REVIEW ARTICLE

Analytical Technique for Carvedilol and Ivabradine Determination from Pure and Pharmaceutical Dosage Forms: A Review

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ABSTRACT

Carvedilol and ivabradine is a drug combination used to treat cardiovascular diseases like hypertension, chronic stable angina pectoris and, chronic heart failure. Both are different in their mode of action. Carvedilol prevents exercise-induced tachycardia via inhibition of beta-adrenoreceptor carvedilol, which also acts on alpha-1 adrenergic receptors and reduces blood pressure. In case of a higher dose also shows antioxidant and calcium channel blocking activity. Ivabradine is a heart rate-reducing drug that works by blocking cardiac pacemaker currents (If) selectively and specifically. The major goal of this review paper is to emphasize the characteristics of carvedilol and ivabradine, such as their pharmacological profiles, mechanisms of action, pharmacokinetic and pharmacodynamic studies, and previously described analytical methodologies for carvedilol and ivabradine determination. Various methods such as UV spectroscopy High-performance liquid chromatography (HPLC), Reverse phase -High performance liquid chromatography (RP-HPLC), Ultra-performance liquid chromatography (UPLC), Mass Spectrometry (MS), High-performance thin layer chromatography (HPTLC). is the most accurate easy method for estimation.

Keywords: Analytical method, Carvedilol, Heart failure, HPLC.

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INTRODUCTION

Heart failure (HF) is a serious public health issue. It has a considerable clinical, social, and economic impact, owing to significant functional limits and decreased patient quality of life. Increased adrenergic tone, altered autonomic regulation of the cardiovascular system, activation of the renin-angiotensin-aldosterone system, and diminished peripheral blood flow are all pathophysiological pathways that cause HF. In patients with ischemic heart disease, studies have indicated that a combination of ivabradine plus beta-blocker such as carvedilol improves exercise tolerance more than beta-blockade alone. Ivabradine works by blocking the enzyme that causes the heart to beat faster. If channel enhances event-free survival in heart failure patients with and without a sufficient beta-blocker.[1] 1-(carbazol-4-yloxy-3-[2-(O-methoxy phenoxy) ethyl]amino] carvedilol -2-propranol is a novel drug that is used to treat hypertension and heart failure (CHF).[2] It completely blocks adrenergic stimulation of beta receptors within the myocardium (beta 1 receptors) and within bronchial and vascular smooth muscles (beta 2 receptors) and to a lesser extent alpha 1 receptors within the vascular smooth muscle. Carvedilol works to lower systolic and diastolic blood pressure by lowering total peripheral resistance. Cardiac function is generally preserved and heart rate is either unchanged or decreased slightly.[3] Ivabradine is a unique cardiac medicine that was approved by the Food and Drug Administration (FDA) in April 2015 to help people with stable, symptomatic chronic heart failure avoid hospitalization.[4] Ivabradine works by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, which is responsible for pacemaker generation through the If current in the SA node, therefore decreasing the diastolic contraction if the SA node is up to date. The If current channels do play a role in the creation of spontaneous activity in pacemaker cells, as well as mediating autonomic HR control.[5,6] Several countries, including the United Kingdom, Australia, Saudi Arabia, and the United States, have allowed its use. The medicine has received approval in 108 countries and is available in 93 others. The majority of these nations are members of the European Union. The medicine has been approved in 12 Middle Eastern nations, including Saudi Arabia. These nations have approved the 5 and 7.5 mg film-coated tablet dosages (twice a day).[7] In clinical practice, bradycardia,

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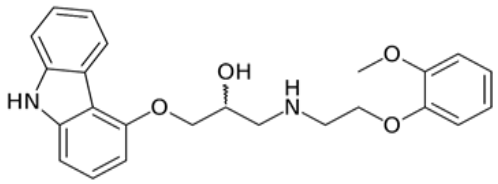

Figure 1: Structure of Carvedilol

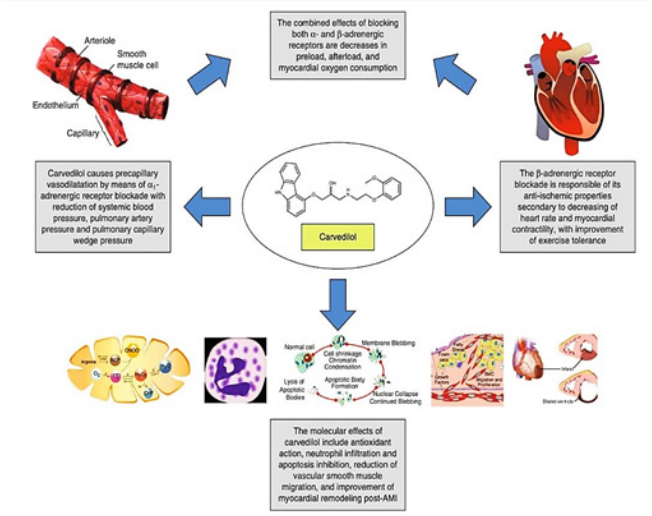

Figure 2: Pharmacodynamic properties of carvedilol.

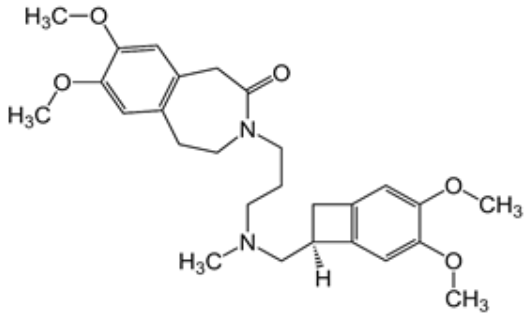

Figure 3: Structure of ivabradine.

AF, and phosphenes are the most prevalent adverse effects observed with ivabradine.[8] In individuals with chronic heart failure, a combination of ivabradine and carvedilol enhances β-blocker up titration.

DRUG PROFILE

Carvedilol

Carvedilol is racemic mixture. Carvedilol is chemically1 is (±)-1-(Carbazol-4- yloxy)-3- [[2-(o-methoxy phenoxy) ethyl] amino]-2-propanol.[9] Details about Carvediol are explained in Figure 1 and Table 1.

Mechanism of Action

Carvedilol is a type of beta-blocker that is not selective (beta-adrenergic receptor antagonist) of the third generation having

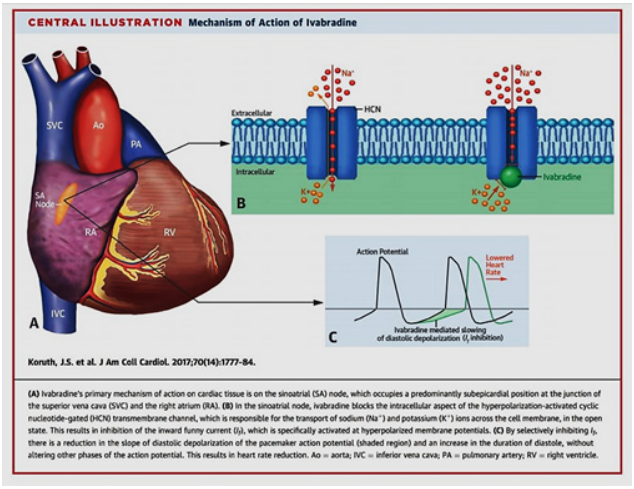

Figure 4: Mechanism of action of ivabradine.

vasodilatory characteristics due to alpha1-adrenergic receptor antagonism carvedilol reduces systolic and diastolic blood pressure acutely primarily by decreasing total peripheral resistance. Cardiac function is generally preserved and heart rate is either unchanged or decreased slightly.[3,10] It is a non-cardio selective lipophilic vasodilator with no intrinsic sympathomimetic effect, giving it better tolerance than older -blockers carvedilol is a β-adrenoceptor antagonist which exerts its vasodilating activity primarily via antagonism of peripheral alpha 1-adrenoceptors. At concentrations higher than those needed to antagonise β-adrenoceptors. It also acts as a calcium channel blocker. This activity is important in regional vascular beds, such as the cutaneous circulation, which has a potent vasodilator effect.

Furthermore, carvedilol has antioxidant properties due to nitric oxide activation, as well as anti-inflammatory properties.[3,11]

Pharmacokinetics

Absorption

Following oral treatment, carvedilol is readily absorbed as a capsule or solution, with peak plasma concentration (C_{max}) attained 1–2 hours after delivery. The dose has a linear effect on the C_{max} values. Carvedilol absorption was slightly slower when delivered with meals, but the food did not affect bioavailability. Carvedilol undergoes significant first-pass hepatic metabolism after oral treatment, resulting in a relatively low and variable absolute bioavailability of roughly 25%. Carvedilol is available as a racemic combination of R (+)- and S (-)-enantiomers and stereoselective differences in pharmacokinetics. The absolute oral bioavailability of the two enantiomers differs, with R (+) enantiomers having 31.1% absolute bioavailability and S (-) enantiomers having 15.1% absolute bioavailability.[9]

Distribution

Carvedilol is an extremely lipophilic medication. It has a wide distribution in extravascular tissues. It is heavily plasma protein bound (95%, primarily to albumin), with the R (+) enantiomer

Table 1: Drug profile of carvediol

Category	*Profile*
IUPAC Name	*1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino] propan-2-ol*
Molecular formula	$C_{24}H_{26}N_2O_4$
Molar mass	406.47 g/mol
Melting point	114.5°C
Solubility	Carvedilol is claimed to be easily DMSO soluble; methylene chloride and methanol soluble; ethanol, isopropanol, and ethyl ether sparingly soluble; and ethyl ether faintly soluble.
Appearance	White or almost white crystalline powder
Partition coefficient	3.84 +/- 0.89
Ionization constant (pK_a)	7.8
Class	Adrenergic antagonist.

Table 2: Drug profile of Ivabradine

Category	*Profile*
IUPAC Name	*3-[3-[[(7S)-3,4-dimethoxy-7-bicyclo [4.2.0] octa-1,3,5-trienyl] methyl-methylamino] propyl]-7,8-dimethoxy-2,5-dihydro-1H-3-benzazepin-4-one*
Molecular formula	$C_{27}H_{36}N_2O_5$
Molar mass	468.6 g/mol
Melting point	135–140°C
Solubility	Soluble in an organic solvent such as ethanol, DMSO, dimethyl formamide.
Appearance	White to off white powder
Partition coefficient	3.17
Class	Heart rate lowering agent

being more tightly bound than the S (-). Carvedilol (in animals) accumulates in milk due to its fundamental nature.

Metabolism and Elimination

Carvedilol is rapidly and extensively metabolised, with less than 2% of a dosage recovered in urine as an unmodified substance.

Approximately 60% of metabolites are excreted into bile and removed in faeces, with urine recovery accounting for 16% of metabolites. Hepatic CYP2D6 and CYP2C9 primarily mediate enantioselective oxidative metabolic pathways, with the S (-) enantiomer metabolising quicker than the R (+) enantiomer. In hypertensive patients, the terminal phase elimination half-life of carvedilol after oral administration ranges from about 2 to 8 hours and was about 2 to 5 hours in elderly (age > 65 years) hypertensive patients, the elimination half-life of up to 14.5 hours after intravenous administration.

Orally administered Carvedilol has an elimination half-life of 6–7 hours. The elimination half-lives of two enantiomers were found to differ after oral administration of a 50 mg dose, with values of 9.6 hours for R (+) enantiomers and 22.1 hours for S (-) enantiomers.

Pharmacodynamic

Carvedilol inhibits the 1, 2, and alpha1 adrenoceptors competitively.[12]

Antagonism of alpha 1 adrenoceptors accounts for the majority of carvedilol's vasodilatory effect; nonetheless, antagonism of calcium channels has been consistently seen in numerous animal models at high dosages. Although high does not appear to contribute to carvedilol's antihypertensive effects, it may be important in certain vascular beds. It has little inherent sympathomimetic/partial agonist effect and only minor membrane-stabilizing (local anesthetic) activity. Carvedilol has cardioprotective effects in acute myocardial infarction and is more efficacious than propranolol at equivalent blocking dosages in this regard. It is also protecting against neuronal damage in brain ischemia and shows antiproliferative effects in vascular smooth muscle (Figure 2).

Carvedilol's pharmacodynamic characteristics

Carvedilol's antioxidative properties, reduction of neutrophil adhesion and activation, quenching of oxygen free radicals, endothelial function protection, and direct vasodilation have been proposed to ameliorate the detrimental effects of ischemia and reperfusion.

Ivabradine

Ivabradine is a one-of-a-kind cardiovascular drug approved by the Food and Drug Administration (FDA) in April 2015 to help patients with stable, symptomatic cardiovascular disease avoid hospitalization. Ivabradine 3-[3-[[(7*S*)-3,4-dimethoxy-7-bicyclo [4.2.0] octa-1,3,5-trienyl] methyl-methylamino] propyl]-7,8-dimethoxy-2,5-dihydro-1*H*-3-benzazepin-4-one is a novel specific heart rate reducing agent that acts in SA node. Details about the drug are given in the Figure 3 and Table 2.

Mechanism of Action

Ivabradine lowers heart rate by blocking If (funny) channels selectively in a concentration-dependent manner. The If

Table 3: Previously reported analytical methods

S.no.	*Title*	*Method*	*Description*
1	Development and validation of UPLC method for simultaneous quantification of carvedilol and ivabradine in the presence of degradation products using DoE concept[15]	UPLC	Column- C_8 UPLC column Dimension- 100 × 2.1 mm, 1.8 µ Mobile phase- 0.5% triethylamine buffer: Acetonitrile (50:50) Flow rate-0.4 mL /min. UV detection wavelength-285 nm
2	Validated RP-HPLC Method for the Determination of Ivabradine Hydrochloride in Pharmaceutical Formulation[16]	RP-HPLC	Column-Thermosil C_{18} Dimension-150 × 4.5 mm, 5µm Mobile phase- methanol and phosphate buffer pH 6.5 (65:35) Flow rate-1-mL/min UV detection wavelength-265 nm.
3	HPLC Method Development and Validation of S (-)-Carvedilol from API and Formulations[17]	HPLC	Column- n Phenomenex Lux-cellulose–4 Dimension- 250 mm × 4.6 mm; 5 µ Mobile phase- Isopropanol and n-Heptane (60:40 v/v) Flow rate-1-mL/min UV detection wavelength-254 nm
4	Monitoring of the photochemical stability of carvedilol and its degradation products by the RP-HPLC method[18]	RP-HPLC	Column-Chromolit RP C_8 column Dimension-100 mm × 4.6 mm; Mobile phase-acetonitrile and water (45:55, V/V) UV detection wavelength-280 nm
5	Development and Validation of a Stability-Indicating HPLC Method for the Assay of Carvedilol in Pure and Tablet Dosage Forms[19]	HPLC	Column- C_{18} column Dimension-5 µ, 4.6×250 mm Mobile phase-acetonitrile and water (60:40, v/v) Flow rate-0.7 mL/min. UV detection wavelength-240 nm
6	Chemo metrically Assisted RP-HPLC Method Development for Efficient Separation of Ivabradine and its Eleven Impurities[20]	RP-HPLC	Column- Zorbax Eclipse Plus C_{18} Dimension- 100 × 4.6 mm, 3.5 µm Mobile phase- phosphate buffer and acetonitrile (80:20, v/v) Flow rate-1.6 mL/min UV detection wavelength-220 nm
7	Stability indicating RP-HPLC method for the simultaneous estimation of ivabradine and metoprolol in bulk and tablet formulation[21]	RP-HPLC	Column- Denali C_{18} Dimension- 150 mm × 4.6 mm, 5 µm Mobile phase- orthophosphoric acid (0.1%) buffer: acetonitrile (60:40 V/V) Flow rate- 0.8 mL/minute. UV detection wavelength-260 nm
8	Method development and its validation for the quantitative estimation of ivabradine by RP-HPLC in bulk drug and marketed formulation with the stability studies[22]	RP-HPLC	Column- Symmetry C_{18} column Dimension- 250 mm x 4.6 mm and 5µm Mobile phase- Methanol: Ammonium Acetate buffer (40: 60%) Flow rate- 1.0 mL/min UV detection wavelength-282 nm.

channels are found in the sinoatrial node. Sinoatrial node cells are unique, in that they can cause a cyclical shift in their resting membrane potential, bringing it closer to the threshold for involuntary depolarization.

This depolarization causes recurrent and spontaneous action potentials, which explains the automaticity of the process (Figure 4).

The pacemaker or "funny" current (If), which conducts a slow, inward-depolarizing mixed sodium-potassium current, initiates this depolarization. A nonselective, hyperpolarization-activated cyclic nucleotide-gated transmembrane channel generates the funny channel (If). Ivabradine reduces heart rate by selectively reducing cation migration by blocking the intracellular portion of this transmembrane channel. As a result, the slope of the diastolic depolarization of the pacemaker action potential decreases.[13]

Pharmacokinetic

Absorption

Ivabradine is promptly released from the standardized film-coated tablet dosage form after oral consumption and then transferred into the circulatory system. When given as a single oral dosage when fasting, absorption is quick, with a time to peak of one hour. This time to peak is extended to 2 hours in the fed state. When consumed when fasting, ivabradine has a bioavailability of around 40%, whereas when given in the fed state, it has a bioavailability of 20–40%. Ivabradine exhibits a linear pharmacokinetic profile in the oral dosage range of 0.5–24 mg. With increasing ivabradine dosages (15–20 mg twice a day), heart rate decreases practically linearly.[14]

Distribution

Ivabradine binds to plasma proteins around 70% of the time and has a steady volume of distribution of about 100

L. Because ivabradine has a low affinity for CYP3A4 and does not appear to activate or inhibit CYP3A4 to a clinically significant degree, it is unlikely to affect the metabolism or plasma concentrations of CYP3A4 substrate medicines. On the other hand, co-administered medicines that produce considerable inhibition or induction of CYP3A4 may affect plasma ivabradine concentrations.

Metabolism

The cytochrome p450 system oxidizes ivabradine, which is primarily metabolised in the liver and digestive tract (CYP3A4). The N-demethylated derivative is the major active agent. The plasma elimination half-life of ivabradine is 2 hours, but the effective half-life is 11 hours (70–75% of the area under the plasma concentration-time curve [AUC]). Renal clearance is 70 mL/min, while total clearance is roughly 400 mL/min.[8,14]

Excretion

Metabolites are eliminated in faeces and urine to a comparable proportion. In the urine, around 4% of an orally taken dosage of the medicine is eliminated as an unmodified drug. Ivabradine clearance is unaffected by mild or moderate renal or hepatic impairment, hence it hasn't been examined in patients with severe renal or hepatic failure.[4,14]

Pharmacodynamic

Ivabradine is a true heart rate-lowering medicine that works by directly and selectively inhibiting the hyperpolarization-activated cyclic-nucleotide gated funny (If) current, a mixed sodium-potassium inward channel in the sinoatrial node. This current is in charge of regulating heart rate and controlling spontaneous diastolic depolarization. Ivabradine's action is limited to the If current and sinus node, hence it has no further direct cardiovascular effects. Ivabradine has no inotropic adverse effects and is effective in reversing left ventricular remodeling.

In adults, especially those with chronic heart failure, ivabradine causes a dose-dependent drop in heart rate. There was a trend towards a plateau in the impact of ivabradine on heart rate in trials looking at its pharmacodynamics at dosages more than 20 mg twice a day. Ivabradine caused a quick, sustained, and dose-dependent reduction in heart rate during rest and exercise in a variety of animal models, with no notable effects on atrioventricular conduction, left ventricular contraction-relaxation, or vascular tissues. In individuals with heart failure and left ventricular dysfunction, ivabradine has been found to reverse cardiac remodeling.[4,14]

Analytical Methods

This includes all methods for determining carvedilol and ivabradine in commercial formulations as well as biological fluids such as human plasma. These are all-analytical procedures that were discovered throughout the literature review. This article reviews the reported analytical methods for carvedilol and ivabradine estimation in pharmaceutical dosage forms and individuals.

Chromatographic Methods

Chromatography is the separation of analytes between the stationary and mobile phases where the analyte molecule interacts with a stationary phase either by adsorption or partition. A chromatographic approach is used in both quantitative and qualitative analysis. It is classified as thin-layer (TLC) chromatography, affinity chromatography, gel permeation chromatography, high-pressure liquid chromatography (HPLC), gas chromatography (GC), ion-exchange chromatography, ultra-high-performance liquid chromatography (UHPLC), etc.

Table 3 discusses about the work done till date on the combination Carvediol and Ivabradine.

CONCLUSION

In this article, we review the information about the previously reported analytical methods for the analysis of carvedilol and ivabradine in their bulk and pharmaceutical dosage form. Most techniques have a flow rate of 0.7–1.6 min/mL. This article mainly gives the basic knowledge and information required for developing new analytical methods for carvedilol and ivabradine.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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