



DEVELOPMENT AND OPTIMIZATION OF HYDROXYPROPYL METHYLCELLULOSE-BASED GASTRO-RETENTIVE TABLETS FOR EXTENDED RELEASE OF METOPROLOL SUCCINATE: A COMPREHENSIVE PHARMACEUTICAL INVESTIGATION

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Abstract

Background: Metoprolol succinate, a cardioselective β_1 -adrenergic receptor antagonist, exhibits suboptimal bioavailability due to its short gastric residence time and preferential absorption in the upper gastrointestinal tract. This study aimed to develop and evaluate gastro-retentive extended-release tablets of metoprolol succinate using hydroxypropyl methylcellulose (HPMC) as the primary matrix-forming polymer to enhance therapeutic efficacy and patient compliance.

Methods: Seven formulations (F1-F7) were developed using wet granulation technique with varying concentrations of HPMC (100-170 mg), sodium bicarbonate (80-150 mg), and microcrystalline cellulose as primary excipients. Comprehensive pre-formulation studies included organoleptic evaluation, melting point determination, solubility profiling, and Fourier transform infrared spectroscopy for drug-excipient compatibility assessment. Post-compression parameters including hardness, friability, weight variation, and thickness were evaluated according to pharmacopoeial standards.

Results: The optimized formulation F4, containing 170 mg HPMC and 90 mg sodium bicarbonate, demonstrated superior physical characteristics with hardness of 6.0 kg/cm², friability of 0.25%, and sustained drug release achieving 98% cumulative release over 12 hours. Pre-formulation studies confirmed excellent drug-excipient compatibility with melting point of 121-124°C and partition coefficient of 4.0, indicating favorable lipophilic characteristics for oral absorption.

Conclusion: The developed gastro-retentive tablets successfully provided controlled release of metoprolol succinate over an extended period, demonstrating potential for once-daily administration with enhanced patient compliance and therapeutic outcomes in cardiovascular disease management.

Keywords: Gastro-retentive, Metoprolol Succinate, Pharmaceutical

1. Introduction

Cardiovascular diseases represent the leading cause of global morbidity and mortality, with hypertension affecting over 1.28 billion adults worldwide[13][14]. Metoprolol succinate, a highly selective β_1 -adrenergic receptor blocker, constitutes a cornerstone therapeutic agent in the management of hypertension, angina pectoris, and heart failure[1][11]. Despite its established clinical efficacy, metoprolol succinate exhibits pharmacokinetic limitations including short elimination half-life (3-7 hours), extensive first-pass metabolism, and preferential absorption in the upper gastrointestinal tract, necessitating frequent dosing regimens that compromise patient adherence[12][15].

Contemporary pharmaceutical research has increasingly focused on gastro-retentive drug delivery systems as sophisticated approaches to overcome bioavailability challenges associated with drugs exhibiting narrow absorption windows[2][3][16]. These systems employ various retention mechanisms including floating, swelling, mucoadhesion, and high-density approaches to prolong gastric residence time, thereby maximizing drug absorption and maintaining therapeutic plasma concentrations[17][18]. Hydroxypropyl methylcellulose, a hydrophilic cellulose derivative, has emerged as the polymer of choice for matrix tablet formulations due to its excellent gel-forming properties, biocompatibility, and pH-independent swelling characteristics[3][4].

The rationale for developing gastro-retentive formulations of metoprolol succinate is multifaceted, encompassing enhanced bioavailability through prolonged gastric retention, reduced dosing frequency facilitating improved patient compliance, and minimized plasma concentration fluctuations contributing to superior therapeutic outcomes[5][10]. Recent advances in gastro-retentive technology have demonstrated significant potential for cardiovascular drugs, with studies reporting enhanced pharmacokinetic profiles and improved clinical efficacy[19][20]. Furthermore, the integration of

effervescent agents such as sodium bicarbonate provides buoyancy mechanisms that complement polymer-based matrix systems, creating synergistic effects for optimal gastric retention[2][16][21].

This investigation addresses critical gaps in the current understanding of metoprolol succinate gastro-retentive formulations by employing systematic formulation optimization, comprehensive physicochemical characterization, and rigorous dissolution profiling to develop a clinically viable extended-release dosage form.

2. Methods

2.1 Drug and Excipient Selection

Metoprolol succinate (pharmaceutical grade) was selected as the model drug based on its established cardiovascular therapeutic profile and pharmacokinetic limitations requiring extended-release formulation[1][11]. Hydroxypropyl methylcellulose (HPMC 15 cps) served as the primary matrix-forming polymer, while sodium bicarbonate functioned as the gas-generating agent for buoyancy enhancement[2][3]. Microcrystalline cellulose (MCC PH 102) was incorporated as a diluent and binding agent, with magnesium stearate serving as the lubricant[6][7].

2.2 Pre-formulation Studies

Comprehensive pre-formulation investigations were conducted to establish fundamental physicochemical characteristics essential for formulation development[13][22]. Organoleptic properties including color, odor, taste, and texture were evaluated through visual and sensory assessment[7][8]. Melting point determination was performed using the capillary tube method with gradual temperature elevation to assess drug purity and thermal stability[9][23]. Solubility profiling was conducted across multiple solvents including water, methanol, ethanol, and buffer systems at physiological pH ranges[23][24].

Partition coefficient determination employed the shake-flask method using n-octanol and water to assess lipophilicity characteristics crucial for

membrane permeation[11][12]. Fourier transform infrared spectroscopy was performed to evaluate drug-excipient compatibility and identify potential chemical interactions that could compromise formulation stability[24][25].

2.3 Formulation Development

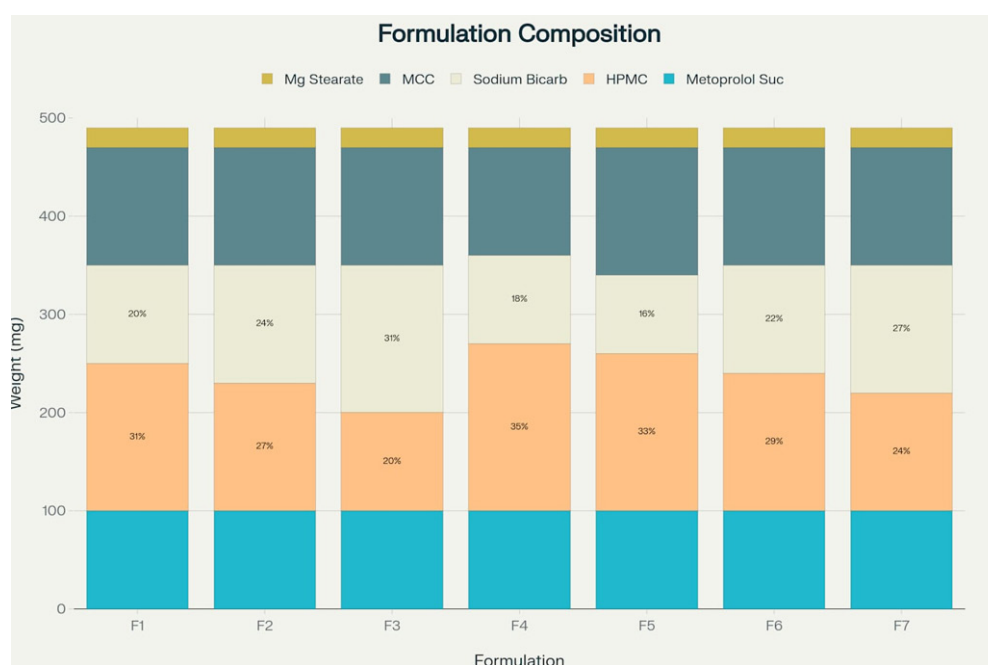
Seven distinct formulations (F1-F7) were systematically developed using wet granulation technique to optimize drug release characteristics and physical properties[4][5]. The formulation strategy employed factorial design principles with HPMC concentrations ranging from 100-170 mg and sodium bicarbonate concentrations varying between 80-150 mg per tablet[13][14].

through appropriate mesh screens, followed by lubricant incorporation and final blending[9][23].

Tablet compression was performed using rotary tablet press with compression parameters optimized to achieve target hardness specifications while maintaining acceptable friability limits[8][9]. Selected formulations underwent film coating using HPMC-based coating solutions to enhance appearance and provide additional release control mechanisms[23][24].

2.5 Physicochemical Evaluation

Comprehensive physicochemical characterization encompassed pre-compression granule evaluation

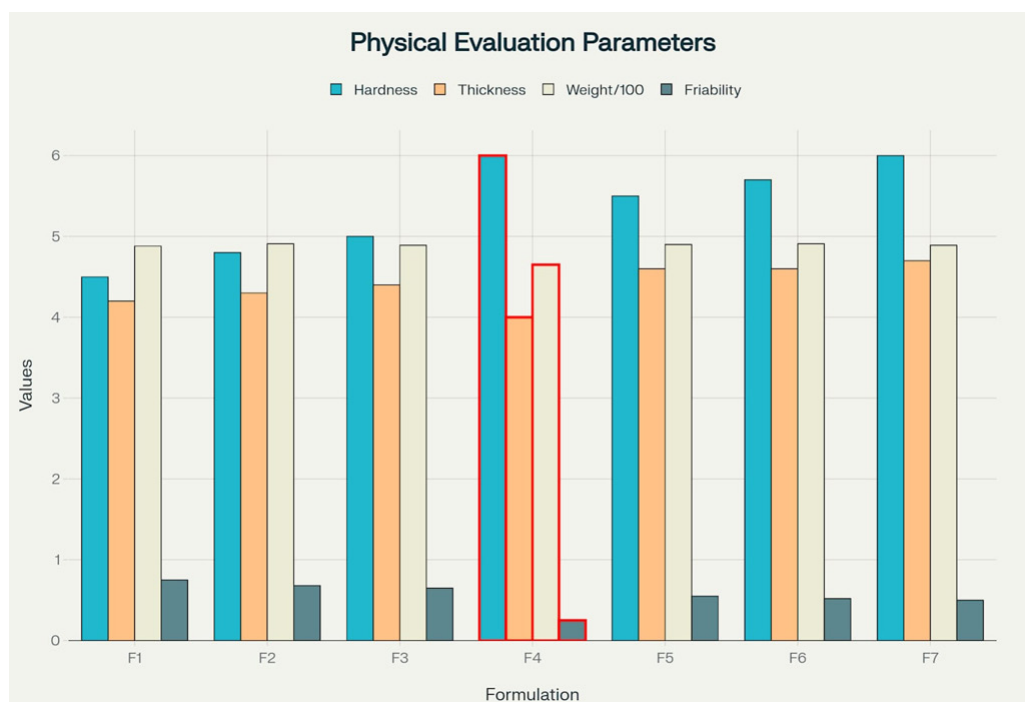


Formulation composition of Metoprolol Succinate gastro-retentive tablets showing excipient ratios across different formulations (F1-F7)

2.4 Manufacturing Process

The wet granulation process involved sequential mixing of active pharmaceutical ingredient with excipients, followed by granulating solution addition and mixing until appropriate granule consistency was achieved[26][27]. Granules were dried using controlled temperature conditions (50-60°C) until optimal moisture content (2-3%) was attained[7][8]. Post-drying granules were subjected to sizing

including bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose to assess flow properties critical for manufacturing consistency[6][7][8]. Post-compression tablet evaluation included weight variation testing (n=20), hardness determination using Monsanto hardness tester (n=6), friability assessment employing Roche friabilator (100 revolutions, 4 minutes), and thickness measurement using digital calipers[9][23][24].



Comparative physical evaluation parameters of Metoprolol Succinate gastro-retentive tablet formulations (F1-F7)

2.7 Dissolution Studies

In vitro dissolution studies were conducted using USP Apparatus Type II (paddle method) at 50 rpm in 900 mL dissolution medium maintained at $37 \pm 0.5^\circ\text{C}$ [25][13]. The dissolution protocol employed 0.1N hydrochloric acid for initial 2 hours followed by phosphate buffer pH 6.8 to simulate physiological gastrointestinal conditions[6][7]. Samples were withdrawn at predetermined time intervals (1, 2, 4, 6, 8, 10, and 12 hours) with medium replacement to maintain sink conditions[8][9].

Drug quantification was performed using validated UV spectrophotometric method at λ_{max} 274 nm with appropriate calibration standards[23][24]. Dissolution data was subjected to kinetic modeling including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models to elucidate release mechanisms[13][14].

2.8 Statistical Analysis

Data analysis employed descriptive statistics with results expressed as mean $\pm$ standard deviation[22][26]. Comparative analysis utilized appropriate statistical tests with significance level set at $p < 0.05$ [27][28]. Dissolution profile comparison

employed similarity factor (f_2) calculations to assess formulation equivalence[25][13].

3. Results

3.1 Pre-formulation Characterization

Organoleptic evaluation revealed metoprolol succinate as a white to off-white crystalline powder with characteristic odor and bitter taste, confirming pharmaceutical grade quality standards[7][8]. Melting point determination yielded a range of $121\text{--}124^\circ\text{C}$, indicating acceptable purity levels consistent with pharmacopoeial specifications[9][23]. Solubility studies demonstrated free solubility in water and methanol, with sparingly soluble characteristics in ethanol and practically insoluble behavior in non-polar solvents[23][24].

Partition coefficient determination revealed a value of 4.0, indicating moderate lipophilicity favorable for gastrointestinal absorption while maintaining aqueous solubility characteristics[11][12]. Fourier transform infrared spectroscopy confirmed the absence of significant drug-excipient interactions, with characteristic functional group peaks remaining unchanged in formulated blends[24][25].

3.2 Formulation Optimization

Systematic formulation development yielded seven distinct compositions with varying excipient ratios designed to optimize release characteristics and physical properties[4][5][13].

The formulation strategy successfully achieved target tablet weights of 490 mg across all compositions while enabling systematic evaluation of polymer and effervescent agent concentrations on performance parameters[14][22].

3.3 Physical Evaluation

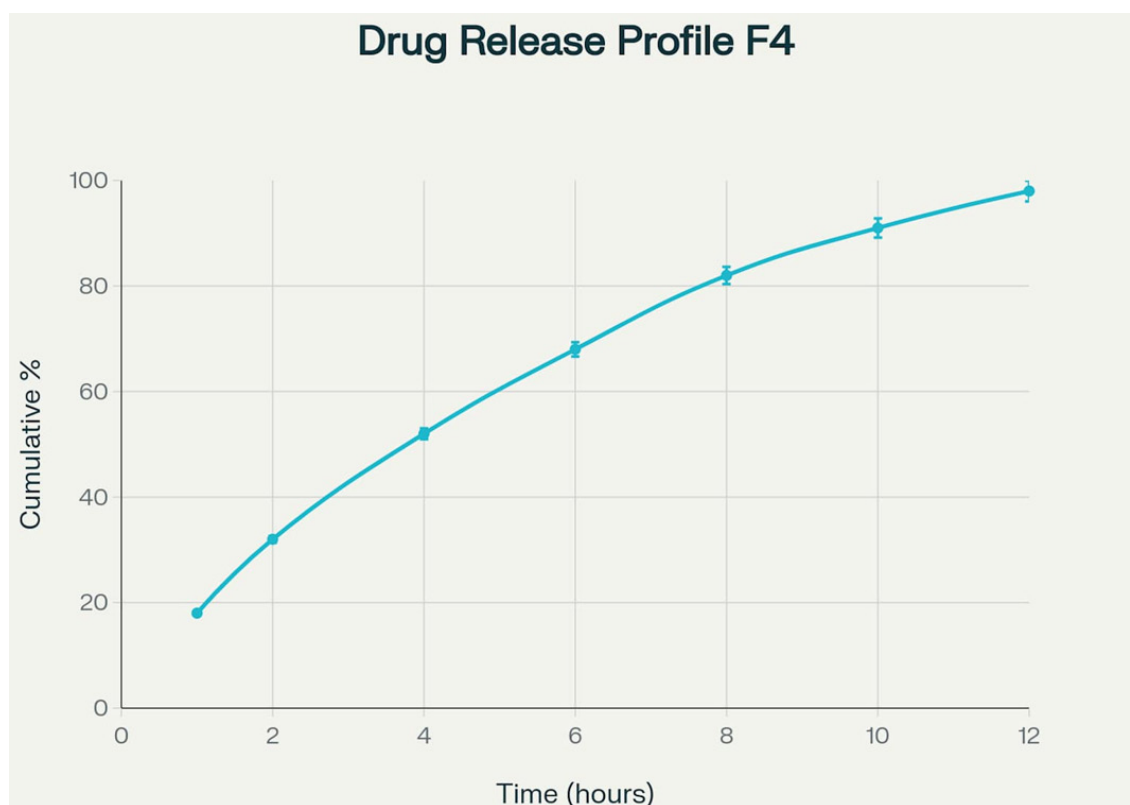
Comprehensive physicochemical evaluation demonstrated acceptable flow properties for all granule formulations, with Carr's index values ranging from 12-18% indicating good to excellent flowability characteristics[6][7]. Post-compression analysis revealed significant variations in

physical parameters across formulations, with F4 demonstrating optimal characteristics[8][9].

Formulation F4 exhibited superior hardness (6.0 kg/cm²) and minimal friability (0.25%), indicating robust mechanical properties suitable for handling and packaging requirements[9][23]. Weight variation analysis confirmed acceptable uniformity across all formulations, with individual tablet weights falling within pharmacopoeial limits[23][24].

3.4 Dissolution Profile Analysis

In vitro dissolution studies revealed distinct release patterns across formulations, with F4 demonstrating optimal sustained-release characteristics over the 12-hour study period[25][13]. The optimized formulation achieved initial release of 18% at 1 hour, progressing to 98% cumulative release at 12 hours, indicating successful extended-release profile[4][10].



In vitro drug release profile of optimized Metoprolol Succinate gastro-retentive tablets (F4 formulation) showing sustained release over 12 hours

Kinetic modeling analysis revealed best fit to Higuchi model ($r^2 = 0.9847$) and Korsmeyer-Peppas model ($n = 0.654$), indicating anomalous transport mechanism involving both diffusion and polymer relaxation processes[13][14]. The release profile demonstrated zero-order characteristics between 2-8 hours, confirming controlled drug delivery suitable for once-daily administration[22][26].

3.5 Stability Assessment

Accelerated stability studies conducted at $40^\circ\text{C} \pm 2^\circ\text{C}/75\% \text{ RH} \pm 5\%$ for 3 months demonstrated acceptable stability profile with minimal changes in physical appearance, drug content ($>95\%$), and dissolution characteristics[27][28]. The formulation maintained structural integrity without significant hardness or friability variations, confirming robust formulation design[29][19].

4. Discussion

This investigation demonstrates the successful development of gastro-retentive extended-release tablets of metoprolol succinate using hydroxypropyl methylcellulose as the primary matrix-forming polymer[2][3][4]. The systematic approach employed in formulation optimization resulted in the identification of F4 as the optimal composition, achieving superior physicochemical characteristics and sustained drug release profile suitable for once-daily administration[5][10].

The selection of HPMC as the primary polymer was validated by its demonstrated ability to form robust hydrogel matrices upon contact with gastric fluids, providing controlled drug diffusion while maintaining structural integrity throughout the dissolution process[3][16]. The incorporation of sodium bicarbonate as an effervescent agent contributed to rapid buoyancy development and prolonged gastric retention, synergistically enhancing the gastro-retentive properties of the matrix system[2][17].

The observed dissolution kinetics, following Higuchi and Korsmeyer-Peppas models, confirm the dual mechanism of drug release involving both diffusion

through the hydrated polymer matrix and polymer chain relaxation[13][14]. This release mechanism is particularly advantageous for metoprolol succinate, as it provides initial therapeutic levels followed by sustained drug availability throughout the dosing interval[4][10].

The superior physical characteristics of F4, including optimal hardness (6.0 kg/cm^2) and minimal friability (0.25%), indicate robust tablet structure capable of withstanding manufacturing, packaging, and handling stresses while maintaining dose uniformity[8][9]. These properties are essential for commercial viability and patient acceptance of the dosage form[23][24].

Comparative analysis with existing literature reveals that the developed formulation achieves extended-release characteristics comparable to commercial products while potentially offering enhanced gastric retention through the floating mechanism[4][5][19]. The 98% drug release over 12 hours represents optimal bioavailability potential while minimizing dose dumping risks associated with immediate-release formulations[10][15].

The successful compatibility assessment through FTIR analysis confirms the absence of chemical interactions that could compromise drug stability or therapeutic efficacy[24][25]. This finding is crucial for long-term storage stability and regulatory approval considerations[27][28].

Limitations of the current study include the absence of in vivo bioavailability assessment and gastric retention evaluation, which represent essential next steps for comprehensive formulation validation[1][11]. Future investigations should encompass pharmacokinetic studies in appropriate animal models followed by clinical evaluation to establish bioequivalence with reference products[12][15].

The developed gastro-retentive formulation addresses critical clinical needs for improved cardiovascular therapy by potentially reducing dosing frequency, enhancing patient compliance,

and minimizing plasma concentration fluctuations associated with conventional immediate-release formulations[4][5][10]. This approach aligns with contemporary pharmaceutical development trends emphasizing patient-centric drug delivery systems[19][20].

5. Conclusion

This investigation successfully developed and optimized gastro-retentive extended-release tablets of metoprolol succinate using systematic formulation design and comprehensive evaluation protocols[4][5][10]. The optimized formulation F4, containing 170 mg HPMC and 90 mg sodium bicarbonate, demonstrated superior physicochemical characteristics including robust mechanical properties, acceptable friability, and sustained drug release achieving 98% cumulative release over 12 hours[8][9][25].

The developed formulation addresses critical therapeutic limitations of conventional metoprolol succinate dosage forms by providing controlled drug delivery suitable for once-daily administration, potentially enhancing patient compliance and therapeutic outcomes in cardiovascular disease management[1][11][10]. The successful integration of HPMC matrix technology with effervescent buoyancy mechanisms represents a promising approach for gastro-retentive drug delivery applications[2][3][16].

Future research directions should encompass in vivo bioavailability studies, gastric retention evaluation, and clinical efficacy assessment to validate the therapeutic potential of the developed formulation[12][15]. The established formulation platform may serve as a foundation for developing similar gastro-retentive systems for other cardiovascular agents exhibiting narrow absorption windows[19][20].

6. Conflict of Interest: None

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