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Review Article

METHOD DEVELOPMENT FOR ASSAY OF CARVEDILOL TABLETS BY RP-HPLC METHOD

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ABSTRACT

The present study describes the development of a new rapid, simple, sensitive and reproducible RP-HPLC, HPTLC, UV Spectrophotometry 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 method available for determination and validation of carvedilol in bulk and pharmaceutical dosage forms.

KEY-WORDS:

Carvedilol, Non-cardio selective beta blocker, Method development, RP-HPLC.

INTRODUCTION:

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. It is a non-selective β-adrenergic blocking agent with α-1 blocking activity.

Carvedilol has much greater antioxidant activity than other commonly used β blockers. Tablet containing inactive ingredients as colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium striate, polyethyl glycole, polysorbate, povidone and titanium dioxide. [1 & 2]

GENERIC NAME OF DRUG OF CHOICE: Carvedilol (KAR ve dil ole)

STRUCTURE:

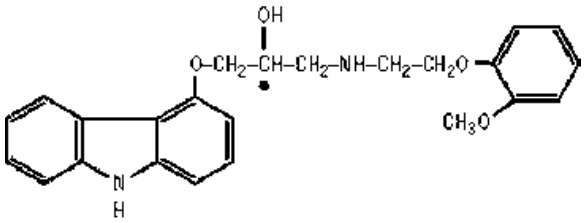


Figure: Carvedilol

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. [3]

RECOMMENDED DOSE FOR OXACEPROL:

Patients weighing less than 85 kg/ 187lb – 25mg twice a day

Patients weighing more than 85 kg/ 187lb – 50mg twice a day

HOW TO USE:

25 mg taken twice a day for two weeks, This dosage is same regardless of the age of weight of the patient. It should be swallowed as a whole tablet and should not crushed, and chewed. Carvedilol should not be taken with food to slow the rate of absorption and reduce the incidence of orthostatic effects, Patient should be observed for one hour after intial dose is given. [3]

STORAGE:

Store in a close, cool and light resistant container.

SOLUBILITY:

Insoluble in water, sparingly soluble in 95% ethanol and isopropanol, slightly soluble in ethyl ether soluble in methanol, methylene chloride, freely soluble in dimethyl sulfoxide. [1 & 2]

MECHANISM OF ACTION:

Carvedilol is a recamic 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. Cavedilol has no intrinsic sympathomimetic activity. [1 & 2]

PRECAUTIONS AND CONTRAINDICATIONS:

You should not take carvedilol if you have asthma, bronchitis, emphysema, severe liver disease, or a serious heart condition such as heart block, "sick sinus syndrome," or slow heart rate (unless you have a pacemaker).

Avoid drinking alcohol within 2 hours before or after taking extended-release carvedilol (Coreg CR). Also avoid taking medicines or other products that might contain alcohol. Alcohol may cause the carvedilol in Coreg CR to be released too quickly into the body.

If you are being treated for high blood pressure, keep using carvedilol even if you feel well. High blood pressure often has no symptoms. You may need to use blood pressure medication for the rest of your life.

OXACEPROL SIDE EFFECTS:

- A light-headed feeling, like you might pass out.
- Slow or uneven heartbeats.
- Swelling, rapid weight gain, feeling short of breath (even with mild exertion).
- Cold feeling or numbness in your fingers or toes.
- Chest pain, dry cough, wheezing, chest tightness, trouble breathing; or high blood sugar (increased thirst, increased urination, hunger, dry mouth, fruity breath odor, drowsiness, dry skin, blurred vision, weight loss).

Weakness	Diarrhoea	Dizziness	Dry eyes
Tired feeling	Weight gain	Cold	Nausea

POSSIBLE DRUG INTERACTION FOR CARVEDILOL:

Many psychotherapeutic and CNS-active agents (e.g., anxiolytics, sedatives, hypnotics, antidepressants, antipsychotics, opioids, alcohol, and muscle relaxants) exhibit hypotensive effects, especially during initiation of therapy and dose escalation. Co-administration with antihypertensive and other hypotensive agents, in particular vasodilators and alpha-blockers, may result in additive effects on blood pressure and orthostasis.

CARVEDILOL INTERACTIONS WITH ALCOHOL:

Alcohol is generally toxic to heart. The combined effect of alcohol and carvedilol may cause excessive dizziness or fainting. [4]

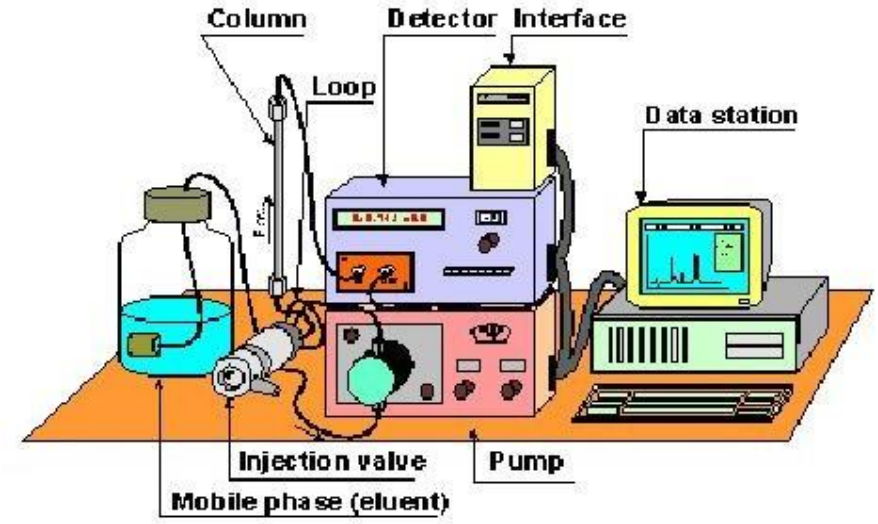
METHOD VALIDTION:

According to method, validation can be defined as “Establishing documented evidence which provides a high degree of assurance that a specific activity will consistently produce a desired result or product meeting its pre-determined specification and quality characteristics.

Method validation is an integral part of the method development; it is the process of demonstrating that analytical procedures are suitable for their intended use and that they support the identity, quality, purity and potency of the drug substances and drug products. Simply, method validation is the process of proving that an analytical method is acceptable for its intended purpose. Method validation, however, is generally a one –time

process performed after the method has been developed to demonstrate that the method is scientifically sound and that it serves the intended analytical purpose. [5]

BASIC PRINCIPLE OF HPLC:



High performance liquid chromatography (HPLC) is a separation technique utilizing differences in distribution of compounds to two phases, called stationary phase and mobile phase. The stationary phase designates a thin layer created on the surface of fine particles andthe mobile phase designates the liquid flowing over the particles. Under a certain dynamic condition, each component in a sample has difference distribution equilibrium depending onthe solubility in the phase and or molecule size. As a result, components move at different speed over the stationary phase and thereby separated from each other. The column is a stainless steel or resin tube, which is packed with spherical solid particles. Mobile phase is constantly fed into the column inlet at a constant rate by a liquid pump. A sample is injectedfrom the sample injector, located near the column inlet. The injected sample enters the column with mobile phase and the components in the sample migrates through it, passing between the stationary and mobile phase. Compound move in the column only when it is inmobile phase. Compounds that tend to be distributed in the stationary phase migrate slower. In this way, each component is separated on the column and sequentially elute from the outlet.Each component eluting from the column is detected by a detector to the outlet of the column. When the separation process is monitored by the recorders starting at the time of sample is injected, a graph is obtained. This graph is called chromatogram. The time required for a compound to elute (called retention time) and the relationship between compound concentration (amount) and peak area depend on the characteristic of the compound.[5]

A COMPARATIVE STUDY ON CARVEDILOL:

Suddhasattya Dey develop HPLC method for the estimation of carvedilol in bulk andpharmaceutical dosage form. The specification of the chromatographic system, column 4.6mm×25cm, 5 micron, with mobile phase containing phosphate buffer: acetonitrile, P^H 2, wavelength 240nm, flow rate 1ml/min and

the oven temperature 55ºC. Retention time was 6.63. A linear response was observed between the concentration rangeof 806-1202µg/ml with a regression co-efficient of 0.99. [6]

Navaneet Verma reported a procedure for simultaneous estimation of carvedilol in itsdosage form. The UV absorbance maxima of the drug at 285 nm. The drug obeyed Beer's law in the concentration range of 4-36µg/ml with molar absorptivity of 12.6×10^3 l/mol. Cmin methanol. [7]

Satish A Patel developed UV spectrophotometric method for the determination of carvedilol in tablet formulation. Simple UV spectrophotometric method is based on determination of carvedilol in 0.1 N HCL at 241.2 nm. Linearity was obtained in the concentration range of 1- 12µg/ml. [8]

M. Imran developed a new and rapid stability indicating ultraviolet spectroscopic methods for the estimation of ezetimibe and carvedilol in pure form and in their respective formulations. The linearity range for ezetimibe and carvedilol obtained as 2-50µg/ml and 2-20µg/ml respectively. [9]

Ivan Savic developed a method to select an appropriate packaging and analysis of itsinfluence on stability of tablets containing carvedilol. After radiation the content wasestimated using a validated HPLC – method. Retention time was 4.5 detected at 240 nm. [10]

T.E.G.K Murthy reported a development of scriminatory method for dissolution ofcarvedilol marketed formulations .In the study four dissolution media with different agitation speeds were employed. An agitation speed of 100 rpm showed more drug release profile than50 and 75 rpm. [11]

Ramesh Gannu developed a HPLC analytical method for carvedilol in human serum.The method employs a liquid-liquid extraction for isolation and sample concentration followed by reversed phase liquid chromatography analysis using ultraviolet detection at 238nm. Serum samples containing the carvedilol and internal standard and amitriptyline were eluted through a C_8 kromasil KR 100 5C8 column. Retention time of carvedilol was 6.10 min. [12]

L. J Patel developed reverse phase high performance liquid chromatography and highperformance thin layer chromatography for estimation of carvedilol in bulk drug andpharmaceutical formulations. For HPLC method Lichrospher 100-c_{18}(200×4.6mm), 5µ column, isocratic mode, with mobile phase containing 50M potassium di hydrogen phosphatebuffer: actonitrile : methanol (60:50:10) was used. The retention time was 4.56.The linearity lies over 1-35µg/ml for HPLC. For HPTLC a CAMAG HPTLC system comprisingof Linomat v automatic sample applicator, Hamilton syringe, Camag TLC scanner-3CamagWin CAT software with stationary phase precoated silica gel 60F_{254} and mobile phase consisting of ethyl acetate: toluene: methanol. The detection of spot carried out at 242 nm. The R_f value was 0.65. The linearity lies over 50 – 300 ng/spot for HPTLC[13]

CH. Ajay. Babu developed a high performance liquid chromatography method for the determination of the carvedilol in human plasma. The method utilizes the liquid-liquid extraction with n-hexane ethyl acetate (3:1v/v). Samples were analyzed by using phenomineGemini C_{18} column with UV detection at 241nm.[14]

Laila Ei Sayed Abdel Fattah reported a spectrofluorimetric determination of carvedilol in dosage form and spiked human plasma through derivatization with 1- dimethylamino-naphthalene-5-sulphonyl chloride. The fluorescence concentration plot was rectilinear over the range of 5.0-8.0ng/ml with a lower detection limit of 1.90ng/ml.[15]

Olga Galanopoulou reported HPLC analysis, isolation and identification of a new degradation product in carvedilol tablets. The separation was achieved with an X-terra C_{18} column using acetonitrile - phosphate buffer pH2.5 as mobile phase.[16]

Sarath Chandiran reported a simultaneous quantification of carvedilol and its metabolite in human plasma by using High-throughput liquid chromatography - tandem massspectrometric method .The method was linear over a concentration range of 0.1 to 250 ng/mlwith a limit of quantification of 0.1ng/ml.[17]

R. K. Jat developed a sensitive and rapid extractive spectrophotometer method for theassay of carvedilol in bulk drug and tablets the complex formed between carvedilol and bromophenol blue in an acidic medium shows maximum absorbance at 414nm. Linearity lies in the range of 5-20µl[18]

F. Behn developed high performance liquid chromatography for the determination of the β receptor blocker .Carvedilol in small volumes of the plasma from paediatric patients. Analysis of the extracts was performed on a spherisorb C_6 column with a mobile phase of 65% acetonitrile and 35% potassium acetate buffer and fluorescence detection. Carvedilol and internal standard showed recoveries of 87.0% and 97.7 % respectively.[19]

J.Stojanovic developed a reverse phase high performance liquid chromatographic method for separation of carvedilol and its impurities from Karvileks tablets. The best separation was achieved on a chromolit RP 8 e column. Use of acetonitrile: water (45 : 55) v/v adjusted to pH 2.5 with formic acid as mobile phase. UV detection was performed at 280nm[20]

CONCLUSION:

In order to develop a RO-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, formulation and commercial samples.

Review of literature on drug strongly indicates that there is few method available for determination and validation of carvedilol in bulk and pharmaceutical dosage forms.

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