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PREFORMULATION AND EVALUATION OF EXTENDED RELEASE TABLET OF METOPROLOL SUCCINATE

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ABSTRACT

The abstract of this study was to develop and evaluate an extended release (ER) tablet formulation of Metoprolol Succinate, a selective beta-1 adrenergic receptor blocker widely used in the treatment of hypertension, angina pectoris, and heart failure. Preformulation studies including solubility analysis, compatibility studies (using FTIR and DSC), and flow properties of drug and excipients were conducted to ensure the suitability of components for formulation. Extended release tablets were prepared by direct compression and wet granulation techniques using hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) as matrix-forming agents. The tablets were evaluated for physical parameters such as hardness, friability, thickness, drug content, and in vitro drug release profiles. The optimized formulation demonstrated consistent extended release over a 24-hour period, complying with USP dissolution specifications. Stability studies were also carried out as per ICH guidelines. The results suggest that the developed ER tablet of Metoprolol Succinate offers a promising approach for maintaining steady plasma drug concentration, improving patient compliance and therapeutic efficacy.

KEYWORDS

Primary Keywords

- *Metoprolol Succinate*
- *Extended Release Tablet*
- *Preformulation Studies*
- *Drug Release Kinetics*
- *Sustained Release*
- *Controlled Drug Delivery*
- *Matrix Tablets*
- *Formulation Development*
- *In vitro Evaluation*
- *Pharmacokinetics*

Secondary Keywords

- *Drug-Excipient Compatibility*
- *FTIR Analysis*
- *Differential Scanning Calorimetry (DSC)*
- *Powder Flow Properties*
- *Dissolution Studies*
- *Stability Studies*
- *HPMC (Hydroxypropyl Methylcellulose)*
- *Compression Properties*
- *Bioavailability*
- *USP Dissolution Apparatus*

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2.INTRODUCTION

The development of extended-release (ER) drug delivery systems is a pivotal advancement in pharmaceutical formulation, aimed at improving therapeutic outcomes, patient compliance, and reducing dosing frequency. **Metoprolol succinate**, a cardioselective β1-adrenergic receptor blocker, is widely prescribed for the management of hypertension, angina pectoris, and heart failure. Due to its relatively short half-life (3–7 hours), frequent dosing is required with immediate-release formulations, which may lead to fluctuating plasma levels and reduced patient adherence.To overcome these limitations, an **extended-release tablet formulation of metoprolol succinate** offers the benefit of maintaining steady plasma drug concentrations over an extended period, minimizing side effects, and enhancing patient compliance.The **preformulation stage** is critical in the design of such a formulation, as it involves thorough characterization of the drug substance—such as solubility, stability, compatibility with excipients, and flow properties—laying a foundation for the rational development of the final dosage form. This study focuses on the preformulation studies, formulation development, and evaluation of an extended-release metoprolol succinate tablet using appropriate polymers and manufacturing techniques to achieve desired release kinetics.

3.MATERIALS AND METHOD

Metoprolol Succinate was received as a gift sample from Bora, Ahmadnagar, India. Polymers like Hydroxypropylmethylcellulose, Ethyl Cellulose, and Microcrystalline Cellulose were purchased from SD Fine Chemicals, Mumbai. Magnesium Stearate was obtained from Loba Chemie Ltd., Mumbai. All solvents used in the study were of analytical grade and purchased from Qualigen, Mumbai.

Method: All the ingredients were accurately weighed. Metoprolol Succinate, Microcrystalline Cellulose, and Hydroxypropylmethylcellulose were mixed thoroughly for 15 minutes. Then, Magnesium Stearate and Ethyl Cellulose were added to the mixture and blended for another 10 minutes. The final mixture was compressed into tablets weighing 200 mg each using 9 mm flat-faced punches on a single-punch tablet press (Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad).Nine different formulations of Metoprolol Succinate Extended-Release tablets were prepared. In each formulation, the amount of Metoprolol Succinate was kept constant at 25 mg. The detailed composition of each formulation is shown in Table No. 1. Post-compression evaluation of all powder blends was also carried out.

Table No 1: Formulation of Extended Release Tablets

INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Metoprolol Succinate	25	25	25	25	25	25	25	25	25
Hydroxypropyl Methylcellulose	65	70	75	80	85	90	95	100	105
Ethyl cellulose	45	45	45	45	45	45	45	45	45
Magnesium stearate	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	55	50	45	40	35	30	25	20	15
TOTAL	200	200	200	200	200	200	200	200	200

The Tablets prepared were evaluated for the following parameters:

- Hardness.
- Friability.
- Weight variation.
- Uniformity of thickness.
- Drug content uniformity.

1.Hardness test: The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Fig:Hardness test apparatus



2. Friability test: The friability of tablets was determined by using Electro lab, USP EF 2 friabilator. It is expressed in percentage (%). 20 tablet were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 100 rpm for 4 minutes. After the test, the tablets were weighed again

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(Wfinal).% Friability of tablets less than 1% is considered acceptable.



Figure: Friablity test apparatus

3. Weight variation test: The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The procedure adopted was base on Indian pharmacopeia. The following percentage deviation in weight variation is allowed



.**Figure: weight variations apparatus**

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4.Uniformity of thickness: The crown thickness of individual tablet was measured with a vernier calliper.

5. Drug content uniformity: Four tablets were weighed and crushed in to mortar. The powder equivalent to 10 mg of drug Was weighed and dissolved in 100 ml methanol; from this solution 1 ml of solution was Diluted to 10 ml with methanol. From this diluted solution 1 ml solution was taken and Diluted up to 10 ml with methanol and assayed for drug content at 274 nm.[9, 10]

6. .The tablets from all the formulation batches were subjected to in vitro Dissolution Test: In vitro-dissolution studies were performed on the Extended release tablets prepared by direct Compression method at 37□0.5°C using 6.8 phosphate buffer in USP apparatus I with the Paddle speed 100 rpm. 5 ml of filtered aliquot was withdrawn at pre- determined time Intervals and replaced with 5 ml of fresh 6.8 phosphate buffer solution maintained at the same Temperature. The samples were analyzedat274 nm using UV Spectrophotometer. The Percentage release was determined for each formulation.

7. Study of Release Kinetics: Drug release mechanisms and kinetics are the two important Characteristics of a drug delivery system in describing drug dissolution profile. To describe The kinetics of the drug release from tablet, mathematical models such as zero-order, first Order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used. The criterion for Selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

□ The zero-order kinetics (equation 1) describes the systems in which the drug release rate Is independent of its concentration.

□ The first order kinetics (equation 2) describes the systems in which the drug release rate is Concentration dependent.

□ Higuchi (equation 3) described the release of drug from an insoluble matrix as square root Of time dependent process. The Higuchi square root model also gives the drug release from a Planer surface of an insoluble heterogeneous matrix by diffusion through the intragranular Openings created by porosity of the matrix tablet.

□ The Hixson-Crowell cube root law (equation 4) describes the drug release from systems In which there is a change in the surface area and the diameter of particle present in tablet.

□ In case of Korsmeyer-Peppas model, the drug release from such devices having constant Geometry will be observed till the polymer chains rearrange to equilibrium state.

4. RESULTS AND DISCUSSION

Preformulation Studies of Pure Drug

Colour, Odor, Taste, and Appearance: The drug sample was evaluated for its colour and odor. The results are shown in TableNo-11.

Table No 4: Colour, Odour, Taste and Appearance of Metoprolol Succinate.

Sr. No.	Parameters	Drug
1	Colour	White or colorless
2	Odour	Odourless
3	Taste	Tasteless
4	Appearance	Fine powder

The above observations of colour, odour taste and appearance are as per I.P

Melting point determination: Melting point of the drug sample was determined by capillary Method by using melting point apparatus.

The preformulation studies of Metoprolol Succinate, a cardioselective β1-adrenergic blocker used in treating hypertension, angina, and heart failure, are crucial for designing effective extended-release formulations. Below is a detailed overview of its physicochemical properties:

Physicochemical Properties of Metoprolol Succinate

1Appearance: White to off-white crystalline powder.

2.Solubility:Highly soluble in water.Soluble in methanol.Slightly soluble in ethanol.Practically insoluble in chloroform and acetone.Solubility in phosphate buffer pH 6.8: Approximately 95,896 µg/mL.

3.Melting Point: Approximately 135°C, aligning with literature values.

4.Partition Coefficient (Log P): Approximately 0.61, indicating moderate lipophilicity.

5.**Bulk Density:** Approximately 0.61 g/mL.

6.Tapped Density: Approximately 0.70 g/mL.

7.Compressibility Index: Approximately 12.7%, suggesting fair compressibility.

8.Flow Properties:

Angle of repose: Approximately 33.5°, indicating poor flowability.

Carr's Index: Approximately 12.7%, reflecting moderate flowability.

Hausner's Ratio: Approximately 1.14, suggesting good flow characteristics.

9.Hygroscopicity: Metoprolol Succinate is hygroscopic, absorbing moisture from the environment, which can affect its stability and processing.

Drug-Excipient Compatibility

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Fourier Transform Infrared (FTIR) spectroscopy studies have shown no significant interaction between Metoprolol Succinate and commonly used excipients such as HPMC K4M, HPMC K15M, HPMC K100M, ethyl cellulose, colloidal anhydrous silica, microcrystalline cellulose, and sodium stearyl fumarate.

❣ Implications for Extended-Release Formulation

Solubility:of extended-release formulations, as it can facilitate consistent drug release profiles.

Compressibility: With a moderate compressibility index, the drug can be effectively processed using direct compression methods, which are cost-effective and scalable.

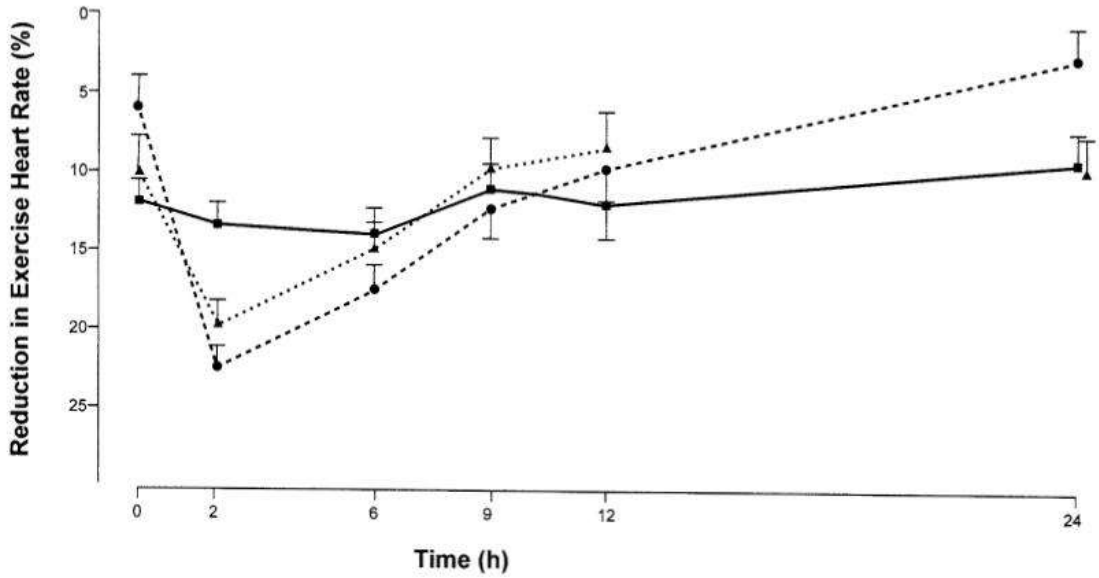
Flowability: Despite moderate flow properties, the drug's flowability can be enhanced by optimizing the formulation and processing conditions.

Hygroscopicity: The hygroscopic nature necessitates the use of moisture-resistant packaging and possibly the inclusion of desiccants to maintain stability. These preformulation characteristics are pivotal in designing Metoprolol Succinate extended-release tablets, ensuring consistent drug release and therapeutic efficacy.

5.CLINICAL TRIALS

Clinical reports published as early as the 1970s suggest-Ed that β-blocker therapy improves myocardial function inpatients with chronic heart failure.29-32 Although these stud-
Ies were not randomized and involved only small numbersOf patients, they stimulated further research into the use ofB-blockers in this patient population. During the 1980s, ad-Vances in basic research began to illustrate the role of theAdrenergic system in chronic heart failure.3

Figure 2. Mean ± SEM percentage reduction in exercise heart rate in healthy volunteers After administration of 5 days of extended-release metoprolol succinate 100 mg once daily(—■), immediate-release metoprolol 100 mg once daily (---●), or 50 mg twice daily (•••▲).Reprinted with permission.20



Although these stud-ies were not randomized and involved only small numbersof patients, they stimulated further research into the use ofβ-blockers in this patient population. During the 1980s, ad-vances in basic research began to illustrate the role of theadrenergic system in chronic heart failure.33,34 However,large-scale randomized trials were slow to develop due tothe focus of research at that time on vasodilators and ACEinhibitors and to the widely held belief that β-blockerswere contraindicated in patients with heart failure.35In the 1990s, large controlled trials evaluating β-blocker therapy in patients with heart failure were published. In 1randomized, placebo-controlled, parallel-group trial, im-mediate-release metoprolol was compared with placebo in383 patients with heart failure due to idiopathic dilated car-diomyopathy.36 Patients treated with immediate-releasemetoprolol had a significantly greater increase from base-line values in LVEF and significantly greater decreases from baseline values in pulmonary wedge pressure and heart rate than those in the placebo group. In addition, immediate-release metoprolol treatment was associated with a 34% risk reduction in the primary endpoint (death or need for heart transplantation), although this difference did not reach statistical significance ($p = 0.058$). These data stimulated further clinical research efforts and the design of large prospective mortality trials.Three randomized, double-blind, placebo-controlled trials evaluated the efficacy of ER metoprolol succinate in the treatment of patients with chronic heart failure: RESOLVD(Randomized Evaluation of Strategies for Left Ventricular Dysfunction),37 a pilot study to evaluate safety in the heartfailure population prior to MERIT-HF (Metoprolol CR/XLRandomized Intervention Trial in Congestive Heart Fail-ure),38 and MERIT-HF, the largest study to date

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evaluatingthe effect of β-blocker therapy on mortality and morbidity inpatients with chronic heart failure.5 All trials included adultswith chronic, stable, symptomatic heart failure (predomi-nantly NYHA functional class II and III) who had an LVEF≤40%. Patients were stabilized on diuretics and an ACE in-hibitor with or without digitalis prior to randomization.5,37,38

6.PILOT TRIALS

In the RESOLVD study, 768 patients wereinitially randomized to receive an angiotensinII receptor antagonist (candesartan), an ACE
inhibitor (enalapril), or a combination of the2.37 After 17 weeks, eligible patients were then randomized to receive ER metoprolol succi-nate (titrated to a maximum target dose of 200mg/d) or placebo for an additional 24 weeks.ER metoprolol succinate was associated with significantly smaller increases than placebo inleft ventricular end-diastolic (mean ± SEM +6± 61 vs. +23 ± 65 mL; $p = 0.01$) and left ven-tricular end-systolic (–2 ± 51 vs. +19 ± 55mL; $p < 0.001$) volumes after 24 weeks of therapy. In addition, the LVEF increased in themetoprolol group, but was unchanged in the placebo group($p = 0.001$).In the MERIT-HF pilot study, 61 patients were random-Ly assigned in a 2:1 ratio to receive ER metoprolol succi-Nate (titrated to a maximum target dose of 150 mg/d overAn 8-wk period) or placebo and then continued therapy forAn additional 26 weeks.38 After 26 weeks of treatment, pa-Tients who received metoprolol (mean achieved dose 99Mg) had significantly greater improvements in LLVE(metoprolol, from 27.5% to 36.3%; placebo, from 26% to27.9%; $p < 0.015$) and electrocardiographic parameters ($p< 0.05$) (i.e., reductions from baseline in episodes of non-Sustained ventricular tachycardia and ventricular couplets)Than patients who received placebo.

7.COMPARISON BETWEEN METAPROLOL AND OTHER DRUG USED IN TREATMENT OF HYPERTENSION:

◆ **1. Metoprolol (Beta-Blocker)**

Mechanism of Action:

Selective β1-adrenergic receptor blocker

Reduces heart rate, cardiac output, and renin release

Common Uses:

- Hypertension
- Angina
- Heart failure (HFrEF)
- Post-MI

Advantages:

- Good for patients with:
  - Previous myocardial infarction (MI)
  - Heart failure with reduced ejection fraction
  - Tachyarrhythmias

Side Effects:

- Bradycardia
- Fatigue
- Depression
- Erectile dysfunction
- Can mask hypoglycemia symptoms

🔻 2. ACE Inhibitors (e.g., Lisinopril, Enalapril)

Mechanism:

- Block conversion of angiotensin I to II
- Lower BP by vasodilation and reduced aldosterone secretion

Advantages:

- Renoprotective (especially in diabetics)
- Beneficial in heart failure and post-MI

Side Effects:

- Dry cough
- Hyperkalemia
- Angioedema
- Contraindicated in pregnancy

🔻 3. ARBs (e.g., Losartan, Valsartan)

Mechanism:

- Block angiotensin II receptors
- Similar effects to ACE inhibitors

Advantages:

- Same as ACE inhibitors but no cough
- Good alternative in ACEI-intolerant patients

Side Effects:

- Hyperkalemia
- Angioedema (rare)
- Contraindicated in pregnancy

🔻 4. Calcium Channel Blockers (CCBs)

- Dihydropyridines (e.g., Amlodipine)
  - Vasodilation > cardiac effect
  - Good for elderly & African-American patients
- Non-dihydropyridines (e.g., Verapamil, Diltiazem)
  - Affect heart rate and contractility

Side Effects:

- Peripheral edema
- Headache
- Bradycardia (non-dihydropyridines)

🔻 5. Thiazide Diuretics (e.g., Hydrochlorothiazide, Chlorthalidone)

Mechanism:

- Inhibit Na/Cl reabsorption in distal tubule → reduced blood volume

Advantages:

- Proven mortality benefit
- Cost-effective
- Good in older adults & African-American patients

Side Effects:

- Hypokalemia
- Hyperglycemia
- Hyperuricemia
- Hyperlipidemia

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✓ Choosing the Right Drug Depends On:

- Comorbidities (e.g., diabetes, heart failure, CKD)
- Ethnicity (CCBs & thiazides work better in Black patients)
- Age
- Side effect tolerance
- Cost & accessibility

8.CONCLUSION

The preformulation studies of metoprolol succinate confirmed its physicochemical properties, compatibility with excipients, and suitability for extended-release (ER) tablet formulation. Various ER formulations were developed using hydrophilic polymers such as HPMC and evaluated for parameters like hardness, friability, drug content, and in vitro drug release. The optimized formulation demonstrated sustained release over 24 hours, matching the desired release kinetics (often zero-order or Higuchi model), with acceptable physical properties and stability. These results suggest that metoprolol succinate can be effectively formulated into an extended-release tablet to enhance patient compliance and therapeutic efficacy.

9.EXPECTED OUTCOME

The study is expected to result in the successful formulation of a stable, effective extended-release (ER) tablet of Metoprolol Succinate that ensures controlled drug release over a 24-hour period. The optimized formulation should meet all preformulation and evaluation criteria, including acceptable physical characteristics (hardness, friability, weight variation), uniform drug content, and a sustained in vitro drug release profile consistent with pharmacopoeial standards. Additionally, the release kinetics are anticipated to follow zero-order or Higuchi model, indicating a controlled and predictable release pattern. This would enhance patient compliance, reduce dosing frequency, and improve overall therapeutic outcomes in hypertension and cardiovascular conditions.

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