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A REVIEW ON ANALYTICAL METHOD DEVELOPMENT OF ANTIHYPERTENSIVE AGENTs

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ABSTRACT

Metoprolol Succinate {butanedioic acid; 1-[4-(2-methoxyethyl) phenoxy]-3-(propan 2-yl amino) propan-2- ol} and Isosorbide mononitrate (8-nitrooxy-2,6-sdioxabicyclo[3.3.0]octan-4-ol) are well known antihypertensive and antianginal agent. In this review article we discuss about various analytical methods like Uv Spectroscopy, HPLC, HPTLC, Stability indicating RP-HPLC, LC-MS, GC-MS for the estimation Metoprolol succinate and Isosorbide mononitrate alone or in combination with other drugs. Analytical method development is the important part Quality assurance and Quality control for IPQC testing of various drug substances and drug product. So this study will helpful for researcher for the development of analytical method for estimation of New Drug substances.

1. INTRODUCTION

Metoprolol Succinate is {butanedioic acid; 1-[4-(2-methoxyethyl) phenoxy]-3-(propan 2-yl amino) propan-2- ol}. It has a molecular weight of 652.8 g/mol and the chemical formula $CH_{56}N_2O_{10}$. It is a white, crystalline powder **[2]**. Metoprolol succinate is an antihypertensive agent (β_1-Adrenergic blocker). Adrenergic β-antagonists are used for treatment of hypertension, cardiac arrhythmias, angina pectoris, glaucoma, migraine headaches and anxiety **[5]**.

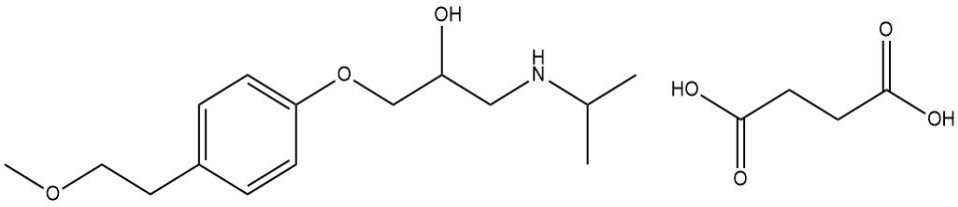

Figure 1: Metoprolol succinate

Isosorbide mononitrate is the 8-nitrooxy-2,6-sdioxabicyclo[3.3.0]octan-4-ol. Undiluted isosorbide mono nitrate has the chemical formula $C_6H_9NO_6$ and a molecular weight of 191.139 g/mol. It is a white, crystalline powder **[4]**. Isosorbide mononitrate is a nitrate- class drug used for prevention of angina pectoris **[3]**. Isosorbide mononitrate can directly vasodilate the coronary arteries and lower the stress on the heart by dilating the veins and arteries **[1]**.

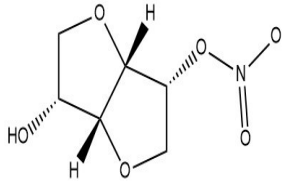

Figure 2: Isosorbide mononitrate

1.1 Drug profile

Table 1: Drug profile of isosorbide mononitrate and metoprolol succinate [1-2]

Sr.no	Parameter	Isosorbide mononitrate	Metoprolol succinate
1	IUPAC Name	8-nitrooxy-2,6 dioxabicyclo [3.3.0]octan-4-ol	1-[4-(2methoxyethyl) phenoxy]-3-(propan-2-ylamino) propan-2-ol
2	State	Solid	Solid
3	Category	Antianginal	Antihypertensive
4	Molecular formula	C6H9NO6	C34H56N2O10
5	Molecular weight	191.139 g/mol	652.8 g/mol
6	PKa	13.34	9.67 -14.09
7	Melting point	62.5 to 63 ˚C	136 to 138 ˚C
8	Log P	-0.15	1.76
9	Solubility	Freely soluble in water, in acetone, in ethanol (96 per cent) and in methylene chloride.	Freely soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane and 2-propanol

2. PHARMACOLOGY

Isosorbide mononitrate is an antianginal agent and vasodilator that relaxes vascular smooth muscle to prevent and manage angina pectoris **[4]**. Nitric oxide, the active metabolite, mediates the pharmacological activity. Nitric oxide relaxes veins and lowers the central venous pressure in both arteries and veins, but it mostly affects veins **[6]**.

2.1 Mechanism of action [4]

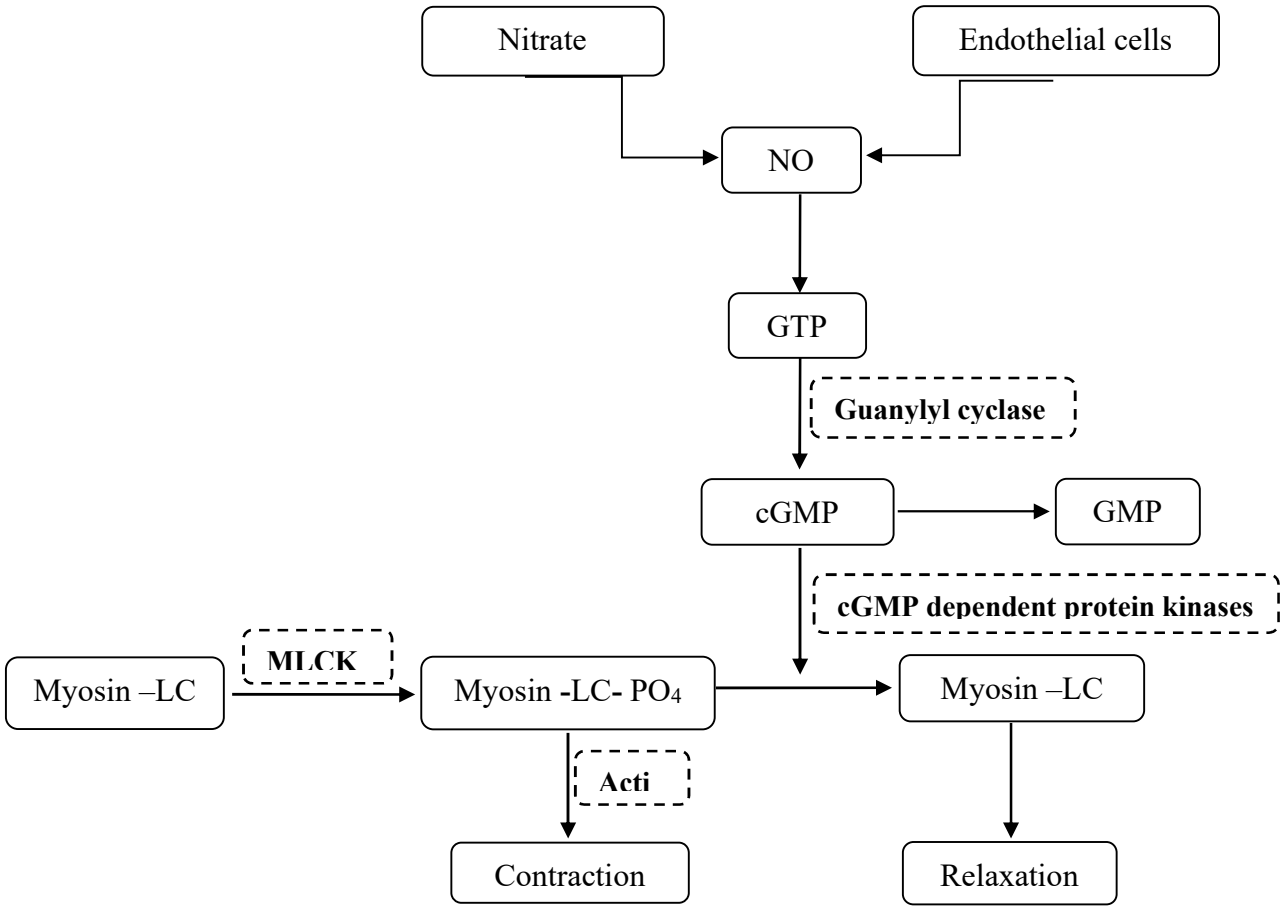

Figure 3: Mechanism of action of nitrates

Metoprolol succinate's general pharmacological principles include:

Metoprolol succinate has β_1 selective antagonist. It has a mild lipophilic character. In the absence of intrinsic sympathomimetic action reduces cardiac output, contractility, and heart rate, which lowers blood pressure **[6-7]**.

2.2 Mechanism of action [6]

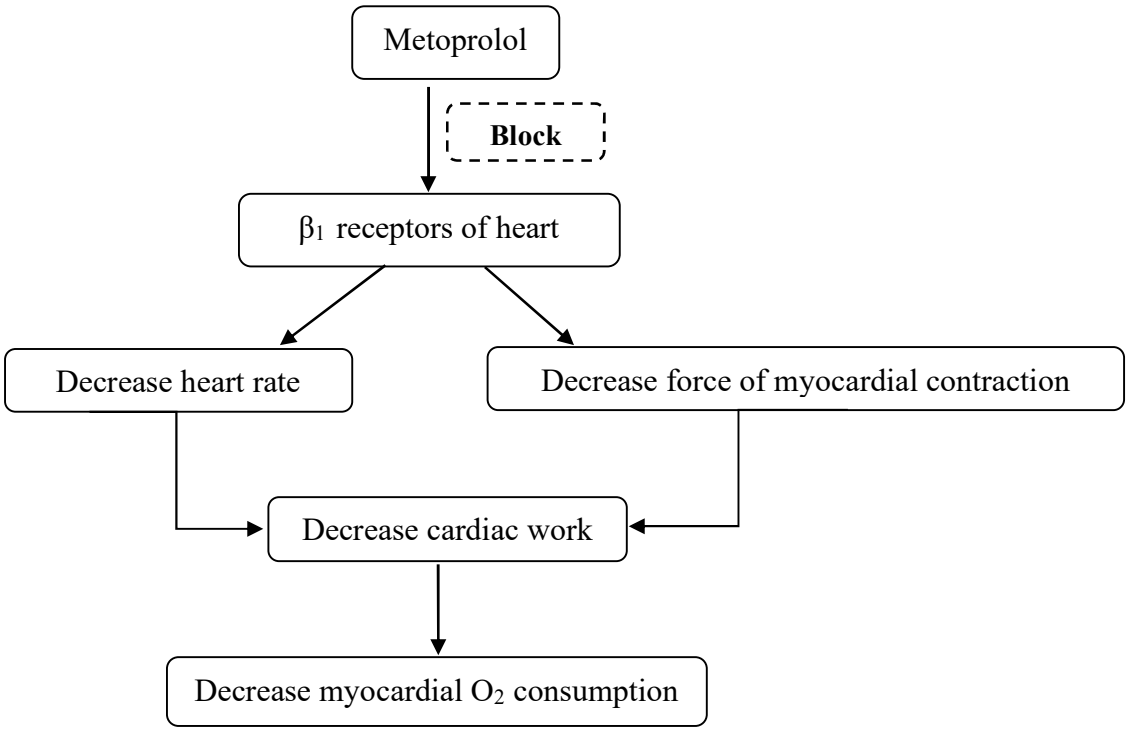

Figure 4: Mechanism of action of β- blocker

3. PHARMACOKINETICS

Metoprolol is primarily metabolised by CYP2D6 and is a racemic combination of the R- and S- enantiomers. It demonstrates stereo-selective metabolism when taken orally and is reliant on the oxidation phenotype **[7]**. The majority of elimination occurs during biotransformation in the liver, and the plasma half-life is between 3 and 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine **[8]**.

Isosorbide mononitrate has a volume of distribution of 0.62 liter/kg, a half-life of about 5 hours, and a systemic clearance of 115 ml/min. Only 1-2% of an orally administered dose is excreted unchanged in the urine, with the remainder being eliminated as inactive metabolites. Following both single and multiple doses, isosorbide mononitrate exhibits dose-linear kinetics **[4]**.

3.1 Marketed formulation

Table 2: Marketed composition, as reported

Sr. no.	Marketed formulation	Manufacturer	Isosorbide mononitrate	Metoprolol succinate
1	MET XL NL 3O MG (Tablet)	Ajanta pharma ltd.	5 mg	25 mg
2	STARPRESS MN 30MG (Capsule)	Lupin ltd.	5 mg	25

4. RP-HPLC METHOD DEVELOPMENT FOR METOPROLOL SUCCINATE AND ISOSORBIDE MONO NITRATE

RP-HPLC may be a particular form of chromatography used in organic chemistry and analysis To separate, recognise, and measure the active chemicals from the mixture of compounds. RP- HPLC is the type of partition chromatography and it is most frequently utilised in the pharmaceutical industry **[11]**. The principle is the chromatographic column is pressurised and pushed while the liquid mobile phase flows alongside the sample injected at the top of the porous stationary phase. Based on changes in the rates of migration across the column resulting from varied solution partitioning between the stationary phase and mobile phase and flow rate of the mobile phase, the sample is separated **[12]**. This article examines the chromatographic analysis of anti-anginal medicines using RP-HPLC method. The method validation according to ICH Q2R1 guidelines **[10]**.

5. LITERATURE REVIEW

Table 3: Methods for evaluating isosorbide mononitrate and metoprolol succinate that have been reported [13-19]

Sr. No	Author	Method	Method Description	Linearity
1	Nidhi s patel *et al.* (2018)	RP-HPLC method for aspirin and isosorbide mononitrate	Wave length :215 nm Mobile phase : phosphate buffer (ph:4): methanol 30:70 (v/v) Flow rate:1ml/min	15-52.5 µg/ml aspirin and 6-21µg/ml isosorbide mononitrate
2	Yogeshwari s. Bhangale *Et al.* (2012)	HPTLC method for isosorbide mono nitrate and metoprolol succinate	Stationary phase:silica gel 60 f_{254}tlc plate Mobile phase : methanol: ethyl acetate:triethylamine (6: 4: 0.1, v/v/v) Wave length :215 nm	1000-7000 m.s(ng / band) 3000-9000 ismn (ng / band)
3	Gulam abbas *et al.* (2019)	HPLC method for propranolol hcl & isosorbide mononitrate	Column :r-hs c-18, 5 µm Mobile phase : methanol:acetonitrile: phosphate buffer (45:10:45) Flow rate:1ml/min Wave length :265 nm	0.9997 for propanolol hcl, 0.9998 for isosorbide mononitrate
4	Ning li*et al.* (2014)	HPLC method for diltiazem hcl, metoprolol Tartrate and isosorbide mononitrate	Column:pinnacle II cyano mobile phase : buffer solution/1-propanol (90/10, v/v) Flow rate:0.8ml/min Wave length :230 nm	0.9965 for ismn, 0.9990 for me, 0.9950 For di
5	Agbaba *et al.* (2006)	HPLC method for isosorbide 5-mononitrate and impurities of Inorganic nitrates	Column : (250 x 4 mm) was packed with 5 µm lichrosorb rp 18 Mobile phase: methanol-water *(30* : 70) Wave length :230 nm Flow rate:1ml/min	0.998 inorganic nitrates, 0.999 for 5 isosorbide mononitrate
6	Rajan k. Verma *et al.* (2002)	HPLC method forisosorbide mononitrate in bulk material	Column:c18 spherisorb (waters, usa), 4.6×250 Mm and 5 m particle size Mobile phase: isocratic elution, water-methanol (80:20,v/v) Flow rate:1ml/min	0.99 isosorbide mononitrate

			Wave length :220 nm	
7	**Vaijanath g. Dongre *et al*. (2007)**	**HPLC method for metoprolol succinate and amlodipine besylate**	**Column : hypersil bds cyano (250 mm × 4.6 mm, 5 µm) Mobile phase : consisting of Buffer (aqueous triethylamine ph 3) and acetonitrile 85:15 (v/v) Flow rate:1ml/min Wave length : 254 nm**	**42–98 g/ml ab And 300–700 g/ml ms**
8	**Raval kashyap *et al*. (2013)**	**HPLC method for chlorthalidon and metoprolol succinate**	**Column : hypersil bds cyano (250 mm × 4.6 mm, 5 µm) Mobile phase : buffer ph 4.5: methanol : acetonitrile (50:25:25) Wave length : 223nm. Flow rate : 1ml/min**	**Chlorthalidon 5-15 µg/ml & metoprolol succinate 20-60 µg/ml**
9	**Rajendra kakde*et al* (2009)**	**HPTLC method for metoprolol succinate and amlodipine besylate**	**Stationary phase : 10 cm × 10 cm aluminum Foil hptlc plates coated with 0.2 mm layers of silica gel 60 f254 Mobile phase: Wave length : 265 nm**	**180 -280 µg ml–1 metoprolol succinate and 18 - 28 µg ml–1 amlodipine Besylate**
10	**Dhwani desai *et al* (2016)**	**HPTLC method for cilnidipine and metoprolol succinate**	**Stationary phase : silica gel g60 f254 Wave length : 231nm Mobile phase : toluene: chloroform: methanol: glacial acetic acid (45: 25: 25: 5 v/v/v/v)**	**100-500 ng/spot clindipine& 500-2500 ng/spot metoprolol succinate**
11	**Patil v.p. *Et al*. (2012)**	**HPTLC method for hydrochlorthiazide and metoprolol succinate**	**Stationary phase: silica gel g60 f254 Wave length : 227 nm Mobile phase : chloroform, methanol, ethyl acetate and formic acid (7.5:2.0:0.5:0.01, v:v:v:v)**	**1000-4000 ng/spot Metoprolol succinate & 200-700 ng/spot hydrochlorthaizide**
12	**Surendra agrawal *et al*. (2017)**	**HPTLC method for trimetazidine hydrochloride and metoprolol succinate**	**Stationary phase : silica gel g60 f254 Mobile phase : n-butanol :water: methanol: ammonia (8.5:0.1:0.1: 0.85, v/v) Wave length : 213nm**	**500-2500 ng band-1 trimetazidine hydrochloride and 500-2500 ng band-1 m.s.**
13	**Mitesh d. Phale *et al*. (2010)**	**Stability indicating HPLC for stress degradation method for metoprolol succinate**	**Column : altima c18 Mobile phase : phase:sodium dihydrogen phosphate buffer–acetonitrile (70 + 30) Wave length : 274nm Flow rate : 1 ml/min**	**0.75–100 mg/ml for metoprolol succinate**
14	**Sagar suman panda *et al*. (2020)**	**RP- HPLC method for metoprolol succinate, telmisartan, and cilnidipine**	**Column : c-18 column (250×4.6 mm i.d., 5 µm) Mobile phase: 0.01 m kh2po4 buffer of ph 3.0 (70:30, %v/v) Wave length : 240 nm Flow rate : 1 ml/min**	**20 µg/ml of metoprolol succinate, 16 µg/ml of telmisartan, and 4 µg/ml of clindipine**
15	**Amlan kanti sarkar *et al* (2008)**	**LC-MS method for metoprolol succinate and amlodipine Besylate**	**Column : c-18 column (33 ×4.6 mm i.d., 5 µm) Mobile phase:methanol–water containing 0.5% formic acid (8:2, v/v). Wave length : 227nm Flow rate : 1 ml/min**	**1–100 ng/ml for metoprolol succinate & 1–15 ng/ml amlodipine Besylate**
16	**Prajakta s. Nawale *et al*. (2012)**	**NORMAL AND REVERSED-PHASE HPTLC methods for telmisartan and**	**Stationary phase : aluminium plates precoated with silica gel 60f254 Mobile phase:propanol : methanol :**	**800–3200 ng *per* band telmisartan and 1600–6400 ng *per* band metoprolol succinate**

		Metoprolol succinate	**triethylamine (8 : 1 : 1 : 0.5 v/v) Wave lengt : 242nm.**	
17	**Singh brijesh *et al* (2009)**	**RP-HPLC method for metoprolol succinate and Hydrochlorothiazide**	**Column : c-18 column (lichrospher® Merck, 250×4 mm, 5µm particle size) Mobile phase:phase:50mm di-sodium hydrogen Phosphate:methanol:acetonitrile in a ratio of 525:225:250.wave length : 222 nm Flow rate : 1 ml/min**	**2 to 32 µg/ml for metoprolol succinate and hydrochlorthiazide**
18	**Nirmal m. Thakker *et al.* (2012)**	**Stability indicating RP-HPLC method for olmesartan medoxomil and Metoprolol succinate**	**Column : ymc pack cn (250×4.6mm5.0µm) Mobile phase:0.05% trifloro acetic acid & acetonitrile (70:30)v/v. Wave length : 220 nm Flow rate : 1 ml/min**	**5 -35 µg/ml for metoprolol succinate and olmesartan medoxomil**
19	**Courtney a. Cruse *et al.* (2020)**	**GC/ VUV method spectroscopy method for issorbide mononitrate**	**Flow rate :3.2 ml/min (gc) Wave length: 185 -225 nm (uv)**	**-**
20	**Anjaly pillai *Et al.* (2020)**	**UV –spectroscopy method for isosorbide mononitrate**	**Wave length :540 nm**	**5 – 60 nm. µg ml-1**
21	**Mayur modi *et al.* (2012)**	**UV –spectrophotometric method for metoprolol succinate and telmisartan**	**Wavelengths:230.2 nm metoprolol succinate) and 237 nm telmisartan**	**0.9995 Metoprolol succinate 0.9991 Telmisartan**
22	**Gajanan shinde *et al.* (2022)**	**Stability indicating UHPLC method for olmesartan medoximil and metoprolol succinate**	**Column: shimpack gist-c18 (100mm x 2.1mm, 2 micron) Mobile phase:0.1% orthophosphoric acid in water and mobile phase-b was acetonitrile Wave length : 225 nm Flow rate: 0.4 ml/min**	**-**
23	**S. B. bari *et al.* (2013)**	**Stability indicating of RP-HPLC Method for s(-)metoprolol succinate & clopidogrel bisulfate**	**Column : hypersil bds c8 (250mm x 4.6mm, 5µm) Mobile phase:phase:methanol: acetonitrile: buffer (15:40:45) v/v Wave length : 220 nm Flow rate : 1.5 ml/min**	**50 & 150 µg/ ml metoprolol succinate & clopidogrel bisulfate**

6. CONCLUSION

Isosorbide mononitrate and metoprolol succinate combination of two drug which are administered for the treatment of angina pectoris and heart failure. This review indicates that the approaches for estimating isosorbide mononitrate and metoprolol succinate that were taken into consideration were spectroscopic and chromatographic. For both single and combination procedures, different spectroscopic and chromatographic techniques are found. Methods for evaluating isosorbide mononitrate and metoprolol succinate that have been reported. Also it was discovered that most chromatographic procedures used mobile phases that included phosphate buffer, methanol, and acetonitrile to provide greater resolution. To get a good

resolution time for the chromatographic method, flow rate is typically observed in the range of 1.0 to 1.5 ml/min. Methanol and water are the most frequently used solvents for most spectroscopic techniques. All of these techniques are touted as being accurate, precise, cost-effective, exact, and repeatable.

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