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Research Article

Method Development and Validation of Metoprolol Succinate by RP-HPLC Method

Murugesan S*, Senthil Kumar S. K., Rajasri V, Rajeshkumar D, Reshma S, Rohini S, Sahana P

Arunai College of Pharmacy, Tiruvannamalai, India

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ABSTRACT

A simple, precise and accurate RP-HPLC method was developed and validated for the estimation of Metoprolol Succinate in pharmaceutical dosage form. Chromatographic separation was achieved on a column C18 (250 mm x 4.6 mm,5µm) using methanol and 0.1% v/v triethylamine in the ratio of (70:30) at a flow rate of 1.0µl , detection wavelength of 234nm and injection volume of 10 micro liter. The drug showed a retention time of 6.8 minutes and good linearity over the concentration range of 0.5, 0.75, 1, 1.25 and 1.5µg/ml with a regression coefficient of 0.999. Percentage recovery was 98-100% and percentage standard deviation was below less than 2%. LOD and LOQ indicated adequate sensitivity. The method complies with ICH guidelines and suitable for routine quality control analysis.

INTRODUCTION

Metoprolol succinate is a selective β-adrenergic receptor blocker widely used in the management of various cardiovascular disorders. It is primarily indicated for the treatment of hypertension, angina pectoris, heart failure and for the prevention of myocardial infraction. By selectively inhibiting β1 receptors in the heart, metoprolol reduces heart rate, myocardial contractility and cardiac output thereby reducing blood pressure and decreasing the oxygen demand of the heart. Metoprolol succinate is well absorbed after oral administration and undergoes hepatic metabolism, mainly by cytochrome P450 enzyme. This drug is commonly prescribed in long term cardiovascular therapy.

DRUG PROFILE:

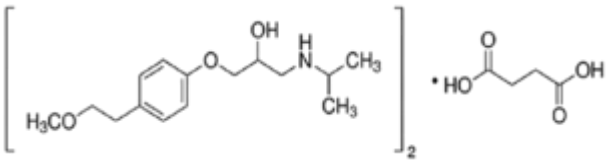

Figure.no:1 Chemical structure of Metoprolol succinate

***Corresponding Author:** Murugesan S
Address: *Arunai College of Pharmacy, Tiruvannamalai, India*
Email : murugesh.analyst@gmail.com

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IUPAC Name: [4-(2-methoxy ethyl) phenoxy]-3-[1-methyl ethyl amino]-2-propane butanedioate.

Molecular formula: C34H56N2O10

Molecular weight: 652.82g/mol

Solubility: Methanol and Purified water

MECHANISM OF ACTION:

Metoprolol succinate is a cardio selective, β1-adrengeric receptor blocker that lowers heart rate, blood pressure and cardiac workload by competitively inhibiting catecholamine binding in the heart. As a long-acting extended-release formulation, it provides sustained 24-hours antagonism, reducing renin secretion and reducing oxygen demand making it effective for the hyper tension, angina and heart failure.

RP-HPLC METHOD

Chromatographic Condition

The isocratic mobile phase consisting of methanol and 0.1%Triethylamine in the ratio of (70:30), flowing through the column and constant flow rate of 1.0ml/min. The mobile phase was filtered through 0.45µm membrane filter and was degassed before used 30 mins. C18 Column (250 mm x 4.6 mm,5µ) as used as a stationary phase.

MATERIALS AND METHODS:

Drug Sample and Formulation used

Metoprolol Succinate bulk drug were Gifted By Madras Pharma, Chennai.

Brand Name	Labeled Name	Source
ACLOMET – XL	25mg	M.R healthcare Pvt, Ltd

Chemicals and Solvents used

All the Chemicals Used were of analytical Grade as well as HPLC grade procured from Great scientific Laboratory and Sumison Laboratory from Tiruvannamalai and Chennai.

The Chemical used for the Study were,

- Methanol (HPLC GRADE)
- Milli-Q Water (HPLC WATER)
- Triethylamine Buffer (Analytical grade)

Apparatus and Glassware's

- 100ml volumetric flask
- 10ml volumetric flask
- Beakers
- Glass rod, etc.

Instruments

Instruments employed for the study were,

A. SHIMADZU AUX – 220 DIGITAL BALANCE
B. SIMADZU prominence HPLC iLC2030 plus
C. Sonica Ultra Sonic Cleaner-Model 2200 plus
D. ELICO PH Meter (Model LI -120)
E. Melting Point Apparatus.

METHOD DEVELOPMENT:

Prepartion of Mobile Phase

1. **For Trail Chromatogram of Metoprolol Succinate:**

Methanol and 0.1 % v/v of Triethylamine in milli-q water(60:40) was taken into a 1000 ml volumetric flask and mixed properly. Then, this mobile phase is sonicated for 15 min and used as the mobile phase by isocratic elution method.

2. For Optimized Chromatogram of Metoprolol Succinate:

Methanol and 0.1 % v/v of Triethylamine in milli-q water (70:30) was taken into a 1000 ml volumetric flask and mixed properly. Then, this mobile phase is sonicated for 15 min and used as the mobile phase by isocratic elution method.

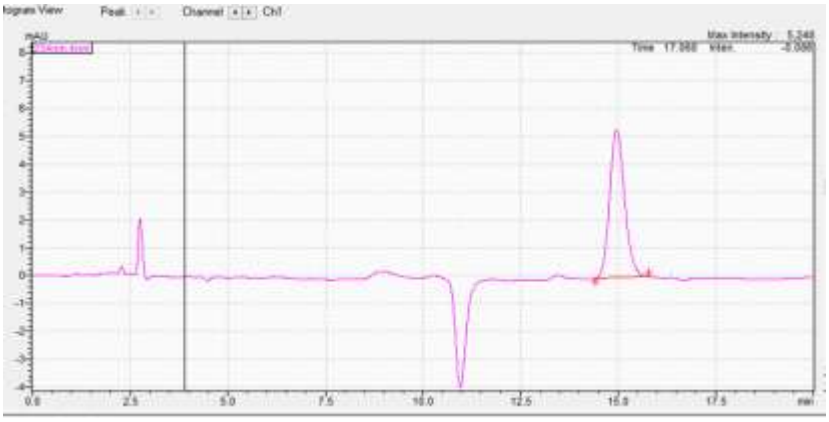
Preparation of Standard Solution

Accurately weighed 25 mg of metoprolol succinate and transferred into 100 ml volumetric flask and dissolved with (methanol and 0.1 % v/v of Triethylamine Solution (70:30)) are added and to adjusted the volume up to the mark of volumetric Flask. From this 1ml was taken and added into 10ml volumetric flask with mobile phase are added and to adjusted the volume upto the mark of the volumetric flask.

Initial Separation Condition: Trail 1

For Method Development of Metoprolol Succinate Using to conducted the First trial injections were performed with mobile phase of Methanol and 0.1 % v/v of Triethylamine in milli-q water (60:40) .

Stationary Phase	C18 Column (250 mm x 4.6 mm,5µ)
Mobile Phase (v/v)	60:40 v/v
Injection Volume (ml/min)	10 micro litre
Flow Rate (ml/min)	1 ml/min
Column Temperature	25 °C
Wavelength (nm)	234nm



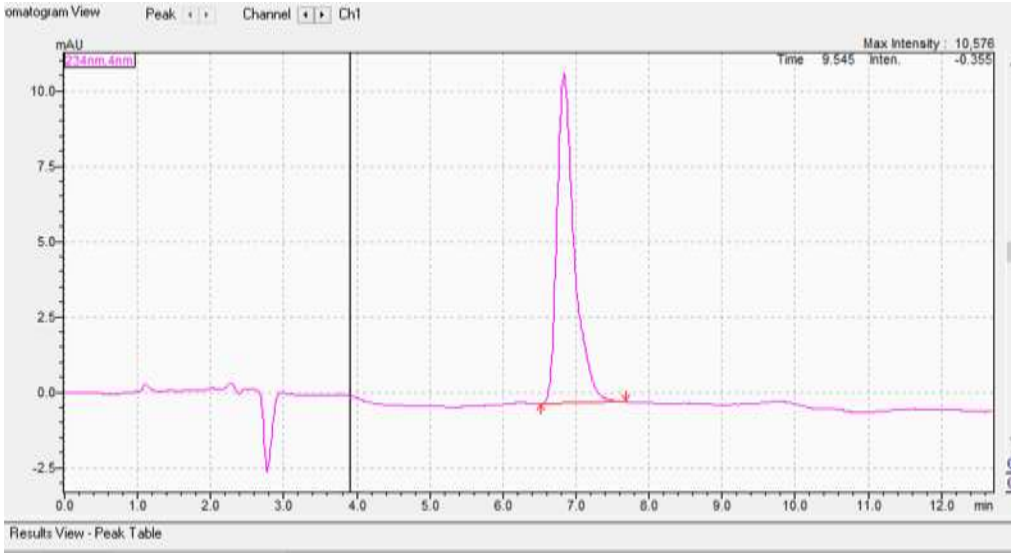
Chromatogram Of Trail 1

Sr. No	Retention Time	Area	Height	Theoretical Plate	Tailing Factor
1	14.966	141047	5316	7491	1.177

Metoprolol Succinate – Optimized Chromatogram:

We get Optimized Chromatogram with 70:30 ratios of mobile phases of Methanol and 0.1 % v/v of Triethylamine in milli-q water to identify the best chromatographic conditions.

Chromatographic Condition	Description
Stationary Phase	C18 Column (250 mm x 4.6 mm,5µ)
Mobile Phase(v/v)	70:30 v/v
Injection Volume (ml/min)	10 micro liter
Flow Rate (ml/min)	1 ml/min
Column Temperature	25 °C
Wavelength(nm)	234nm



Optimized Chromatogram

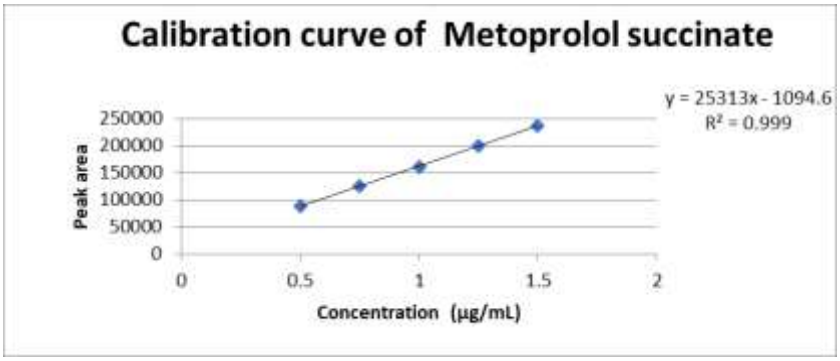
Sr. No	Retention Time	Area	Height	Theoretical Plate	Tailing Factor
1	6.836	180226	10944	4866	1.535

VALIDATAION PARAMETERS:

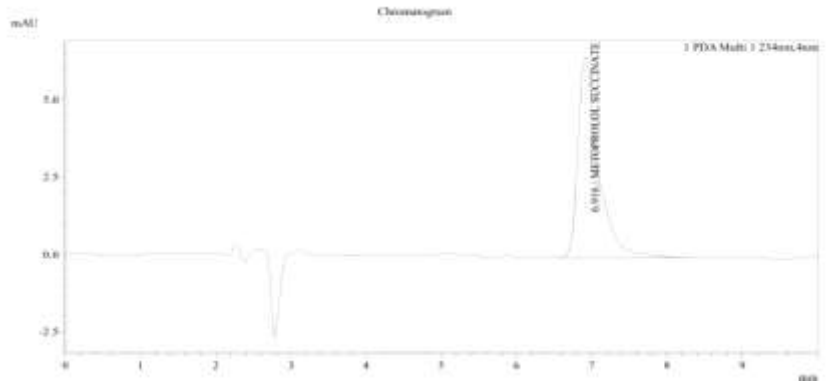
A. Linearity

Linearity studies were carried out in the concentration range of 0.5µg/ml, 0.75µg/ml, 1µg/ml, 1.25µg/ml and 1.5µg/ml. The sample solution was made from the stock solution the readings were obtained by measuring the absorbance at 234 nm and presented in table and linearity curve.

Sr. No	Concentration (Mg/Ml)	Peak Area	Correlation Coefficient	Lod	Loq	Slope	Intercept
1.	0.5	88270	0.999	4.55519	0.00013	25313	1094.6
2.	0.75	124945					
3.	1	159642					
4.	1.25	199542					
5.	1.5	236187					

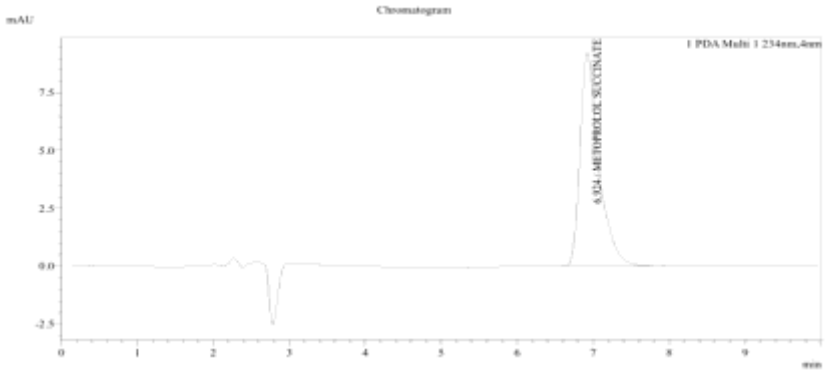


Linearity Chromatogram in 50%



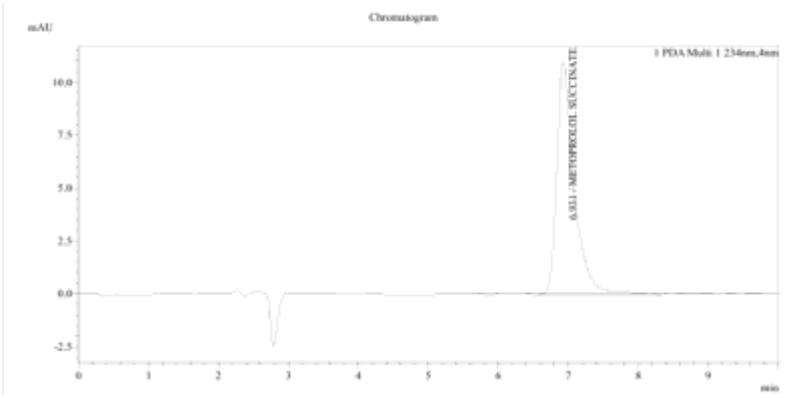
Sr. No	Retention Time	Area	Theoretical Plate	Tailing Factor
1	6.916	118696	4543	1.701

Linearity Chromatogram in 75%



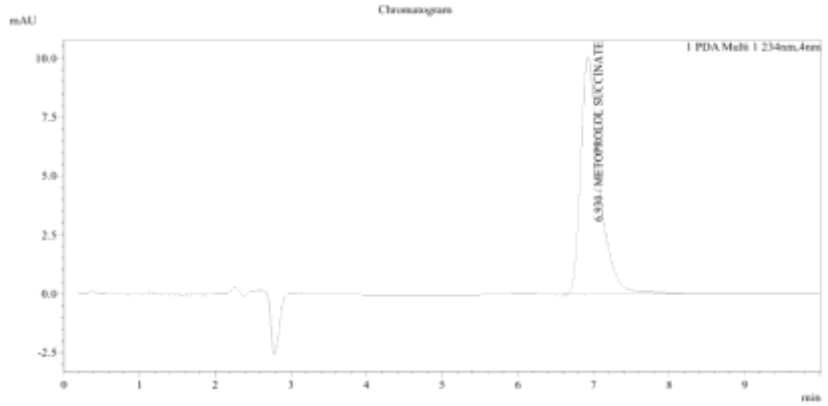
Sr. No	Retention Time	Area	Theoretical Plate	Tailing Factor
1	6.924	156838	4676	1.542

Linearity Chromatogram in 100%



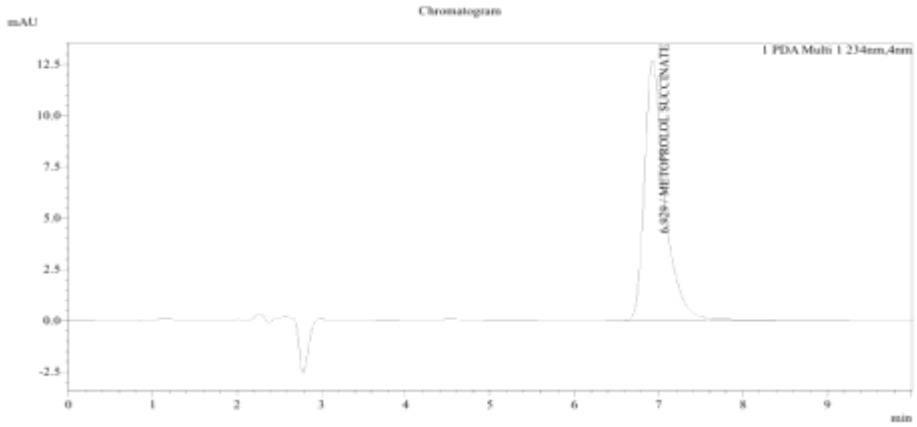
SR. NO	RETENTION TIME	AREA	THERIOTICAL PLATE	TAILING FACTOR
1	6.931	189540	4659	1.541

Linearity Chromatogram in 125%



Sr. No	Retention Time	Area	Theoretical Plate	Tailing Factor
1	6.930	170930	4724	1.504

Linearity Chromatogram in 150%



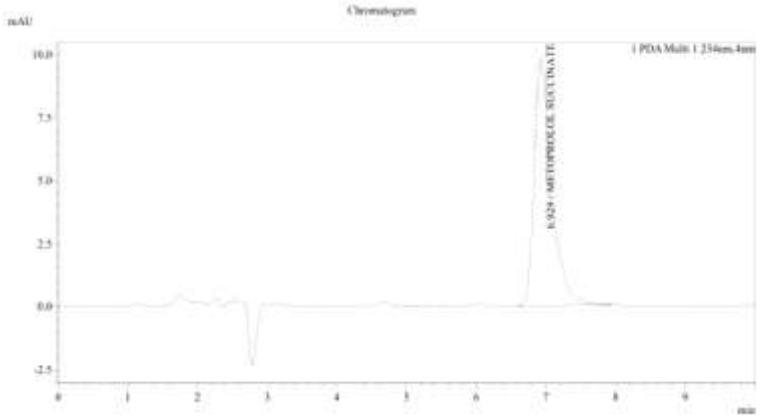
Sr. No	Retention Time	Area	Theoretical Plate	Tailing Factor
1	6.929	213622	4752	1.500

B. Accuracy

Accuracy of the method was evaluated by the standard addition technique at three concentration levels of 80%, 100%, and 120%. Known amount of standard drug solution were added to the pre - analyzed sample to be applied final concentration 20µg/ml, 25µg/ml and 30µg/ml. The solution were diluted with mobile phase composed of Methanol and 0.1%Triethylamine in Water. In the ratio of 70:30 and analyzed under optimized condition.

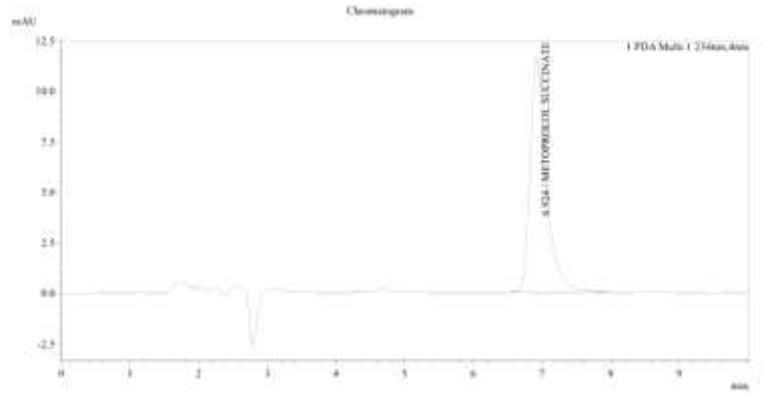
Sr. No	% Concentration	Average Area	Amount Added (mg)	% Recovery	Mean Recovery	SD	% RSD
1.	80%	150665	20	101.49	101.29	263.21	0.1747
2.	100%	187760	25	101.89		131.87	0.0702
3.	120%	221829	30	100.49		139.17	0.0627

Accuracy Chromatogram in 80%



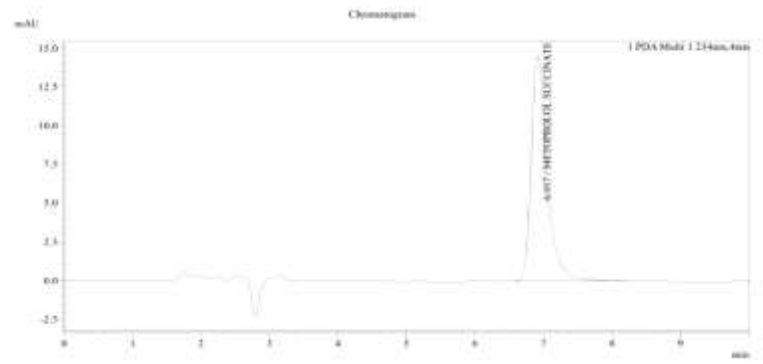
Retention Time	Injection	Area	Theoretical plate	Tailing factor
6.929	1	150665	4703	1.558

Accuracy Chromatogram in 100%



Retention Time	Injection	Area	Theoretical plate	Tailing factor
6.924	2	187760	4955	1.477

Accuracy Chromatogram in 120%

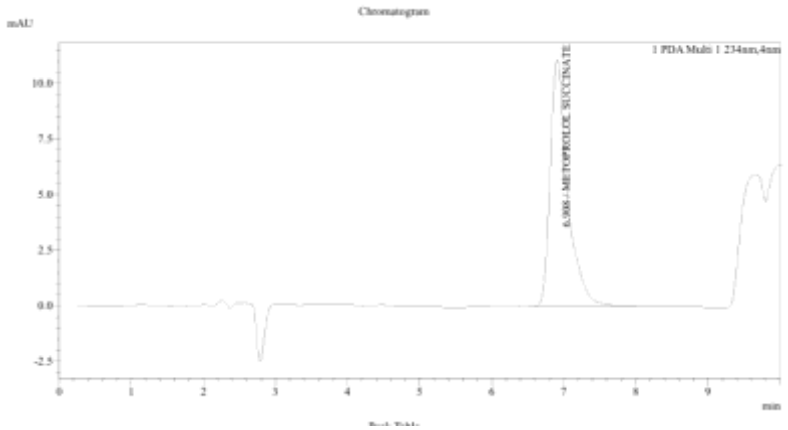


Retention Time	Injection	Area	Theoretical plate	Tailing factor
6.917	3	221829	4988	1.443

The %RSD value less than 2% was found.

C. Precision

1ml of stock solution was pipetted out into 10ml volumetric flask diluted upto mobile phase with the mark. Mixed well and filtered through 0.45µm filter. Therefore, the concentration of the resultant solution was 25µg/ml. The solution was taken and injected for five times within the same day and the chromatogram was recorded. The peak area was measured to calculate the % Relative standard deviation value.



Chromatogram of Precision

Table: Interday Precision

Sr. No	Peak Area	Average	SD	%RSD
1.	186229	186557.3	249.54	0.1337
2.	186347			
3.	186542			
4.	186721			
5.	186920			
6.	186585			

Table: Intraday Precision

Sr. No	Peak Area	Average	SD	%RSD
1.	189229	186557.3	249.54	0.1337
2.	189347			
3.	189542			
4.	189721			
5.	189920			
6.	189585			

The %RSD Value less Than 2% was Found. So the method is highly precise and reproducible.

D. Robustness:

The robustness of the method was determined by introducing small changes in HPLC parameters such as changing in wavelength.

Sr. No	Wavelength (Nm)	Peak Area	Average Area	SD	%RSD
1	232	188371	186017.66	542.844	0.2873
2	234	180226			
3	236	189456			

E. RUGGEDNESS:

The ruggedness of the proposed method was evaluated by applying the developed procedure assay of 25µg/ml of Metoprolol Succinate using the same instrument by two different analyst under the same optimized conditions at different days.

Sr. No	Analyte	Concentration (µg/ml)	Peak Area	SD	%RSD
1.	ANALYTE-1	25	188012	466.750	0.24765
		25	188452		
		25	188945		
2.	ANALYTE-2	25	190390	153.206	0.08047
		25	190344		
		25	190232		

SUMMARY

Summary of Method Development:

Method Development Protocols Analytical method development is a systematic process used to establish a reliable, accurate, and reproducible procedure for the identification, quantification, and analysis of pharmaceutical substances. The primary objective is to develop a method that is specific, sensitive, precise, and robust, suitable for routine quality control and regulatory compliance. The protocol begins with a thorough understanding of the physicochemical properties of the drug substance, including solubility, pKa, polarity, and stability. Based on these properties, HPLC analytical For chromatographic methods, initial conditions such as stationary phase, mobile phase composition, pH, flow rate, and detection wavelength are optimized to achieve good resolution, symmetrical peaks, and acceptable retention time. Subsequently, method optimization is carried out by systematic variation of experimental parameters to enhance performance characteristics.

Summary of Validation Parameters:

Once optimized, the developed method is subjected to method validation in accordance with ICH guidelines (Q2(R1)), ensuring suitability for its intended purpose. Validation parameters include specificity, linearity, accuracy, precision, robustness, and ruggedness. Finally, system suitability testing and documentation are performed to confirm consistent performance. A well-developed and validated analytical method ensures reliable drug analysis, supports stability studies, and plays a crucial role in maintaining pharmaceutical product quality and regulatory acceptance.

Sr. No	Validation Parameter	Objective	Procedure Summary	Acceptance Criteria	Results
1	Linearity	Proportional response	5–6 concentration levels	$r^2 \geq 0.998$	0.999
2	Accuracy	Closeness to true value	Recovery at 80, 100, 120%	98–102%	101.29

3	Intraday Precision	Reproducibility	Different days/analysts	%RSD ≤ 2	0.1152
4	Interday precision	Reproducibility	Within a days/analysts	%RSD ≤ 2	0.1337
5	Robustness	Method reliability	Small deliberate variations	No significant change	No significant change
6	Ruggedness	Inter-lab precision	Different instruments/analysts	%RSD ≤ 2	Within the limit

CONCLUSION:

In this project, an RP-HPLC method was developed and validated for the estimation of metoprolol succinate in bulk and tablet dosage form. The method was found to be simple, fast, accurate and precise. All validation parameters such as linearity, accuracy, precision and robustness were within acceptable limits. Therefore, this RP-HPLC method is suitable for routine quality control analysis of metoprolol succinate in pharmaceutical formulation.

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