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A REVIEW ON METHOD DEVELOPMENT AND VALIDATION OF STABILITY INDICATING UV METHOD FOR CARVEDILOL

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ABSTRACT

The present study describes the development of a new rapid, simple, sensitive and reproducible UV Spectrophotometry RP-HPLC, HPTLC method for the analysis of Carvedilol that offer certain advantages in its simplicity and sensitivity and applicable in routine analysis. It also describes the development of validation work as per ICH guidelines recommended by the Food and Drug Administration (FDA) of the United States. In order to develop a RP-HPLC, HPTLC, UV effective most of the effect should be spent in method development and optimization as this will improve the final method performance. A well- developed method should be easy to validate. A method should be developed with the goal to analyse rapidly, the preclinical samples, formulations and commercial samples. Review of literature on drug strongly indicates that there is few methods available for determination and validation of carvedilol in bulk and pharmaceutical dosage forms.

KEYWORDS: Carvedilol, Non-selective beta blocking agent, Method development, UV, RP-HPLC, Stability indicating.

INTRODUCTION

Carvedilol is used to treat heart failure and hypertension (high blood pressure). It is also used after a heart attack that has caused your heart not to pump as well. Is a non selective β blocking agent with α-1 blocking activity. Carvedilol has much greater antioxidant activity than other commonly used β blockers. It also describes the development of validation work as per ICH guidelines recommended by the Food and Drug Administration (FDA) of the United States.

Carvedilol blocks receptors of the adrenergic nervous system, the system of nerves in which epinephrine (adrenalin) is active. Nerves from the adrenergic system enter the heart and release an adrenergic chemical (norepinephrine) that

attaches to receptors on the heart's muscle and stimulates the muscle to beat more rapidly and forcefully [1] . By blocking the receptors, Carvedilol reduces the heart's rate and force of contraction and thereby reduces the work of the heart.

Carvedilol tablets are used for the treatment of mild to severe chronic heart failure of ischemic or cardio myopathy origin. Usually in addition to diuretics ACE inhibitors and digitalis. They can be used alone or in combination with other antihypertensive agents especially thiazide type diuretics should not be given to patient with severe hepatic impairment. Tablet containing inactive ingredients as colloidal silicon dioxide, crospovidone, Hypromellose, lactose monohydrate, magnesium striates, polyethyl glycol, polysorbate, povidone and titanium dioxide.[2,3]

Generic name of drug of choice

Carvedilol (KAR ve dil ole)

Structure

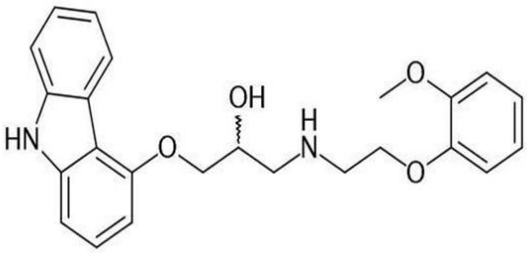

Figure 1: Carvedilol structure.

Chemical name

(±)-[3-(9H-carbazol-4-yloxy)-2 hydroxy propyl] [2-(2-methoxy phenoxy) ethyl] amine.

Indications

Carvedilol is a beta- blocker. Beta-blockers affect the heart and circulation (blood flow through arteries and veins). Carvediolol is used to treat heart failure and hypertension (high blood pressure), It is also used after a heart attack that has caused your heart not to pump as well.[4]

MECHANISM OF ACTION

Carvedilol is a racemic mixture in which non selective beta adreno receptor blocking activity is present in the S(-) enantiomers and alpha 1 adrenergic blocking activity is present in both R(+) and S(-) negative enantiomers equal potency. Carvedilol has no intrinsic sympathomimetic activity.[2,3]

Carvedilol inhibits exercise induce tachycardia through its inhibition of beta adrenoceptors. Carvedilol's action on alpha-1 adrenergic receptors relaxes smooth muscle in vasculature, leading to reduced peripheral vascular resistance and an overall reduction in blood pressure. At higher doses, calcium channel blocking and antioxidant activity can also be seen. The antioxidant activity of carvedilol prevents oxidation of low density lipoprotein and its uptake into coronary circulation.[5]

Route of elimination

16% of carvedilol is excreted in the urine with <2% excreted as unmetabolized drug. Carvedilol is primarily excreted in the bile and feces.[5]

Half-life

The half-life of carvedilol is between 7-10 hours, though significantly shorter half-lives have also been reported.[5]

Clearance: The plasma clearance of carvedilol has been reported as 0.52L/kg or 500- 700mL/mi.

INTRODUCTION OF METHOD DEVELOPMENT

1. SPECTROSCOPY

Spectroscopy as a science began with Isaac Newton separating light using a prism and was called optics.

Thus, was originally the study of visible light which we call color which later, following the research of James Clerk Maxwell, came to include the entire electromagnetic spectrum.[6]

Spectroscopy is a branch of science that studies the interaction of electromagnetic radiation with matter. The most important consequence of such interactions is that energy is absorbed or emitted by matter in discrete amounts called quanta absorption or emission processes are known throughout the entire electromagnetic spectrum from the gamma region (nuclear resonance absorption or Mossbauer effect) to the radio region (nuclear magnetic resonance).

When a measurement of the frequency of radiation is made experimentally, it gives a value for the energy change involved and from this conclusion can be drawn about the set of discrete energy levels that is for existence of matter. How to make measurements of radiation frequencies (emitted or absorbed) and the inferred energy levels constitute spectroscopy practice.[6]

UV SPECTROSCOPY

The uses of a spectrophotometer include quantitative analysis of various known compounds in a mixture. It is used in various fields such as chemistry, biochemistry, chemical engineering etc. This instrument is used by scientists also for various purposes. The spectrophotometer was invented by Arnold J. Beckman in 1940.[7]

UV-Vis spectroscopy is as often as possible utilized to supply characterization information for an assortment of materials. Inorganic or natural, strong or fluid bunches, such as natural particles and utilitarian bunches, can be observed utilizing UV-Visible spectroscopy, as can reflectance estimations for coatings, paints, textiles, biochemical investigation, disintegration energy, band crevice estimations, etc. Depending on the degree of absorbance or transmittance of a diverse wavelength of bar light and the different reactions of tests, the UV- Vis gives these subtle elements.[8]

Ultraviolet and visible spectroscopy is a simple technique compared to other spectroscopic methods, it uses ultraviolet and visible light to analyze complex metal ion solutions and other organic compounds.

We all know about the absorption of visible light because it is what causes the color of objects. Visible light has a wavelength of 4.0-7.0 x 10-7m, so the range becomes 400-700nm. Ultraviolet light has a wavelength of 2.0 to 4.0 x 10 to 7 m, so the range becomes 200 to 400 nm.

When a white light is anticipated into a crystal or an opening, it'll be scattered into range. Lower recurrence ruddy light with less vitality, at one conclusion of the range, whereas the higher recurrence purple light with wealthier vitality, at the other conclusion.[9]

And out of this side, it is the locale of the undetectable electromagnetic radiation. In expansion to bright (UV), there are other shapes of tall vitality imperceptible lights. The UV radiation can harm your skin, once you stand within the sun light.[10]

Concurring to the definition in ISO 21348:2007 by Worldwide Organization for Standardization (ISO), ready to part the bright into 4 sorts (segments), according to the wavelength (the vitality), they are NUV, MUV, FUV, and EUV. Extraordinary ultraviolet (EUV), contrary energies to approach bright, at the conclusion of UV locale, where is near X-rays, and it is the foremost lively one among the 4 sorts. And center bright (MUV) and distant bright (FUV) are in between the EUV and MUV.[11]

Figure 2: Jasco V-730 UV Visible Spectrophotometer.

Table 1: UV Segment with wavelength Range.

Ultraviolet Segment	Wavelength Region [10nm - 400nm]
Extreme Ultraviolet [EUV]	10nm - 121nm
Far Ultraviolet [FUV]	122nm - 200nm
Near Ultraviolet [NUV]	300nm - 400nm

Principle

A molecule or ion will exhibit absorption in the visible or ultraviolet region when radiation causes electronic transitions in its structure. Therefore, the absorption of light by the sample in the ultraviolet or visible region is accompanied by a change in the electronic state of the molecules in the sample. The energy provided by light causes electrons to move from the ground orbital state to a higher energy state, an excited orbital state or an anti-bonding orbital state. There are potentially three types of ground state trajectories that may be involved.[12]

1. σ (bonded) molecular
2. π (bonded) molecular orbital
3. n (unbonded) atomic orbital.

In addition, two types of anti-bonding orbitals may be involved in the transition:

I) σ* (sigma bond) orbital.

II) π* (pi bond) orbital.

There are no n* antibonding orbitals because n electrons do not form bonds. Therefore, the following electronic transitions can occur by absorbing ultraviolet and visible light.

- σ to σ*
- n to σ*
- n to π*
- π to π*

The transitions from σ to σ* and n to σ* require a lot of energy and thus occur in the far ultraviolet or weakly in the 180-240 nm region. Therefore, saturated groups do not show strong absorption in the normal ultraviolet region. The transitions from that to π* and from π to π* occur in molecules with unsaturated centers, they require less energy and occur at longer wavelengths than the transition to the anti-orbital σ* bond. We will now see that the maximum absorption wavelength and absorption intensity are determined by the molecular structure. The transition to the anti-π* bonding orbital that occurs in the ultraviolet region for a particular molecule can also take place in the visible region if the molecular structure is changed. Many inorganic compounds in solution also exhibit absorption in the visible region. They include salts of elements with incomplete inner electron shells (mainly transition metals) whose ions are complexed by hydration. Such absorption is the result of a charge transfer process, in which electrons are moved from one part of the system to another by the energy provided by visible light.[13]

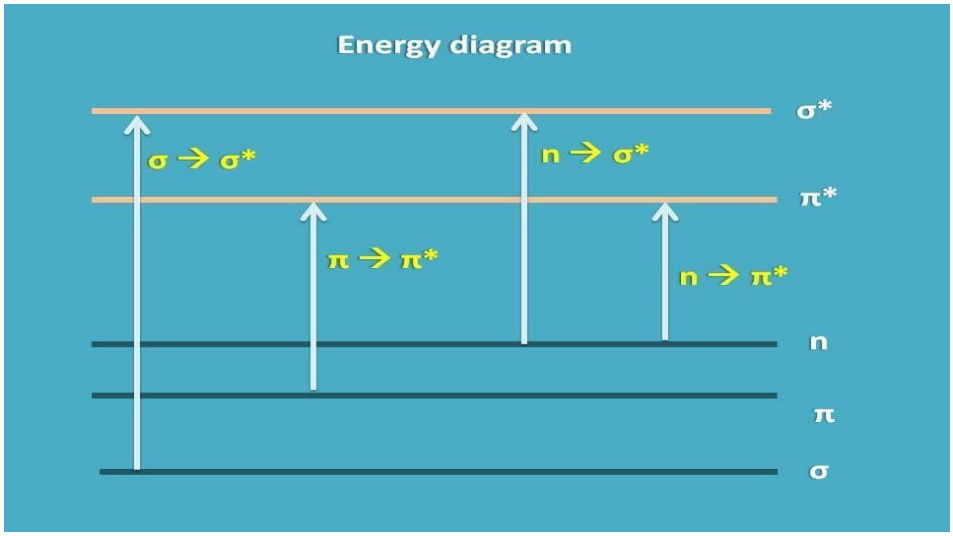

Figure 3: Electron Transition graphically represented.

Beer-Lambert's Law

The greater the number of molecules capable of absorbing light of a given wavelength, the greater the extent of light absorption. Furthermore, the more effectively a molecule absorbs light of a given wavelength, the greater the extent of light absorption.[14]

According to the Beer-Lambert law, there is a linear correlation between the concentration of a solution, its molar absorption coefficient, and its optical coefficient.

A= abc

Where,

A = absorbance

a = molar absorption

b = path length (cm)

c = concentrations

Instrumentation of Uv Spectroscopy

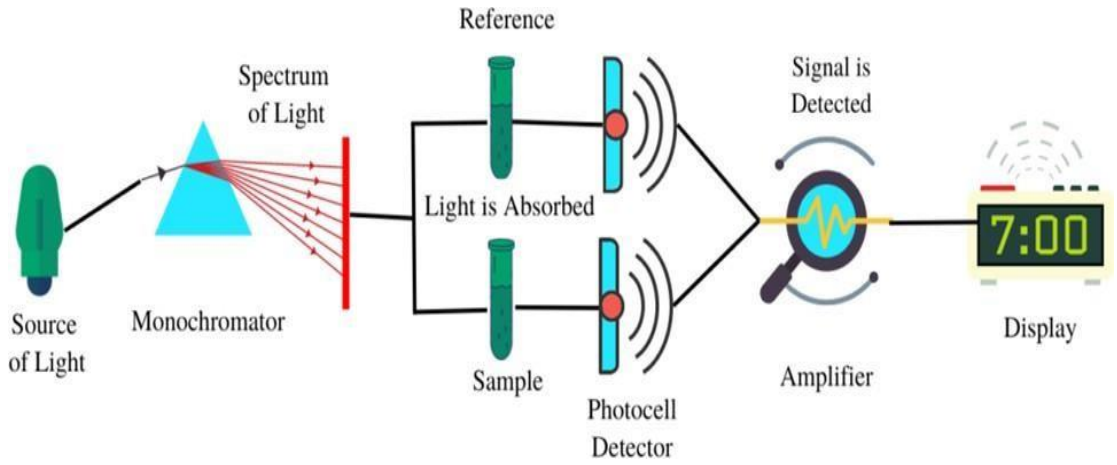

Figure 4: Instrumentation of Uv-Vis. Spectroscopy.

1) Source of Light

Tungsten filament lamps are often used as visible light sources. This type of lamp is used in the wavelength range from 350 to 2500 nm. The energy emitted from a tungsten filament lamp is proportional to the fourth power of the operating voltage. This means that to produce stable energy, the voltage of the lamp must be very stable. Voltage regulators or constant voltage transformers are used to ensure this stability.[15]

2) Monochromator

By filtering unwanted wavelengths of light from the radiation source, the monochromator produces monochromatic light. Through the input slit, multi-wavelength polychromatic light enters the monochromator. After collimation, the beam is directed at an angle toward the scattering component. The grating or prism separates the wavelengths of the beam into individual components. Only radiation of a specific wavelength exits the monochromator through the exit slit when the dispersion element or exit slit is moved.

Types of monochromators

1. Prism monochromator
2. Grating monochromator

All monochromators contain the following components:

- Inlet slot
- Collimator lens
- Dispersion device
- Converging lens
- Exit slit

Radiation at multiple wavelengths, or polychromatic radiation, enters the monochromator through the entrance slit. After collimation, the beam is tilted toward the scattering component. The grating or prism separates the wavelengths of the beam into individual components. Only radiation of a specific wavelength will escape from the monochromator through the exit slit by changing the dispersion element or exit slit.

3) Sample Cells (Cuvette)

Cuvettes are sample containers that are transparent to all wavelengths of light passing through them and are used to hold samples for spectroscopic measurements. The cuvette is made of quartz, has a square shape, has a path length of 1 cm and can be used for wavelengths between 190 and 200 nm.

4) Detector

The light energy is converted by the detector into an electrical pulse that is read by the reading device. The incoming radiation reaches the detector, which determines the amount of radiation absorbed by the sample. Absorption spectrophotometers use the following types of detectors.

Detector type

1. Barrier layer cell/ photocell 2.Phototube/Photo emissive tube 3.Photomultiplier tube

Working

A UV/Vis spectrophotometer analyzes the chemical structure of a substance using visible and ultraviolet light. The spectrometer is a type spectrometer used to measure light intensity, proportional to wavelength. When ultraviolet rays fall on various organic compounds, these compounds absorb it. As a result, you can use a UV/VIS spectrophotometer to measure the absorbance of a compound and obtain its molecular structure and related information.[16]

VALIDATION PARAMETERS OF UV SPECTROSCOPY

Components of method validation

The following are typical analytical performance characteristics which may be tested during methods validation:

1. Accuracy
2. Precision
3. Linearity
4. Detection limit
5. Quantitation limit
6. Specificity
7. Range
8. Robustness

1. Linearity

An analytical technique is deemed to be linear if it can produce test findings that are directly proportional to the concentration (quantity) of the analyte in the sample, within a certain range.

2. Accuracy

The degree of agreement between the value discovered and the value recognized as either a conventional true value or an approved reference value is what determines an analytical procedure's accuracy.

3. Precision

The degree of agreement (or scatter) between a set of measurements made by repeatedly sampling the same homogeneous sample under specified conditions is expressed as the precision of an analytical method. Three levels of accuracy can be distinguished: reproducibility, moderate precision, and repeatability.

4. Range

The range of a method is the period between the higher and lower concentration (amounts) of analyte in the sample (containing these concentrations), for which it has been established that the analytical procedure has an appropriate level of precision, accuracy, and linearity.

5. Limit of Detection (LOD)

The range of a method is the period between the higher and lower concentration (amounts) of analyte in the sample (containing these concentrations), for which it has been established that the analytical procedure has an appropriate level of precision, accuracy, and linearity.

6. Limit of Quantification (LOQ)

The quantitation limit of an analytical process refers to the smallest quantity of analyte in a sample that can be quantitatively quantified with sufficient precision and accuracy. The quantitation limit is a parameter used in quantitative tests to determine contaminants and degradation products in sample matrices with low concentrations of substances.

7. Robustness

The robustness of an analytical technique is a measure of its ability to stay unaffected by little but purposeful modifications in method parameters, and it indicates its dependability throughout routine use.

8. Ruggedness

The ability of a method or system to maintain consistent performance and produce reliable results despite small, intentional variations in environmental conditions, operational parameters, or procedural steps.[17]

FORCED DEGRADATION STUDIES IN STABILITY TESTING BY UV SPECTROSCOPIC METHOD

Forced degradation studies, also known as stress testing, are accelerated stability studies conducted under exaggerated environmental conditions to identify potential degradation pathways of a drug substance or drug product. These studies aim to generate degradation products intentionally by exposing the compound to extreme conditions such as heat, light, oxidizing agents, and acidic or basic environments. The primary goals of forced degradation studies are.[18-19]

Understanding Stability Profiles: To identify the chemical behavior of a drug under various stress conditions and determine its inherent stability.

Identification of Degradation Products: To identify and analyse probable degradation products that may develop under standard storage or usage circumstances.

Development of Stability-Indicating Methods: To ensure that analytical methods can reliably separate and quantify both the API and its degradation products.

Regulatory Compliance: Forced degradation studies are mandated by regulatory authorities, including the ICH, to ensure drug safety and efficacy throughout its shelf life.

Strategic development of Forced Degradation: Forced degradation factors necessary include acid and base hydrolysis, thermal degradation, photolysis, and oxidation and may include freeze–thaw cycles and shear.[20]

Stress degradation studies

Stress degradation by hydrolysis under acidic condition

To 3ml of stock solution (1000µg/ml) of Carvedilol, 1ml of 3N HCl was added in 10ml volumetric flask and the volume were made upto the mark with methanol. Kept at normal condition for 90mins, 60mins, time interval, 1ml of solution was pipette out from this flask, and diluted with methanol the volume up to 10ml the appropriate concentration (30µg/ml). This solution was taken in cuvette. For the blank, 0.5ml solution of 3N HCl and 0.5ml solution of 3N NaOH were diluted with methanol in 10ml of volumetric flask. After 90mins, again 1ml of the solution was pipette out from the flask and the above procedure was repeated.

Stress degradation by hydrolysis under alkaline condition

To 3ml of stock solution (1000µg/ml) of Carvedilol, 1ml of 0.1N NaOH was added in 10ml volumetric flask methanol. Then, at normal condition for 90mins. After 60mins, time interval, 1ml of solution was pipette out from this flask, diluted with methanol in order to make the volume up to 10ml (30µg/ml). This solution was taken in cuvette. For the blank, 0.5ml solution of 0.1N HCl and 0.5ml solution of 0.1N NaOH were diluted with methanol in 10ml of volumetric flask. After 90mins, again 1ml of the solution was pipette out from the flask and the above procedure was repeated.

Dry heat induced degradation

Carvedilol sample was taken in a Petri plate and exposed to a temperature of 70°C for 48hours in an oven. After 48hours, 10mg of the sample was diluted with methanol in order to make the volume up to 10ml. From this solution, dilutions were carried out to achieve the concentration (30µg/ml) and the solution was taken in a cuvette for the UV-VIS analysis.

Oxidative degradation

To 1.5ml of the stock solution of Carvedilol (1000µg/ml), 1ml of 30%w/v of hydrogen peroxide added in 10ml of volumetric flask by using methanol. The volumetric flask kept at room temperature for 15min. For the blank, 1ml of the 30%w/v of hydrogen peroxide was kept at normal condition for overnight in 10ml of volumetric flask. Both the solutions were heated on boiling water bath to remove excess of hydrogen peroxide. Finally, after 15mins dilutions were made from the stock solution to achieve the concentration (30µg/ml). The solution was then taken in a cuvette and analyzed in UV.

Photolytic degradation

Sample of Carvedilol was exposed to near ultraviolet lamp in photo stability chamber providing illumination of not less than 1.2 million lux hours. 10mg sample was dissolved in methanol and volume made up to 10ml (30µg/ml) and taken in curette for the UV analysis.

CONCLUSION

The proposed method is specific in estimating the commercial formulation without interference of excipients and the other additives. Hence, this method can be used for routine determination of CARVEDILOL in the bulk sample and pharmaceutical formulation. The proposed method for stability study shows that there is appreciable degradation of CARVEDILOL found in stress conditions. A new simple analytical method has been developed to apply for the evaluation of the stability of CARVEDILOL to quantify and its degradation products in a solid premix dosage forms.

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