressure (BP)/HTN, angina and is relatively safe. A starting dose of 5mg is usually recommended with a maximum daily dose of 10mg. Amlodipine besylate is scientifically known as [RS]-3-ethyl-5 methyl-2-[2-aminoethoxymethyl]-4-[2-chlorophenyl]-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate benzene sulphonate. Amlodipine is a white or almost white powder with 97.0% - 102.0% anhydrous substance which are slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in 2-propanol. It is identified by infrared absorption spectrophotometry. It possesses optical rotation (-0.10˚ to + 0.10˚) when 0.250g of amlodipine is dissolved in methanol R and dilute to 25.0 ml with the same solvent. It can be assayed using the method liquid chromatography. It can be stored in an airtight container and protected from light.

Chemistry:

IUPAC NOMENCLATURE: [RS]-3-ethyl-5 methyl-2-[2-aminoethoxymethyl]-4-[2-chlorophenyl]-1, 4- dihydro-6-methyl-3, 5-pyridinedicarboxylate benzene sulphonate.

Structure activity relationship:



General structure activity relationship of dihydropyridine calcium channel blockers can be summarised as follows:

- R1 should be unsubstituted
- R1 should be easily detachable group
- Basic amino ethyl ether chain at R2 increases the potency of drug. While H/aryl group results in loss of activity of drug.
- Substitution of R3 and R5 with alkoxy carbonyl group gives optimum activity.
- Branching of alkyl chain of ester group decreases the activity.
- R4 must be phenyl ring.
- S-enantiomers are more active than R-enantiomers.

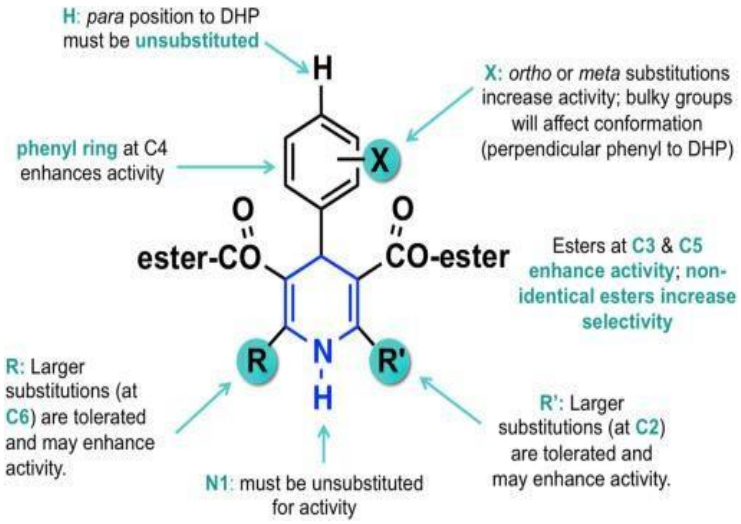


Fig no 2: - structural activity relationship of amlodipine.

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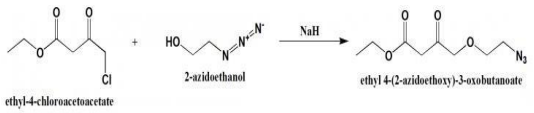
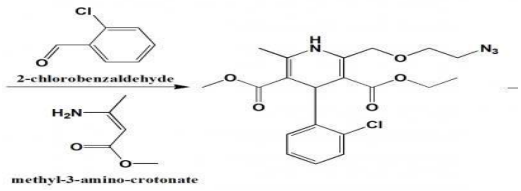
METHOD OF SYNTHESIS:

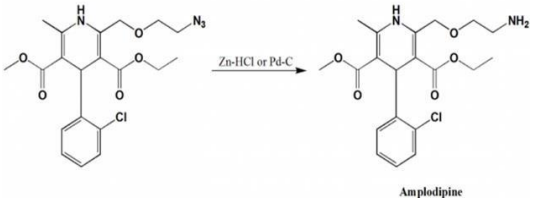
Ethyl-4-cholroacetoacetate reacts with 3-azidoethanol in presence of sodium hydride to give ethyl-4- (2-azidoethoxy)-acetoacetate.



Ethyl-4-(2-azidoethoxy)-acetoacetate reacts with 2-cholorobenzaldehyde and methyl-3- aminocrotonate to give 3-ethyl-5methyl-2-[(-azidoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6- methyl-3, 5-pyridinecarboxylate.



i. On reduction of the above formed compound, amlodipine is formed.



SI .NO	PHYSICALAND CHEMICAL PROPERTIES	
1	MOLECULAR WEIGHT	408.9g/mol
2	PHYSICAL APPEARANCE	SOLID
3	MELTING POINT	199-201˚C
4	OCTANOL/WATER PARTITION COEFFICIENT	3
5	SOLUBILITY	SLIGHTLY SOLUABLE IN WATER
6	NUMBER OF CHIRAL CENTRES	1

Table no 1: - Physical and chemical properties of amlodipine

Pharmacology: Classification:

- Dihydropyridines
- Calcium channel blockers

Mechanism of action:

Generally, when calcium enters the cell via voltage-dependent L-type calcium channels, contraction of vascular smooth muscles takes place. The calcium then binds to the intracellular calmodulin which binds to and activates myosin light-chain kinase (MLCK). MLCK is responsible for the phosphorylation of the myosin light chain, which then leads to the muscle contraction and vasoconstriction. The released calcium from the sarcoplasmic reticulum amplifies the vascular smooth muscle contraction. This series of events leads to a decreased vascular cross-sectional area, increased vascular resistance and increased blood pressure.

Amlodipine works by blocking the voltage-dependent L-type calcium channels, thereby inhibiting the initial influx of calcium. Thereby intra cellular calcium level reduces which leads to decreased vascular smooth muscle contractility, increased smooth muscle relaxation and resultant vasodilatation.

Amlodipine's role in relieving stable angina is due to the lowering of afterload secondary to its vasodilatory and antihypertensive properties. Reduced afterload leads to lower myocardial oxygen demand at any level of exertion, as the heart does not need to work as hard to pump blood into the systemic circulation. Amlodipine also alleviates Prinz metal or variant angina by blocking coronary spasms and restoring blood flow in the coronary arteries.

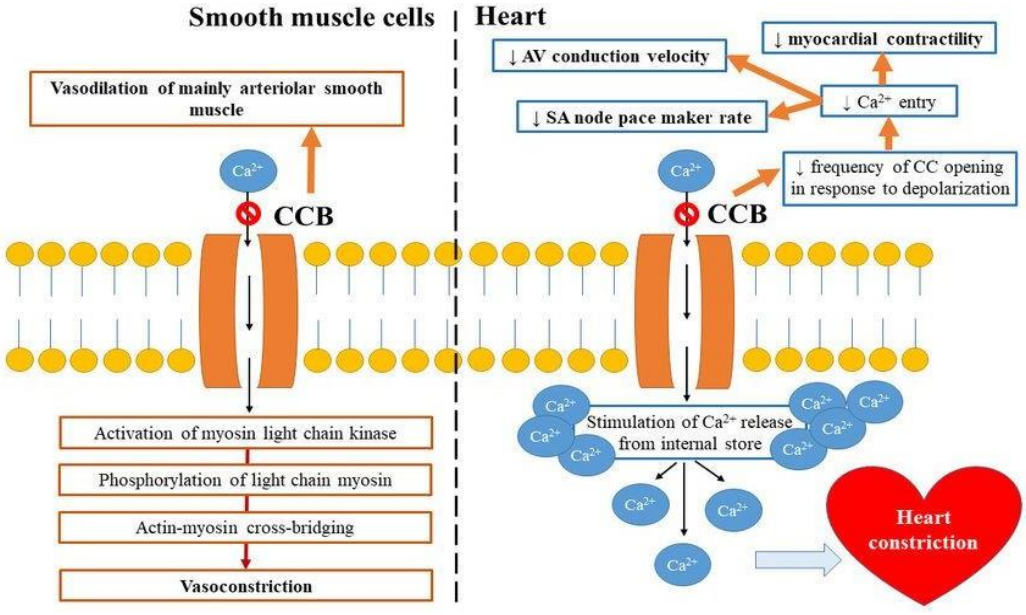


Fig no 3:- Mechanism of action of amlodipine.

Uses of amlodipine:
The medication is used to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks and kidney problems. Use this medication regularly to get the most benefit.

It also used to help blood flow more easily to your heart when the arteries in your heart are blocked.

Amlodipine is also used to treat coronary artery disease and angina (chain pain).

Amlodipine has antioxidant properties and an ability to enhance the production of nitric oxide (NO), an important vasodilator.

Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

Side effects:
- Dizziness, Drowsiness
- Swelling of your legs or ankles.
- Irregular heartbeat
- Pounding heartbeats or fluttering in your chest.
- Muscle stiffness.
- Uncontrolled muscle movements.
- Feeling tired.
- Stomach pain, Nausea.
- Flushing (sudden warmth, redness or tingly feeling).

Adverse drug reaction:
- If you experience any of the following symptoms, call your doctor immediately or get emergency medical treatment.
- Hypersensitivity reaction: - hives, difficulty breathing; swelling of your face, lips, tongue, or throat.
- In rare case, your chest pain may get worse or could have a heart attack.
- Chest pain or pressure, pain spreading to your jaw or shoulder.
- Nausea and sweating.
- Blisters or peeling skin
- Fever, sore throat, chills, and other signs of infection.
- Unusual bleeding or bruising.
- Hypokalaemia.

Drug forms and strengths:
Generic: Amlodipine Form: Oral tablet
Strengths: 2.5 milligram (mg), 5 mg, 10 mg. Brand:
Form: Oral tablet
Strengths: 2.5 mg, 5mg, 10mg.

Dosange for high blood pressure (hypertension):
Adult dosage (age 18 to 64 years)
- Typical starting dosage: 2.5 mg to 5 mg taken once per day.
- Dosage increases: your doctor may change your dosage based on your blood pressure goals. If your blood pressure is still not managed after 7 to 14 days of treatment, your doctor may increase your dosage.
- Maximum dosage: 10 mg per day.

Child dosage (age 0 to 5 years)
This drug is not usually prescribed for use in children younger than 6 years.

Geriatric dosage (age 65 years and older)
- Typical dosage: 2.5 mg taken by mouth once per day.

Adult dose for coronary artery disease:
Maintenance dose: 5-10mg orally once a day

Adult Dose For Angina Pectoris: -
Maintenance dose: 5-10 mg orally once a day
Geriatric dose: initial dose 5 mg orally once a day
Paediatric dose: 6 to 17 Year: - 2.5 -5mg orally once a day

Interaction with other medications:
Amlodipine oral tablet can interact with other medications, vitamins or herbs you may be taking. An interaction is when a substance changes the way a drug works. This can be harmful or prevent the drug from working well.
Heart medication
Taking diltiazem with amlodipine can increase the level of amlodipine in your body. This may cause more side effects.
Antifungal medication
Taking amlodipine with these drugs can increases the level of amlodipine in your body. They may cause more side effects.
Eg:
- Ketoconazole
- Itraconazole
- Voriconazole

Antibiotic:
Taking clarithromycin with amlodipine can increases the level of amlodipine in your body. They may cause more side effects.
Medications for erection problems
Taking amlodipine with these drugs can increase your

risk of low blood pressure (hypotension).
Eg:

- Sildenafil (Viagra)
- Tadalafil (Cialis) how
- Avanafil
- Vardenafil (Levitra)

Cholesterol medication:
Taking with simvastatin can cause the levels of simvastatin to increase ion your body. (Simvastatin is a cholesterol medication). This may increase the risk of simvastatin's side effects.

Drugs that control your immune system:
Taking amlodipine with these drugs can cause the level s of these medications to increase in your body. This may lead to more side effects.

Eg :

- Cyclosporine (Engraft, Neural, Sand immune)
- Tacrolimus

How To Take Amlodipine:
All possible dosage and forms may not be included here. Your dose, form, and how often you take it will depend on:

- Your age.
- The condition being treated.
- how sever your condition is.
- other medical conditions you have.
- other medications you take.
- how you react to the first dose.

UV spectrophotometer:

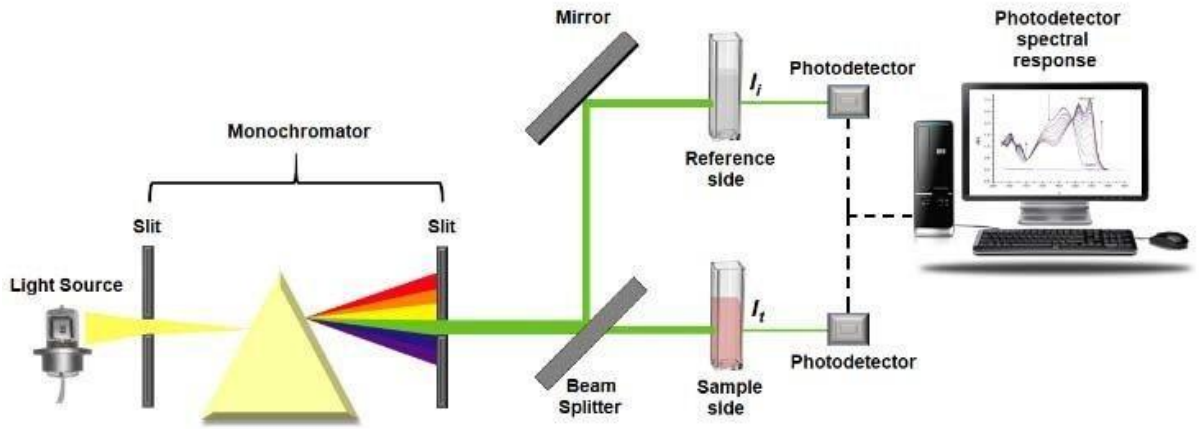


Fig no 4: - Schematic representation of UV Spectrophotometer

Introduction:
The ability of electromagnetic radiation to discretely interact with atoms and molecules and produce distinctive absorption or emission profiles is essential for spectroscopic activities. The wavelength of electromagnetic radiation is the characteristic that governs the perceived colour spectrum. The visible section of the electromagnetic spectrum is that portion of the spectrum that the human eye can see. These visible wavelengths span a region between 400 & 800nm.

Principle:
UV Visible spectroscopy is an example for absorption spectroscopy. The Beer-Lambert Law is the principle behind absorbance spectroscopy. Ultraviolet and visible absorption spectrophotometry is the measurement of the absorption of monochromatic radiation by solutions of chemical substances, in the range of 185nm-380nm, and 380nm-780nm of the spectrum respectively. The magnitude of the absorption of a solution is expressed in terms of the absorbance A, defined as the logarithm to the base of 10 of the reciprocals of transmittance (T) for monochromatic radiation.

$A=\text{Log}_{10}(I0/I)$
Where,
I0= the intensity of the incident radiation I= the intensity of the transmitted radiation

The absorbance depends upon the concentration of the absorbing substance in the solution and the thickness of the absorbing layer taken for measurement. The specific absorbance of a 1%w/v

solution is adopted in the pharmacopoeia for several substances which refers to the absorbance of a 1%w/v in a 1cm cell and measured at a defined wavelength which can be calculated by the equation,

A(1%,1cm) = A/cl
Where,
C is the concentration of the absorbing substance expressed as percentage w/v L is the thickness of the absorbing layer in cm

The value of $A_{1\%1cm}$ at a particular wavelength in a given solvent is a property of the absorbing substance.

Beers lamberts law:
The Beer-Lamberts Law relates the attention of light to the properties of the material through which the light is travelling.

If the intensity of the light passing through the sample, I is less than I_0 then the sample has absorbed some of the light.
Beers law states that the absorbance is directly proportional to the concentration (c) of the solution of the sample used in the experiment.
i.e.; $A \alpha C$
The absorbance (A) is defined via the incident intensity I_0 and transmitted intensity I by
$A = \log_{10}(I_0 / I)$
Lamberts law states that the absorbance is directly proportional to the length of the light path (I), which is equal to the width of the cuvette.
i.e.; $A \alpha l$ therefore, $A \alpha cl$
$A = €cl$
The constant € is called Molar Extinction Coefficient and is a measure of the probability of the electronic transition.

Instrumentation:

Figure no 5 : UV Spectrophotometer

The essential components of UV-Visible spectrophotometer are as follows:

1. Source (UV and Visible)
2. Monochromator
3. Sample container (cuvette)
4. Detector
5. Amplifier and Recorder

Source:
A continuous source that produces radiation at a variety of wavelength is necessary for UV-Visible spectroscopy. Some examples for the sources are hydrogen lamp, deuterium lamp, tungsten lamp, xenon discharge lamp etc…

Hydrogen lamp:
These are reliable, steady which emit radiations continuously between 169 and 380nm. This consists of hydrogen gas at high pressure and causes electrical discharge. These excited hydrogen molecules produce the radiation.

Deuterium lamp:
This is the frequently used UV source which emits radiation in the range of 160-450nm. This is much expensive than hydrogen lamp.

Tungsten lamp:
The most typical light source used in the spectrophotometers is the tungsten lamp which possess a wavelength range of 330-900nm. This comprise of a tungsten filament which is encased in a glass envelope and is utilised for the visible spectrum.

Xenon discharge lamp:
A xenon discharge lamp is a discharge light source that contains xenon gas inside a bulb which provides radiations at a range of 250-600nm.

Monochromators:

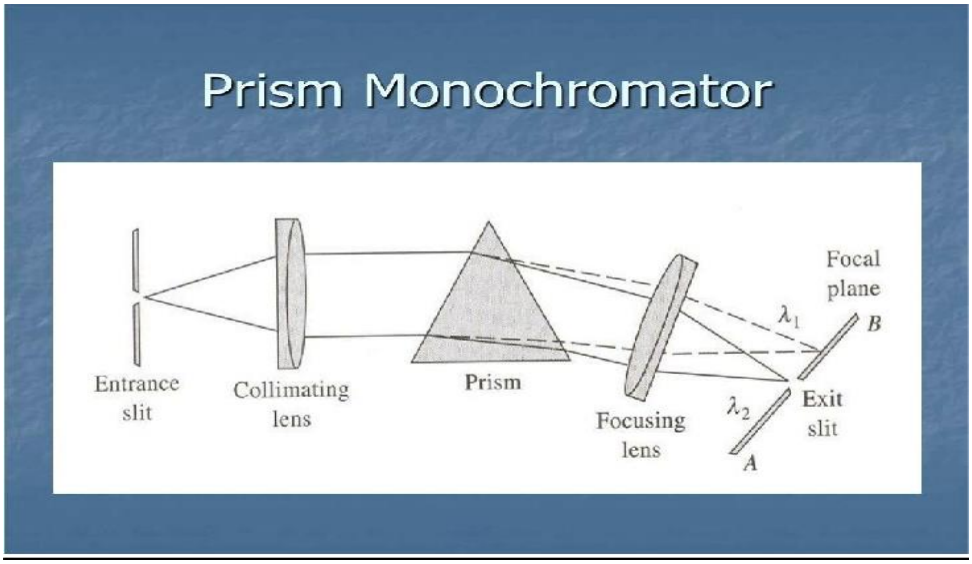


Figure no 6: Prism monochromator

The monochromator creates a monochromatic light by filtering out the undesirable wavelengths from the radiation source source light. The multi-wavelength polychromatic light enters the monochromator through the entrance slit. Following collimation, the beam is directed at an angle towards the dispersion component. The grating or prism monochromators separates the beam's wavelengths into their individual components. Only radiation of a specific wavelength exits the monochromator through the exit slit when the dispersing element or the exit slit is removed.

Types of monochromators; Prism monochromator Grating monochromator
The components of monochromator;

- An entrance slit
- A collimating lens
- A dispersing device
- A focusing lens
- An exit slit

Sample container (cuvette):
The sample containers are known as cuvette which

are transparent to all wavelengths of light flowing through them and are used to hold samples for spectroscopic measurements. The cuvette is composed of quartz, which is square in shape has a 1cm route length.

Detectors:

Detectors converts the light energy into electrical impulses that are read out by the readout devices. The transmitted radiations strikes the detector an determines the amount of radiation absorbed by the sample.

The types of detectors available are as follows;

- Barrier layer cell / photo voltaic cell
- Photo tubes / photo emissive tube
- Photomultiplier tube

The two empty cells used for the solutions under examination and the reference liquid must have the same spectral characteristics. The solvent cell must be placed in the reference beam when double beam recording instruments are used. Then verify the wavelength scale using the absorption maxima. Check the absorbance using suitable filters which gives for each wavelength the exact values and permitted limits of the specific absorbance. The tolerance of the absorbance is +-0.01.

CONCLUSION:

The UV analysis of amlodipine has demonstrated a simple, rapid and sensitive method for the detection and quantification of amlodipine. The results showed a linear relationship between absorbance and concentration, with a high correlation coefficient and a detection limited. The precision and accuracy of the method were also validated with a relative standard deviation. The advantages of this method include its simplicity, low cost and rapid analysis time, making it a valuable tool for the analysis of amlodipine. Overall, the UV analysis of amlodipine provides a reliable and efficient means of detecting and quantifying this important cardiovascular drug.

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