IJPSR (2021), Volume 12, Issue 12 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 December 2020; received in revised form, 05 May 2021; accepted, 28 May 2021; published 01 December 2021

IVABRADINE AND METOPROLOL: A REVIEW OF ANALYTICAL METHODS FOR PHARMACEUTICAL QUALITY CONTROL AND MONITORING

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Keywords:

Ivabradine, Metoprolol, Spectrophotometry, Chromatography

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ABSTRACT: Beta-blockers are widely used in combination with Ivabradine in people with coronary heart disease (CHD), one of the leading causes of death. Thus, monitoring of these drugs is important because it is accessible to manage heart failure amongst people with CHD. In addition, its quality control is fundamental to provide quality medicines. Method of analysis can be the first step in the rational use of pharmaceuticals. In this context, a detailed study of literature and official compendia for the pharmaceutical quality control of Ivabradine and Metoprolol were done. Among the analytical methods in the evaluation of Ivabradine and Metoprolol, HPLC is predominantly followed by HPTLC and UV. It was found that in the literature that analysis of Ivabradine and Metoprolol-based pharmaceutical products are more common than analysis of Ivabradine and Metoprolol in biological matrices. Pharmaceutical analyses have an impact on analytical decisions as well as effective and reliable results. The method must be suitable for the intended investigation. Although, there is a lack of Analytical Methods for estimation of Ivabradine and Metoprolol in their combined dosage form.

INTRODUCTION: Coronary heart disease (CHD), also known as ischemic heart disease, is one of the leading causes of death. CHD develops because of the build-up of fatty deposits (plaque) on the walls of the coronary arteries. When arteries are blocked or narrowed, the heart does not receive enough blood to function properly, which can cause pain and tightness in the chest (angina). There are several types of angina, the most common being stable angina pectoris (AP). When you exercise or become stressed, the heart needs to work harder in order to pump enough oxygen around the body. When a person is suffering from AP, this extra stress on the heart causes severe pain in the chest.

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DOI: 10.13040/IJPSR.0975-8232.12(12).6221-32

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(12).6221-32

This type of angina is usually treated using medications and changing a person's lifestyle so that they do not put unnecessary strain on the heart. There is a wide range of drugs that can be prescribed to help people with (anti-anginal agents) [1]. Beta-blockers (beta-blockers, β-blockers, *etc*.) are a class of medications that are predominantly used to manage abnormal heart rhythms and to protect the heart from a second heart attack (myocardial infarction) after a first heart attack (secondary prevention).

They are also widely used to treat high blood pressure (hypertension). Beta-blockers widely used in combination with Ivabradine in people with heart failure with LVEF (Left ventricular ejection fraction is the measurement of how much blood is pumped out of the left ventricle of the heart) lower than 35 percent (in Angina Pectoris LVEF lowers than 35%) inadequately controlled by beta blockers alone and whose heart rate exceeds 70 beats per minute. In people not sufficiently managed with

beta-blockers for their heart failure adding Ivabradine decreases the risk of hospitalization for heart failure.

Ivabradine selectively inhibits the pacemaker If current. Blocking this channel reduces cardiac pacemaker activity, selectively slowing the heart rate and allowing more blood flow to flow to the myocardium. (Beta Blocker) Metoprolol Succinate blocks β1 adrenergic receptors in heart muscle cells. So, Ivabradine with Metoprolol safely and effectively reduces the heart rate and makes the heart more efficient at pumping blood throughout the body [2].

The Newly developed combination of beta-blocker (Metoprolol) with Ivabradine is safely and effectively treating Coronary Heart Disease. So, this combination is more widely used in Angina Pectoris. Therefore, the quality control of this pharmaceutical product is fundamental to provide quality medicines to the population [3].

Thus, A review of existing analytical methods in the literature and in official compendia for evaluation of Ivabradine and Metoprolol was made in this paper.

Ivabradine: [4, 5]

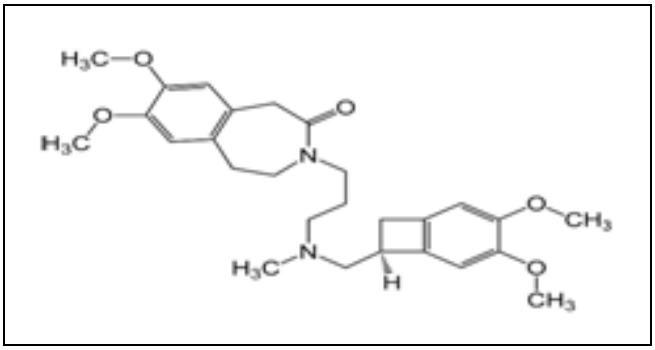

FIG. 1: STRUCTURE OF IVABRADINE

Chemical Name: 3-[3-({[(7S)-3,4-dimethoxybicyclo [4.2.0]octa-1,3,5-trien-7-yl] methyl} (methyl) amino)propyl]-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-2-one

Molecular Formula: $C_{27}H_{36}N_2O_5$

Molecular Weight: 468.594 g/mol

Mechanism of Action: Ivabradine lowers heart rate by selectively inhibiting If channels ("funny channels") in the heart in a concentration-dependent manner without affecting any other cardiac ionic channels (including calcium or potassium).

Ivabradine binds by entering and attaching to a site on the channel pore from the intracellular side and disrupts If ion current flow, which prolongs diastolic depolarization, lowering heart rate.

The If currents are located in the sinoatrial node and are the home of all cardiac pacemaker activity. Ivabradine, therefore, lowers the pacemaker firing rate, consequently lowering heart rate and reducing myocardial oxygen demand. This allows for an improved oxygen supply and therefore mitigation of ischemia, allowing for a higher exercise capacity and reduction in angina episodes.

Metoprolol: [6-10]

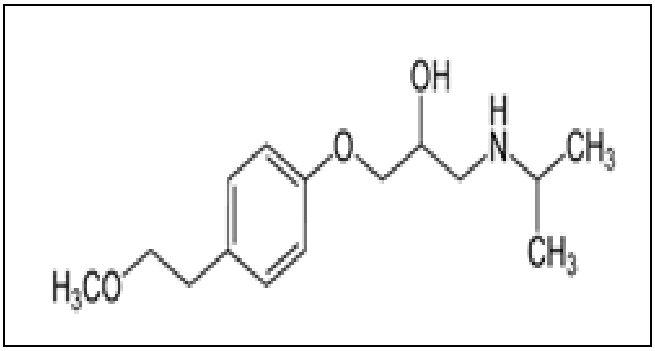

FIG. 2: STRUCTURE OF METOPROLOL

Chemical Name: 1-[4-(2-methoxyethyl)phenoxy]-3-[(propan-2-yl)amino]propan-2-ol

Molecular Formula: $C_{15}H_{25}NO_3$

Molecular Weight: 267.364 g/mol

Mechanism of Action: Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart.

Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure.

Marketed form of Metoprolol: Metoprolol succinate, Metoprolol tartrate, Metoprolol fumarate

Mechanism of Action (in Combination): Ivabradine selectively inhibits the pacemaker If current. Blocking this channel reduces cardiac pacemaker activity, selectively slowing the heart

rate and allowing more time for blood to flow to the myocardium. (Beta Blocker) Metoprolol Succinate blocks β1 adrenergic receptors in heart muscle cells.

So, Ivabradine with Metoprolol safely and effectively reduces the heart rate and makes the heart more efficient at pumping blood throughout the body.

Applications: Ivabradine and Metoprolol tartrate in combination is marketed in the form of tablets. The typical dose is 5 mg Ivabradine and 25/50 mg Metoprolol tartrate.

Methods for Analysis: Quality control is essential to certify the quality, safety, and efficacy of pharmaceutical products.

Therefore, Analytical Methods are used to check quality. The methods found in the literature for evaluation of Ivabradine and Metoprolol were Titrimetric, UV, Visible spectroscopy, dissolution study using HPLC, IR, HPLC, HPLC coupled with MS (LC-MS), HPTLC, UPLC, UPLC coupled to MS, UPLC-MS/MS. UPLC-MS method is the most used in the analysis of biological samples, whereas the HPLC method is the most used in the analysis of pharmaceutical samples shown in the figure.

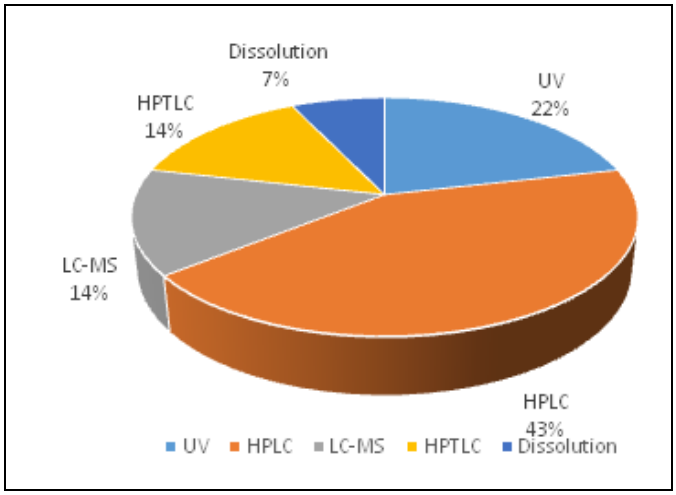

FIG. 3: METHODS FOUND IN LITERATURE FOR EVALUATION OF IVABRADINE

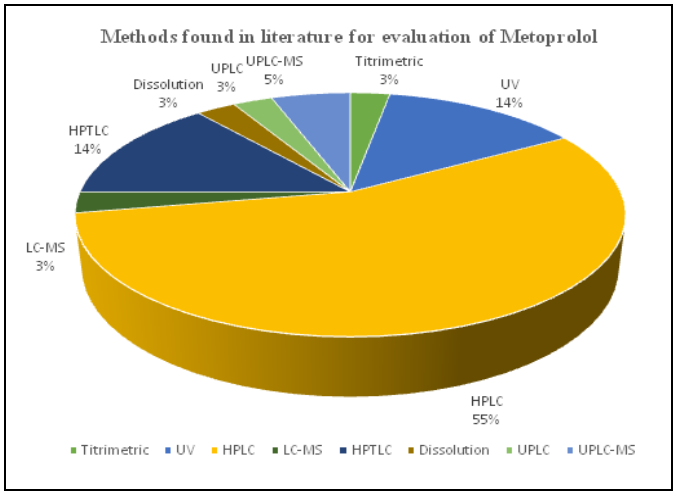

FIG. 4: METHODS FOUND IN LITERATURE FOR EVALUATION OF METOPROLOL

Literature reveals that Ivabradine is estimated in combination with various drugs like Carvedilol, Metoprolol, Roboxetine whereas Metoprolol is estimated in combination with Amlodipine, Clinidipine, Metformin, Olmesartan, Telmisartan, Atorvastatin, Ramipril, Caffeine, Tolbutamine, Dapson.

Various articles are available on the analysis of pharmaceutical samples of Ivabradine and Metoprolol alone.

Very few articles are reported for the analysis of Ivabradine and Metoprolol in biological matrices.

DISCUSSION: Ivabradine and Metoprolol in pharmaceutical or biological matrixes can be evaluated by different methods of analysis.

Pharmaceutical analyses have an impact on making analytical decisions as well as getting effective and reliable results. The method must be suitable for the intended investigation.

Ivabradine is a newly approved drug, so the analytical method is not available in any official compendia, whereas Metoprolol is official in IP(IP 2018)6and USP (USP 40 NF 35)7.

In Official compendia analytical methods for Metoprolol are available in various salt form like succinate, tartrate and fumarate.

The official method for analysis of Metoprolol tablet uses HPLC wherein buffer and acetonitrile are used as a mobile phase. A dissolution study was performed in phosphate buffer.

Titration was done using perchloric acid. Reported Methods for Estimation of Ivabradine and Metoprolol are given in the table.

TABLE 1: REPORTED METHOD FOR ESTIMATION OF IVABRADINE

S. no.	Drug	Description	Ref no.
1	Ivabradine in controlled-release formulations by UV Spectrophotometric Method	Detection Wavelength: 286 nm Solvent: Phosphate Buffer (pH 6.8) Linearity Range:10-50 µg/mL Correlation co-efficient:0.9994	11
2	Ivabradine in controlled-release formulations by UV Spectrophotometric and RP-HPLC methods for dissolution study	UV Method: Detection Wavelength: 286 nm, Solvent: Water, HCl Buffer (pH 1.2), Phosphate Buffer (pH 6.8) Linearity Range: In Water: 5-60 µg/mL, In HCl Buffer (pH 1.2): 5-60 µg/mL In Phosphate Buffer (pH 6.8): 5-60 µg/mL Correlation co-efficient: In Water: 0.9998, In HCl Buffer (pH 1.2): 0.9998 In Phosphate Buffer (pH 6.8): 0.9999 RP-HPLC Method: Mobile phase: Phosphate buffer pH 7.4: Methanol (35:65) Solvent: Phosphate Buffer (pH 6.8), Phosphate buffer (pH 7.4): methanol (35:65) Stationary Phase: 250 mm × 4.6 mm, 5µm, C18, 100Aº Kromasil column Linearity Range: In Phosphate Buffer (pH 6.8): 5-60µg/mL In phosphate buffer pH 7.4: methanol (35:65): 40-60 µg/mL Retention Time: 7.4 min, Flow Rate: 1 ml/min Correlation co-efficient: In Phosphate Buffer (pH 6.8): 0.9992 In phosphate buffer pH 7.4: methanol (35:65): 0.9993 LOD:0.05 µg/mL, LOQ:0.2 µg/ml	12
3	Ivabradine Hydrochloride in Bulk and Pharmaceutical dosage form by RP-HPLC method	Detection Wavelength: 286 nm Solvent: Methanol: ACN (80:20 v/v) further dilution in Methanol, Mobile phase: Methanol: ACN (80:20 v/v) Stationary Phase: ZorbaxEclipsPlus C18, 250×4.6 mm, 5 µm column Linearity Range: 2.5-50 µg/mL, Retention Time: 5.8 min Flow Rate: 1 ml/min, Correlation co-efficient: 0.9998 LOD: 0.0216 µg/mL, LOQ: 0.06537 µg/mL	13
4	Ivabradine Hydrochloride in Tablets by RP-HPLC method	Detection Wavelength: 285 nm, Mobile phase: Methanol:25 mM phosphate buffer (60:40 v/v) pH 6.5 Stationary Phase: SS Wakosil C18AR, 250×4.6 mm, 5 µm column Linearity Range: 30-210 µg/mL, Retention Time: 7.4 min Flow Rate: 0.8 ml/min, Correlation co-efficient: 0.9998	14
5	Ivabradine HCl in Pharmaceutical Dosage Form by Stability Indicating UV Spectrophotometric Method and RP-HPLC Method	UV Method: Detection Wavelength: 286 nm, Solvent: Methanol Linearity Range: 4.2-31. 6µg/mL LOD: 0.06 µg/ml, LOQ: 0.2 µg/ml, Correlation co-efficient: 0.99974 RP-HPLC Method: Detection Wavelength: 286 nm, Solvent: Water: Acetonitrile (50: 50 v/v). Further dilution was made in Methanol Mobile phase: 0.5% Formic Acid (pH=7.0): Acetonitrile (65: 35 v/v), Stationary Phase: Inertsil ODS-3V [250 mm x 4.6mm] 5µcolumn, Linearity Range: 4.2-31. 6 µg/mL, Retention Time: 7 min, Flow Rate: 0.7 ml/min, Correlation co-efficient: 0.9989, LOD: 0.06 µg/ml, LOQ: 0.2 µg/ml Degradation: Thermal: 105º C for 24 Hrs, UV: 254 nm for 48 Hrs Acid:2 mL 5 N HCl (60°C for 30 min) %Degradation: 10.96%, Alkali:2 mL 5 N NaOH (60°C for 30 min) Oxidation:3% H_2O_2 (60°C for 30 min), %Degradation: 3.71%, Humidity: 40°C/75%RH for 24 h Marked Degradation observed in acid hydrolysis and Oxidation condition	15

6	Ivabradine HCl in Solid Oral Dosage Form by Stability Indicating RP-HPLC Method	Detection Wavelength: 285 nm Solvent: Water Mobile phase: 10 mM ammonium acetate buffer pH 6.0: Methanol (50:50) (v/v) Stationary Phase:Phenomenex KinetexC_{18} column (150 × 4.6 mm, 5 µm Retention Time: 3.1 min, Linearity Range: 70 - 130µg/ml. Flow Rate: 1 ml/min, Correlation co-efficient: 0.9997 Degradation: Thermal: 105º C for 24 Hrs, %Degradation: 13% Photolytic: 1.2 million lux h & 200 W h / sq. m Acid:1 N hydrochloric acid (10% / 75°C for 6 h) Alkali:1 N sodium hydroxide (10% / 75°C for 6 h) Oxidation:3% H_2O_2 (10% /75°C for 6 h), %Degradation: 3% Humidity:92%RH at 25°C for 48 h Marked Degradation observed in acid Thermal and Oxidation condition	16
7	Ivabradine in Bulk and Pharmaceutical Dosage Form by RP HPTLC Method	Solvent: DMSO, Detection Wavelength:254 nm, 366 nm Mobile phase: Acetonitrile: Water (60:40, v/v) Stationary Phase: Kieselgel 60 F254 S Linearity Range: 0.2–1.2 µg/spot R_f Value:0.26, Correlation co-efficient: 0.999	17
8	Ivabradine in Bulk and Pharmaceutical Dosage Form by Stability Indicating HPTLC Method	Detection Wavelength:287 nm Mobile phase: Ethyl acetate: 0.389 M Ammonium acetate in Methanol (1:5, v/v) Stationary Phase: silica gel 60F254 aluminum plates Linearity Range: 1200-2800 ng/spot, R_f Value:0.36 ± 0.01 LOD: 255.86 ng/spot, LOQ: 775.33 ng/spot Correlation co-efficient: 0.9956	18
9	Ivabradine in Bulk and Pharmaceutical Dosage Form by Stability Indicating HPTLC Method	Solvent: Methanol, Detection Wavelength:286 nm Mobile phase: Chloroform: Methanol (1:1 *v/v*) Stationary Phase: Aluminum Plate precoated with Silica Gel 60 F254 Linearity Range: 400–2000 ng/band, R_f Value:0.63 ± 0.02 LOD: 20.73 ng/band, LOQ: 62.83ng/band Correlation co-efficient: 0.997 Degradation: Photolytic: 1.2 million lux h & 200 W h / sq. m Acid:1 N hydrochloric acid (10% / refluxed at 60°C for 30 min), Alkali: 0.1 N sodium hydroxide (10% / room temperature for 24 h), Oxidation:3% H_2O_2 (10% / room temperature for 24 h), Dry Heat: In Oven 80°C for 6 hr No Degradation peak observed	19
10	Ivabradine in Human Plasma by LC-MS/MS-ESI Method	Solvent: Methanol Mobile phase: 0.1% formic acid: Methanol (60:40, v/v) Stationary Phase: Aglient Eclipse XDB C8 column (150 × 4.6 mm, 5 µm) Linearity Range:0.1–200 ηg/mL, Flow Rate: 1 ml/min Correlation co-efficient: 0.9970	20
11	Ivabradine and N-desmethylivabradine in Urine and in Human Plasma by LC-MS/MS Method	Solvent: Methanol Internal Standard: Diazepam Mobile phase: Methanol and Aqueous 5 mM Ammonium acetate buffer containing 0.2% formic acid (80:20, v/v) Stationary Phase: Diamonsil C18 column (150 mm 4.6 mm, 5 mm Linearity Range: In Plasma: Ivabradine: 0.1013–101.3 ng/mL, N-desmethylivabradine: 0.085–25.5 ng/mL In Urine:Ivabradine: 10.13–6078 ng/mL N-desmethylivabradine: 8.5–850 ng/mL Flow Rate: 0.6 ml/min, Correlation co-efficient: 0.999	21
12	Ivabradine Impurity 3,3'-(propane-1,3-diyl) bis(7,8-dimethoxy-1,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one)	Spectroscopic Method: Detection Wavelength: 479 nm, Solvent: Distilled water Oxidation of drug impurity by excess cerium (IV) sulphate in acidic medium and the subsequent reaction of the remaining Ce (IV) with a known amount of ferrous ammonium sulphate. The resultant ferric ion is then made to react with thiocyanate in acid medium to form a brown coloured complex which is	22

	by Spectroscopic and Volumetric Method	analyzed spectrophotometrically against the reagent blank. Linearity Range:0.5–100 mg/lCorrelation co-efficient:0.9984, LOD: 0.14, LOQ: 0.42 Volumetric Method: un-reacted Ce (IV) is titrated against standard ferrous ammonium sulphate to estimate the quantity of IVA-9.	
13	Ivabradine and Carvedilol in their fixed dose combination by RP- HPLC Method	Wavelength: 275 nm Solvent: 50:50 (v/v) methanol/water further dilution by using 85:15:0.1 (v/v/v) acetonitrile/water/formic acid Mobile phase: Acetonitrile: Phosphate Buffer (pH 3) (75:25) Stationary Phase: Hypersil ODS C18, Flow Rate: 1 ml/min Linearity Range: Ivabradine: 50-300 µg/ml, Carvedilol: 150-400 µg/ml Retention Time:Ivabradine: 8.40 min, Carvedilol: 12.14 min Correlation co-efficient:Ivabradine:0.9983, Carvedilol:0.9999 LOD:Ivabradine: 3.64, Carvedilol: 4.83 LOQ:Ivabradine: 11.03, Carvedilol: 14.64	23

TABLE 2: REPORTED METHOD FOR ESTIMATION OF METOPROLOL

S. no.	Drug	Description	**Ref no.**
1	Metoprolol succinate in Bulk and in Pharmaceutical dosage forms by UV Spectrophotometric method	In Distilled water: Detection Wavelength: 221 nm, Linearity Range: 5-25 µg/mL Correlation coefficient: 0.995 LOD: 1.389 µg/mL, LOQ: 4.2084 µg/ml In phosphate buffer pH 6.8: Detection Wavelength: 223 nm, Linearity Range: 5-25µg/mL Correlation coefficient: 0.995 LOD: 0.1399 µg/mL, LOQ: 0.4240 µg/ml	24
2	Metoprolol tartrate in Pharmaceutical dosage forms byUV Spectrophotometric and Complexation method	UV Spectrophotometric method: Detection Wavelength: 274 nm, Linearity Range: 68.4-205.4 µg/mL, Correlation coefficient: 0.998 LOD: 8.10 µg/mL, LOQ:26.98 µg/ml Complexation method: Complexation withcopper (II) at pH 6.0, using Britton-Robinson buffer solution, Detection Wavelength: 675 nm Linearity Range: 8.5-70µg/mL, Correlation coefficient: 0.998 LOD: 5.56 µg/mL, LOQ: 7.11 µg/ml	25
3	Metoprolol succinate in Bulk and Pharmaceutical Dosage Form by RP-HPLC Method	Detection Wavelength: 280 nm Mobile phase: Acetonitrile: water: 1 % ortho phosphoric acid (70:27:3 v/v/v) Stationary Phase: Aligent C-8, RP column (4.6 mm i.d x 250 mm), Linearity Range:10–200 µg/mL Retention Time: 6.84 min, Flow Rate: 1 ml/min LOD:0.0284 µg/mL, LOQ:0.094 µg/ml	26
4	Metoprolol tartrate in Human Plasma by RP-HPLC Method	Internal Standard: Pinacidil monohydrate Detection Wavelength: 275 nm Mobile phase: Acetonitrile: Water: Triethylamine 18:81:1 (v/v) pH 11, Stationary Phase:250 mm × 4 mm, 10-µm particle, Novapack C_{18} column, Linearity Range: 20–200 µg/mL, Retention Time: 6.84 min, Flow Rate: 1 ml/min	27
5	Metoprolol Tartrate and Hydrochlorothiazide in Bulk and in Pharmaceutical dosage forms by RP-HPLC Method	Detection wavelength: 226 nm, Solvent: Methanol Mobile phase: Phosphate buffer: Methanol (60:40) (v/v) Stationary Phase: Inertsil ODS-3, 250 mm, 4.6 mm ID, packed with 5 µ particle size, Flow Rate:1.0 ml/min Linearity Range: Metoprolol tartrate: 100 to 600 ppm, Hydrochlorthiazide: 12.5 to 75 ppm Retention Time: Metoprolol tartrate: 10.81, Hydrochlorthiazide: 4.13 Correlation coefficient: Metoprolol tartrate: 0.9995, Hydrochlorthiazide: 0.9998	28
6	Metformin, Metoprolol and its	Mobile phase: Methanol: Water containing 0.1% formic acid (39:61, v/v) Stationary Phase: Agilent HC-C18 column (4.6 × 250 mm, 5 µm), Flow Rate: 0.2	29

	Metabolites in Rat Plasma by LC–MS-MS Method	ml/min Linearity Range: Metoprolol: 19.53–40,000 ng/mL, Metformin: 3.42–7,000 ng/mL, α-hydroxymetoprolol (HMT): 2.05–4,200 ng/mL, O-desmethylmetoprolol (DMT): 1.95–4,000 ng/mL Retention Time: Metoprolol: 6.9 min, Metformin: 3.6 min, α-hydroxymetoprolol(HMT): 3.8 min, O-desmethylmetoprolol (DMT): 3.1 min	
7	Metoprolol Succinate and Olmesartan Medoxomil in Tablet Dosage Form by Stability Indicating RP-HPLC Method	Detection wavelength: 228 nm, Solvent: Methanol Mobile phase: Methanol: 0.05% v/v O-phosphoric acid in water (50:50 v/v) , Stationary Phase: Chromasil 250 × 4.6 mm, i.d 5 µm C-18 column, Flow Rate: 1ml/min Linearity Range: Metoprolol Succinate: 5-80 µg/ml, Olmesartan Medoxomil: 5-70 µg/ml Retention Time:Metoprolol Succinate: 3.485 min, Olmesartan Medoxomil: 7.085 min Correlation coefficient: Metoprolol Succinate: 0.9990, Olmesartan Medoxomil: 0.9993 Degradation: Thermal: 80º C for 48 Hrs in oven, Photodegradation:(U.V.) in Photostability chamber equipped with UV ligt with energy of not less than 200watt hours/square meter, (Fluroscence light)in Photostability chamber equipped with Fluroscence light illumination not less than 1.2 million lux hours Acid: 10 mL 1 N HCL and heated for 30 min at 60º C, 2 impurities that is at Rt 2.950, 5.033 Alkali: 10 mL 1 N NaOH and refluxed for 30 min at 60º C 2 impurities that is at Rt 2.893, 5.030 Oxidation: (i) 30 % H_2O_2 heated for 2 hrs at 60º C in water bath Neutral: 10 ml distilled water and refluxed for 2 hrs at 60º C Degradation was observed in Acidic and Alkaline condition	30
8	Metoprolol Succinate and Olmesartan Medoxomil in Tablet Dosage Form by Stability Indicating RP-HPLC Method	Detection wavelength: 220 nm, Solvent: ACN: Water (1:1) Mobile phase: 0.05% Trifluoro acetic acid (TFA): Acetonitrile (70:30 v/v) , Stationary Phase: YMC-Pack CN 250 x 4.6 mm, i.d 5 µm C-18 column, Flow Rate: 1ml/min Linearity Range: Metoprolol Succinate: 5-35 µg/ml, Olmesartan Medoxomil: 5-35 µg/ml Retention Time: Metoprolol Succinate: 4.1 min, Olmesartan Medoxomil: 7.9 min Correlation coefficient: Metoprolol Succinate: 0.998, Olmesartan Medoxomil: 0.999 LOD:Metoprolol Succinate: 1.05 µg/ml, Olmesartan Medoxomil: 0.085 µg/ml LOQ:Metoprolol Succinate: 3.19 µg/ml Olmesartan Medoxomil: 0.259 µg/ml Degradation: Thermal: (Dry heat): heated at 105º C for 24 Hrs in oven impurities that is at Rt 8.4, 8.6 min for OLM and 4.8, 6.1, 6.7, 6.8 min for MET Humidity: 75% RH for 24 hrs impurities that is at Rt 8.4, 8.6 min for OLM and 4.8, 6.1, 6.7 min for MET Photodegrdation:(U.V.) in UV light at 254 nm for 24 hrs impurities that is at Rt 8.4, 8.6 min for OLM and 4.8, 5.3, 6.1, 6.7 min for MET(In Sun light)for 24 hrs impurities that is at Rt 8.4, 8.6 min for OLM and 4.8, 5.3, 6.1, 6.7 min for MET, Acid: 0.1 N HCl and heated for 1 hr at 100º C, impurities that is at Rt 5.8 min for OLM and 4.9, 5.3 min for MET Alkali: 0.1 N NaOH heated for 1 hr at 100º C impurities that is at Rt 5.9 min for OLM and 4.9, 5.3 min for MET Oxidation: (i) 0.1 % H_2O_2 heated for 24 hrs at 100º C impurities that is at Rt 5.8 min for OLM and 5.3 min for MET Degradation was observed in Acidic, Alkaline and Oxidation Condition	31
9	Olmesartan Medoximil and Metoprolol	Solvent: Methanol, Detection Wavelength: 233 nm Mobile phase: Water: Methanol: Ammonium sulphate (4.5:4.5:1.5 v/v/v) Stationary Phase: Precoated silica gel aluminium plate 60 F254	32

	Succinate in Tablet Dosage Form by HPTLC Method	Linearity Range: Olmesartan: 100-700 ng/spot, Metoprolol succinate: 100-700 ng/spot Rf Value: Olmesartan: 0.65, Metoprolol succinate: 0.78 Correlation co-efficient: Olmesartan: 0.9991, Metoprolol succinate: 0.9992 LOD: Olmesartan: 12.07 ng, Metoprolol succinate: 17.3 ng LOQ: Olmesartan: 37 ng, Metoprolol succinate: 51.7 ng	
10	Caffeine, Tolbutamide, Metoprolol, and Dapsone in Rat Plasma by UPLC–MS-MS Method	Detection wavelength: 220 nm, Internal Standard: Phenacetin Solvent: Methanol: Water (5:5, v/v) Extraction: Dichloromethane: Butanol (10:1, v/v) Mobile phase: Acetonitrile: Water (containing 0.1% formic acid) (15:85, v/v)Stationary Phase: Waters Acquity UPLC BEH HILIC C18 column (2.1 3 50 mm, 1.7 mm), Flow Rate: 0.25 mL/min Linearity Range: Metoprolol: 2.5–250 ng/mL, Caffeine: 2.5–1,000 ng/ml,Dapson: 2.5–1,000 ng/ml, Tolbutamide: 5–5,000 ng/mL Retention Time: Metoprolol: 2.31 min, Caffeine: 1.15 min Dapson: 3.10 min, Tolbutamide: 2.31 min Correlation coefficient: Metoprolol: 0.9998, Caffeine: 0.9936 Dapson: 0.9966, Tolbutamide: 0.9990	33
11	Cilnidipine and Metoprolol succinate in bulk drugs and combined dosage form by UV spectrophotometric method (Q-Absorbance Ratio)	Solvent: Methanol, Detection Wavelength: 230.60 nm and 223.40 nm, i.e. isoabsorptive point Linearity Range: Clinidipine: 2-10 µg/mL, Metoprolol succinate: 10-50 µg/ml At 230.60 nm wavelength: Correlation coefficient: Clinidipine: 0.9991, Metoprolol succinate: 0.9986LOD: Clinidipine: 0.0529 µg/ml, Metoprolol succinate: 0.1647 µg/mlLOQ:Clinidipine: 0.16058 µg/ml, Metoprolol succinate: 0.4993 µg/ml At 223.40 nm wavelength: Correlation coefficient: Clinidipine: 0.9995, Metoprolol succinate: 0.9998LOD: Clinidipine: 0.0909 µg/ml, Metoprolol succinate: 0.1281 µg/mlLOQ:Clinidipine: 0.2757 µg/ml, Metoprolol succinate: 0.3884 µg/ml	34
12	Clnidipine and Metoprolol succinate in bulk drugs and Tablet dosage form by RP-HPLC Method	Detection wavelength: 225 nm Solvent: Water and Methanol (50:50) Mobile phase: Buffer (0.1%OPA): Methanol (45:55 v/v) Stationary Phase: Altima C_{18} (4.6 × 150mm, 5µm) column Flow Rate: 1 ml/min Linearity Range: Metoprolol Succinate: 12.5-75µg/ml, Clnidipine: 5-30µg/ml Retention Time: Metoprolol Succinate: 2.249 min, Clnidipine: 3.062 min Correlation co-efficient: Metoprolol succinate: 0.9995, Clnidipine: 0.9992	35
13	Clnidipine and Metoprolol succinate in combined dosage form by HPTLC Method	Solvent: Methanol, Detection Wavelength: 231 nm Mobile phase: Toluene: Chloroform: Methanol: Glacial acetic acid (45: 25: 25: 5 v/v/v/v) Stationary Phase: Silica Gel G60 F254 TLC plate Linearity Range: Clnidipine: 100-500µg/ml, Metoprolol succinate: 500-2500 µg/ml Rf Value: Clnidipine: 0.70 ± 0.01, Metoprolol succinate: 0.34 ± 0.005Correlation co-efficient: Clnidipine: 0.9954, Metoprolol succinate: 0.9991LOD: Clnidipine: 4.936001 µg/ml, Metoprolol succinate: 4.936001µg/mlLOQ: Clnidipine: 27.18213 µg/ml, Metoprolol succinate: 82.3701µg/ml	36
14	Metoprolol Succinate and Amlodipine in Tablet Dosage Form by RP-HPLC Method	Detection wavelength: 221 nmSolvent: 0.02 M phosphate buffer solution: acetonitrile (70:30v/v, pH 3.0) Mobile phase: 0.02 M phosphate buffer solution: acetonitrile (70:30v/v, pH 3.0) Stationary Phase: KromasilC_{18} (250 x 4.6 mm, 5 µm) columnFlow Rate: 1 ml/min Linearity Range: Metoprolol Succinate: 10-110 µg/ml, Amlodipine: 10-110 µg/mlRetention Time: Metoprolol Succinate: 4.49 min, Amlodipine: 2.57 minCorrelation coefficient: Metoprolol Succinate: 0.9992, Amlodipine: 0.9991 LOD: Metoprolol succinate: 0.025 µg/ml, Amlodipine: 0.029 µg/mlLOQ: Metoprolol succinate: 0.075 µg/ml, Amlodipine: 0.090 µg/ml	37

15	Amlodipine besylate and Metoprolol succinate in bulk and Tablets by HPTLC Method	Solvent: Methanol, Detection Wavelength: 254 nm, Mobile phase: Toluene: Ethyl acetate: Methanol: Triethylamine (4:1:1:0.4 v/v/v)Stationary Phase: Precoated silica gel aluminium plate 60 F_{254} (10×10 cm)Linearity Range: Amlodipine besylate: 400-1400 ng/spot, Metoprolol succinate: 3800-13300 ng/spot Rf Value: Amlodipine besylate: 0.39, Metoprolol succinate: 0.59 Correlation co-efficient: Amlodipine besylate: 0.9990±0.0013 Metoprolol succinate: 0.9993±0.0013LOD: Amlodipine besylate: 39.99 ng/spot, Metoprolol succinate: 121.20 ng/spot LOQ: Amlodipine besylate: 234.31 ng/spot, Metoprolol succinate: 710.03 ng/spot	38
16	Telmisartan and Metoprolol Succinate in Tablet Dosage Form by Stability Indicating HPLC Method	Solvent: Methanol, Detection Wavelength: 223 nm Mobile phase: Methanol: 10 mM potassium dihydrogen phosphate buffer: 10 mM hexane sulphonic acid (80:10:10 v/v/v) Stationary Phase: HiQ Sil C_{18} (250 × 4.6 mm, 5 µm) column Linearity Range: Telmesartan:5-60 µg/mL, Metoprolol succinate: 5-80 µg/mL Flow rate: 1 ml/min Retention time: Telmesartan: 5.653 min, Metoprolol succinate: 3.067 min Correlation co-efficient: Telmesartan: 0.9980, Metoprolol succinate: 0.9990	39
17	Telmisartan and Metoprolol succinate in Pharmaceutical formulation by Normal and Reversed-Phase HPTLC Method	Normal Phase HPTLC Method: Solvent: Methanol, Detection Wavelength: 242 nm Linearity Range: Telmisartan: 800–3200 ng/band, Metoprolol succinate: 1600– 6400 ng/spot Mobile phase: Toluene: Propanol: Methanol: Triethylamine (8: 1: 1: 0.5 v/v) Stationary Phase: Precoated silica gel aluminium plate 60 F_{254} Rf Value: Telmisartan: 0.45 ± 0.02, Metoprolol succinate: 0.70 ± 0.02 Correlation co-efficient: Telmisartan: 0.997, Metoprolol succinate: 0.997 LOD: Telmisartan: 2.79 ng/spot, Metoprolol succinate: 58.69 ng/spot LOQ: Telmisartan: 8.45 ng/spot, Metoprolol succinate: 177.86 ng/spot Reversed-Phase HPTLC Method Solvent: Methanol,Detection Wavelength: 242 nm Linearity Range: Telmisartan: 800–3200 ng/band, Metoprolol succinate: 1600– 6400 ng/spot Mobile phase: Methanol: Water: Triethylamine (6: 4: 0.5 v/v) Stationary Phase: RP-18 silica gel 60 F254S Rf Value: Telmisartan: 0.55 ± 0.02, Metoprolol succinate: 0.41 ± 0.02 Correlation co-efficient: Amlodipine besylate: 0.996, Metoprolol succinate: 0.998 LOD: Amlodipine besylate: 43.97 ng/spot, Metoprolol succinate: 64.18 ng/spot LOQ: Amlodipine besylate: 133.26 ng/spot Metoprolol succinate: 194.49 ng/spot	40
18	Atorvastatin Calcium and Metoprolol Succinate in Capsules by HPTLC Method	Solvent: Methanol,Detection Wavelength: 276 nm Mobile phase: Toluene: Methanol: Ethyl acetate: Glacial acetic acid (7: 1.5: 1: 0.5 v/v/v/v) Stationary Phase: Precoated silica gel aluminium plate 60 F_{254} Linearity Range: Atorvastatin: 500–3000 ng/band Metoprolol succinate: 1000-6000 ng/spot Rf Value: Atorvastatin: 0.28 ± 0.1, Metoprolol succinate: 0.58 ± 0.1 Correlation co-efficient: Atorvastatin: 0.9974, Metoprolol succinate: 0.9927 LOD: Atorvastatin: 15.001 ng, Metoprolol succinate: 45.457 ng	41

		LOQ: Atorvastatin: 78.736 ng, Metoprolol succinate: 238.595 ng	
19	Atorvastatin Calcium and Metoprolol Succinate, Ramipril in Capsules by Stability-Indicating RP-UPLC Method	Solvent: Methanol, Detection Wavelength: 210 nm Mobile phase: 0.0045 M Sodium lauryl sulphate as buffer, at ratio of buffer: Acetonitrile (50:50 v/v) Stationary Phase: Zorbax® XDB-C_{18} (4.6 mm × 50 mm, 1.8 µm) column Flow rate: 1 ml/min Retention time: Ramipril: 2.6 min, Atorvastatin: 2.1 min, Metoprolol succinate: 1.3 min Degradation: Thermal: (Dry heat): heated at 105º C for 15 Hrs, %Degradation: 33.5% for RAM, 32.3% ATV Humidity: 25 º C, 90% RH for 7 days Photo degradation:(U.V.) in Photostability chamber equipped with UV light with energy of 200 Watt-hours/square meter for 24 hr(In Visible light)in Photostability chamber equipped with Fluorescence light illumination not less than 1.2 million lux hours for 24 hrs Acid: 0.1 N HCl Refluxed at 60 º C for 30 min, %Degradation: 2.7% for MET Alkali: 0.1 N NaOH Refluxed at 60 º C for 30 min, %Degradation: 2.6% for RAM Oxidation: 3 % H_2O_2Refluxed at 60 º C for 30 min, %Degradation: 4.8% for RAM, 2.2% ATV Purified Water: 60 º C for 1 hr Degradation was not observed in visible light, UV, humidity and water hydrolysis stress studies. Significant degradation was not shown in acid hydrolysis, base hydrolysis and oxidative conditions. However, thermal stress showed significant degradation.	42
20	Ivabradine, Roboxetine and Metoprolol in Human plasma by UPLC-MS/MS Method	Internal Standard:Deuterium-labeled drugs (d3- ivabradine, d5-reboxetine and d7-metoprolol), Flow rate: 0.5 ml/min Mobile phase: mixture of water and methanol, each containing 2 mM ammonium acetate Stationary Phase: Waters ACQUITY BEH C_{18} column (50 mm × 2.1 mm i.d., 1.7 m particle size) Linearity Range: Ivabradine: 1 ng/mL to 500 ng/mL, Metoprolol: 1 ng/mL to 500 ng/mL,Roboxetine: 1 ng/mL to 500 ng/mL Retention time: Ivabradine: 2.1 min, Metoprolol: 1.8 min, Roboxetine: 2.6 min	43
21	Ivabradine and Metoprolol in bulk and tablet dosage form by Stability Indicating RP-HPLC Method	Detection wavelength: 260 nm, Solvent: ACN: Water (60:40) Mobile phase: Orthophosphoric acid (0.1%) buffer: acetonitrile (60:40 V/V) Stationary Phase: Denali C_{18} column of dimension 150 mm × 4.6 mm, 5 µm Flow Rate: 0.8 ml/min, Run Time: 6 min Linearity Range: Ivabradine: 5-30 µg/mL, Metoprolol: 25-150 µg/mL Retention Time: Ivabradine: 2.290 min, Metoprolol: 3.520 min Correlation coefficient: Ivabradine: 0.9993, Metoprolol Succinate: 0.999 LOD: Ivabradine: 0.38 µg/ml, Metoprolol: 0.27 µg/ml LOQ: Ivabradine: 0.69 µg/ml, Metoprolol: 0.71 µg/ml Degradation: Dry heat: heated at 90º C for 1Hr Acid: 2 N HCl boil for 1 hr %Degradation: 0.455% Rt: 2.655 min Alkali: 2 N NaOH boil for 1 hr %Degradation: 0.586% Rt: 4.05 min Oxidation: 30 % H_2O_2 boil for 1 hr, %Degradation: 1.453% Rt: 2.655 min and 3.327% Rt: 5.072 Marked Degradation was observed in Acidic, Alkaline and Oxidation condition	44

CONCLUSION: This review depicts the reported Spectroscopic and Chromatographic methods developed and validated for the estimation of Ivabradine and Metoprolol. Literature review reveals that there are various spectroscopic and chromatographic methods available for the estimation of Ivabradine and Metoprolol alone and in combination with other drugs. HPLC and HPTLC methods were found to be very common. Ivabradine in combination with Metoprolol and Roboxetine was estimated by UPLC/MS-MS method in human plasma. Recently an article on the stability-indicating HPLC method was published for estimation of Ivabradine and Metoprolol in their combined dosage form. There is only one reported method for Ivabradine and Metoprolol in their combined dosage form. So, there will be a great scope for the development of highly precise, accurate and simple analytical methods for newly developed combined dosage form of Ivabradine and Metoprolol.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Gandhi NK and Ezhava SB: Ivabradine and metoprolol: a review of analytical methods for pharmaceutical quality control and monitoring. Int J Pharm Sci & Res 2021; 12(12): 6221-32. doi: 10.13040/IJPSR.0975-8232.12(12).6221-32.