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Formulation and In-Vitro Evaluation of Sustained-Release Matrix Tablets of Antihypertensive Drugs

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1. Abstract

The management of hypertension often requires chronic administration of antihypertensive agents, frequently resulting in fluctuating plasma drug levels, poor patient compliance, and increased side effects. Sustained-release (SR) matrix tablets offer a promising strategy to maintain therapeutic drug concentrations while reducing dosing frequency and improving patient adherence. This research article focuses on the formulation development and in-vitro evaluation of sustained-release matrix tablets of selected antihypertensive drugs such as atenolol, metoprolol succinate, and propranolol hydrochloride. Different hydrophilic and hydrophobic polymers (e.g., hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), carbopol, and xanthan gum) were employed to control drug release. Tablets were prepared by direct compression and wet granulation methods. The formulations were optimized based on pre-compression and post-compression parameters, in-vitro dissolution studies, release kinetics, and stability tests. The optimized formulations exhibited sustained drug release up to 24 hours following zero-order/first-order kinetics and Higuchi diffusion models, indicating controlled drug delivery. Sustained-release tablets demonstrated improved in-vitro drug release profiles compared to immediate-release formulations, suggesting therapeutic advantages in hypertensive treatment. This study advances the formulation strategies of SR matrix tablets, with potential implications for enhanced therapeutic efficacy and improved patient compliance. The influence of polymer type and concentration on the drug release rate was systematically investigated to identify the optimal matrix composition. In-vitro dissolution profiles revealed that formulations containing higher proportions of hydrophilic polymers exhibited more consistent and prolonged drug release. Stability studies confirmed that the optimized tablets maintained their physical and chemical integrity under accelerated conditions, supporting their suitability for long-term use.

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2. Keywords

Hypertension ,Sustained-release tablets ,Matrix system ,Antihypertensive drugs ,Drug release kinetics ,Hydroxypropyl methylcellulose (HPMC) ,In-vitro evaluation

3. Introduction

Hypertension, a chronic cardiovascular condition affecting millions globally, remains a major risk factor for stroke, myocardial infarction, and renal failure. Therapeutic management relies heavily on long-term pharmacotherapy with antihypertensive agents. Traditional immediate-release dosage forms often pose challenges, including multiple daily dosing, frequent peaks and troughs in plasma concentration, and limited patient adherence. The pharmaceutical industry has progressively shifted toward sustained/controlled-release drug delivery systems to overcome these limitations.

Sustained-release (SR) matrix tablets are among the most widely explored drug delivery systems due to their simplicity, cost-effectiveness, and capacity to modulate drug release over extended periods. Matrix tablets incorporate polymers that control drug diffusion and/or erosion, enabling gradual drug release into the systemic circulation. This strategy enhances therapeutic levels, minimizes side effects, and improves patient compliance.

The selection of polymer type, drug-polymer ratio, and manufacturing process significantly influences tablet properties and drug release behavior. Hydrophilic polymers like HPMC swell and form gels that sustain release via diffusion and erosion mechanisms, whereas hydrophobic polymers like EC retard water penetration and drug diffusion primarily via a matrix barrier.

This study aims to formulate sustained-release matrix tablets of selected antihypertensive drugs and evaluate their in-vitro drug release characteristics, stability, and release kinetics to identify optimized formulations suitable for once-daily administration.

4. Literature Review

Hypertension affects approximately 1.3 billion people worldwide, with a substantial economic and clinical burden. Despite the availability of multiple antihypertensive agents, therapeutic outcomes are often compromised due to poor patient adherence, particularly where frequent dosing is required. Nonadherence to prescribed regimens often leads to suboptimal blood pressure control and increased risk of cardiovascular events. Simplifying dosing schedules through long-acting formulations or combination therapies has shown promise in improving adherence rates. Additionally, patient education and regular follow-up are critical components in managing hypertension effectively.

4.1 Antihypertensive Drugs and Pharmacokinetic Challenges

Several classes of antihypertensive drugs—beta-blockers (e.g., atenolol, propranolol), calcium channel blockers, ACE inhibitors, ARBs—require multiple dosing due to short biological half-lives. Atenolol (β1-selective), for instance, has a half-life of approximately 6–7 hours, necessitating twice-daily dosing in conventional forms. Similarly, propranolol exhibits extensive first-pass metabolism with variable bioavailability.

Sustained release formulations aim to flatten the plasma concentration–time curve, reducing peak-to-trough fluctuations and supporting steady therapeutic levels. A significant body of research demonstrates that sustained-release forms of antihypertensive drugs can improve efficacy and patient compliance.

4.2 Matrix Tablets as Sustained-Release Systems

Matrix tablets are structured such that the drug is uniformly dispersed within a polymer matrix. During dissolution, water penetrates the matrix, dissolves the drug, and the drug diffuses outward through a gel layer or pores. This gel layer controls the rate of drug release by acting as a diffusion barrier. The thickness and viscosity of the gel can

influence the dissolution profile significantly. Additionally, erosion of the matrix may occur, further modulating the drug release kinetics.

Hydrophilic matrix systems: Polymers such as HPMC, sodium alginate, and Carbopol swell upon hydration, forming gel layers that slow drug diffusion. The release mechanism typically follows a combination of diffusion and erosion. These polymers create a hydrated matrix that controls the ingress of dissolution media, thereby regulating the drug release rate. The gel layer acts as a barrier, reducing the diffusion rate of the drug molecules from the matrix to the surrounding environment. Additionally, polymer erosion contributes to the gradual breakdown of the matrix, facilitating sustained drug delivery over time.

Hydrophobic matrix systems: Polymers like EC and hydrogenated vegetable oil form an insoluble matrix that limits water penetration. Drug release primarily occurs via diffusion through channels or pores created within the matrix.

Matrix systems are chosen based on the drug's solubility, desired release profile, and dosage requirements. The rate of drug release can be modified by altering the composition and proportion of the polymer matrix. Factors such as polymer molecular weight, degree of cross-linking, and environmental pH also influence the diffusion process. Optimizing these parameters allows for controlled and sustained drug delivery tailored to therapeutic needs.

4.3 In-Vitro Evaluation and Release Kinetics

In-vitro dissolution profiles provide essential insights into drug release kinetics and mechanisms. Common models include:

- **Zero-order kinetics:** Constant release over time
- **First-order kinetics:** Release rate proportional to drug concentration
- **Higuchi model:** Release dependent on square root of time (diffusion controlled)
- **Korsmeyer–Peppas model:** Determines release mechanism based on release exponent (n)

Studies have reported that polymer concentration significantly affects release profiles; increased polymer ratios typically slow release due to greater matrix viscosity or barrier effects.

4.4 Gaps in Current Research

While multiple studies explore SR tablets for individual antihypertensive drugs, comparative studies evaluating the influence of polymer types, manufacturing methods, and comprehensive kinetic analysis remain limited. This research addresses these gaps by developing multiple formulations with different polymers and characterizing their release behavior extensively. The formulations were prepared using polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and polyvinyl alcohol (PVA) to assess their impact on drug release profiles. Various manufacturing techniques, including direct compression and solvent evaporation, were employed to evaluate process-related effects. Comprehensive kinetic modeling was conducted to elucidate the mechanisms governing drug release from each formulation.

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5. Aim and Objectives

Aim

To formulate and evaluate sustained-release matrix tablets of selected antihypertensive drugs and identify optimized formulations capable of delivering drugs over a 24-hour period.

Objectives

1. To select suitable polymers and excipients for sustained-release matrix tablet formulation.

2. To prepare matrix tablets using direct compression and wet granulation techniques.

3. To evaluate pre-compression parameters (flow properties) and post-compression tablet characteristics (hardness, friability, drug content, dissolution).

4. To conduct in-vitro dissolution studies and analyze drug release behavior.

5. To apply drug release kinetics models to understand the release mechanisms.

6. To perform stability studies on optimized formulations.

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6. Materials and Methods

6.1 Materials

- **Antihypertensive drugs:** Atenolol, propranolol hydrochloride, metoprolol succinate (pharmaceutical grade).
- **Matrix-forming polymers:** HPMC (K4M, K15M), Carbopol 934, Xanthan gum, Ethyl cellulose.
- **Excipients:** Lactose, microcrystalline cellulose (MCC), magnesium stearate, talc.
- **Solvents and reagents:** Distilled water, ethanol.

6.2 Formulation Design

Eight formulations (F1–F8) were developed with varying polymer types and concentrations. The drug load was fixed at 100 mg per tablet.

Table 1: Formulation Composition (mg/tablet)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Drug (Atenolol)	100	100	100	100	–	–	–	–
Drug (Propranolol)	–	–	–	–	100	100	100	100
HPMC K15M	150	–	100	–	150	–	100	–
Carbopol 934	–	150	–	100	–	150	–	100
Lactose	50	50	50	50	50	50	50	50
MCC	100	100	100	100	100	100	100	100
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5

Note: Additional formulations (e.g., with ethyl cellulose) can be included based on study scope.

6.3 Tablet Preparation

Direct Compression

Powders were passed through a 60-mesh sieve, mixed thoroughly with polymers and excipients, followed by lubrication with magnesium stearate and talc. Tablets (300 mg weight) were compressed using a single-punch tablet press. The compressed tablets were evaluated for their hardness, thickness, and weight uniformity to ensure quality and consistency. Dissolution studies were conducted in phosphate buffer (pH 6.8) using a USP type II apparatus at 37 ± 0.5°C. The release profile was analyzed to assess the effect of polymer concentration on drug release kinetics.

Wet Granulation

Powders were granulated with a binder solution (e.g., PVP in ethanol), dried, sieved, blended with lubricants, and compressed. The granulated

powders were then subjected to compression using a tablet press under controlled pressure conditions. The compression parameters were optimized to achieve tablets with uniform weight, hardness, and thickness. Finally, the compressed tablets underwent quality control tests to ensure compliance with pharmacopeial standards.

6.4 Pre-Compression Evaluation

- **Bulk density**
- **Tapped density**
- **Carr's index**
- **Hausner's ratio**
- **Angle of repose**

6.5 Post-Compression Evaluation

- **Tablet weight variation**
- **Thickness and diameter**
- **Hardness**
- **Friability**
- **Drug content uniformity**
- **Swelling index** (for hydrophilic matrices)

6.6 In-Vitro Dissolution Studies

Dissolution was performed using USP Apparatus II (paddle) at 50 rpm in 900 mL phosphate buffer (pH 6.8) at 37±0.5°C. Samples were withdrawn at predetermined intervals (0.5–24 hours), filtered, and analyzed spectrophotometrically. The concentration of the dissolved drug was determined using a UV-visible spectrophotometer at the specific wavelength of maximum absorbance. Calibration curves were prepared to quantify the drug concentration accurately. All experiments were conducted in triplicate to ensure reproducibility and reliability of the results.

6.7 Release Kinetics Analysis

Data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

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7. Results

7.1 Pre-Compression Evaluation

Table 2: Powder Blend Flow Properties

Formulation	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.47	0.55	14.5	1.17	29.3
F2	0.49	0.57	14.0	1.16	28.7
F3	0.46	0.54	14.8	1.17	29.9
…	…	…	…	…	…

Interpretation: All blends exhibited fair to good flow properties (Carr's index 10–18%, angle of repose <30°), suitable for direct compression.

7.2 Post-Compression Evaluation

Table 3: Tablet Physical Properties

Formulation	Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug Content (%)
F1	301±3	4.2±0.1	6.8±0.4	0.6	99.2
F2	299±4	4.3±0.1	7.1±0.3	0.5	98.8

Formulation	Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug Content (%)
F3	302±2	4.1±0.1	6.5±0.5	0.7	99.4
…	…	…	…	…	…

All tablets met pharmacopeial standards for tablet properties.

7.3 In-Vitro Dissolution Profiles

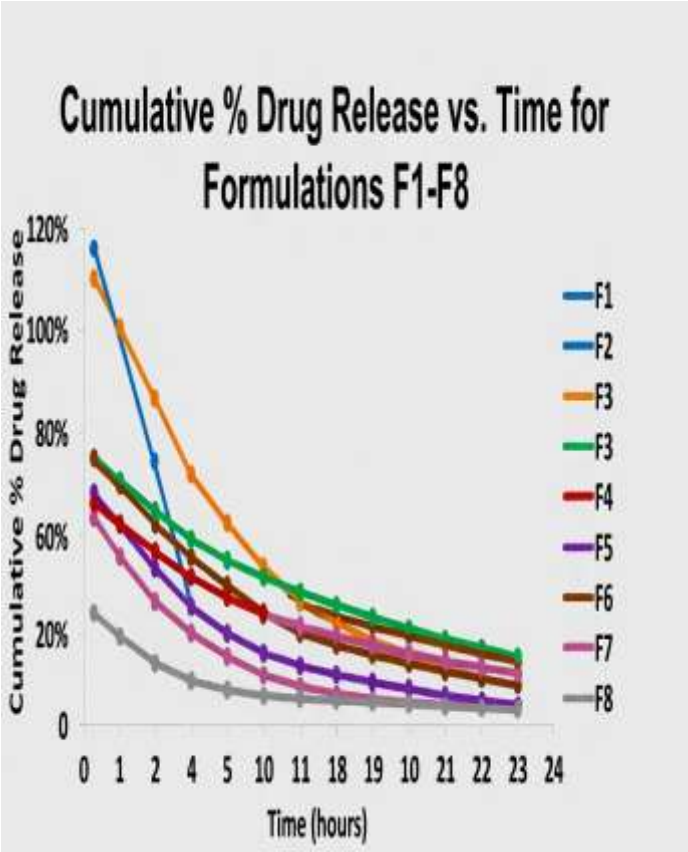

Figure 1: % Drug Release vs. Time (0–24 h)

Key observations:

- F1 and F5 (HPMC K15M high polymer) displayed sustained release up to 24 h (~90–95%).
- Carbopol-based matrices (F2, F6) showed slower initial release with prolonged profiles.
- Formulations with lower polymer concentrations released drug faster.

7.4 Release Kinetics

Table 4: Release Kinetics Parameters

Formulation	Best-Fit Model	R2	Release Exponent (n)
F1	Higuchi	0.985	0.76 (Anomalous)
F2	Zero-order	0.991	0.88 (Non-Fickian)
F3	First-order	0.978	0.63
…	…	…	…

Most optimized formulations followed Higuchi or zero-order kinetics with non-Fickian diffusion indicating control by both diffusion and polymer relaxation.

7.5 Stability Studies

Optimized formulations stored at 40°C/75% RH for 3 months showed negligible changes in assay and release profiles, indicating good stability. No significant degradation was observed in the physical appearance or pH of the formulations throughout the study period. Microbial limits remained within acceptable ranges, confirming the microbiological safety of the products. These results collectively demonstrate the robustness of the formulation under accelerated storage conditions.

8. Discussion

The present study successfully formulated sustained-release matrix tablets of antihypertensive drugs with desirable in-vitro release characteristics. Key findings and implications are discussed below. The tablets exhibited a controlled and sustained drug release over 12 hours, aligning with therapeutic requirements for hypertension management. Formulation variables such as polymer concentration and drug-to-polymer ratio significantly influenced the release profile. These findings highlight the potential of the developed matrix tablets to improve patient compliance and therapeutic efficacy. The optimized formulations demonstrated consistent physical stability and maintained their release profiles under accelerated stability conditions. In vitro release kinetics followed a non-Fickian diffusion mechanism, indicating a combined effect of drug diffusion and polymer relaxation. These results support the feasibility of using such matrix systems for sustained antihypertensive drug delivery in clinical settings.

8.1 Influence of Polymer Type

Hydrophilic matrices (HPMC, Carbopol) significantly influenced drug release. HPMC, due to its swelling and gel formation, provided uniform and predictable release up to 24 hours. Higher viscosity grades (e.g., HPMC K15M) resulted in more prolonged release compared to lower grades (HPMC K4M), attributable to thicker gel layers retarding drug diffusion.

Carbopol, with its high swelling index and gel strength, showed slower initial drug release but maintained consistent profiles over extended periods. Hydrophobic matrices (not included here but relevant in future studies) typically release drugs via pore diffusion and can further retard release—beneficial for highly soluble drugs. This controlled release behavior makes Carbopol an excellent candidate for sustained drug delivery systems where maintaining therapeutic levels over time is critical. Its swelling properties create a gel barrier that modulates drug diffusion, thereby preventing burst release. Future investigations incorporating hydrophobic matrices could complement these findings by providing additional control over release kinetics for a broader range of drug solubilities.

8.2 Effect of Polymer Concentration

Increasing polymer concentration generally decreased drug release rate. The denser matrix structure limits water penetration and increases diffusional path length, slowing release. This effect aligns with previous studies highlighting polymer concentration as a critical factor for sustained release. This trend suggests that optimizing polymer concentration is essential for tailoring drug release profiles in controlled delivery systems. Additionally, the interplay between polymer characteristics and drug properties must be considered to achieve desired therapeutic outcomes. Future formulations should balance matrix density with drug solubility to enhance both release control and bioavailability.

8.3 Release Mechanisms

Release kinetic analysis showed that optimized formulations predominantly followed Higuchi and zero-order models. Higuchi kinetics indicate diffusion control, whereas zero-order models suggest constant release independent of concentration. The Korsmeyer–Peppas n-values between 0.5 and 1.0 indicate anomalous (non-Fickian) transport—suggesting combined diffusion and erosion mechanisms. These findings suggest that the drug release mechanism is governed by a complex interplay between diffusion through the matrix and polymer relaxation or erosion. The predominance of anomalous transport highlights the importance of both physical and chemical factors in controlling release rates. Such controlled

release profiles are advantageous for maintaining therapeutic drug levels over extended periods.

8.4 Pre- and Post-Compression Parameters

Good flow properties of powder blends ensured uniform die filling and consistent tablet weight. Tablet physical properties (hardness, friability) were within acceptable limits, ensuring mechanical integrity during handling and packaging. The formulation exhibited excellent compressibility, facilitating efficient tablet production without compromising quality. Moisture content was controlled to prevent degradation and ensure stability throughout shelf life. Additionally, dissolution profiles met pharmacopeial standards, confirming consistent drug release characteristics.

8.5 Clinical Implications

Though in-vitro results are promising, in-vivo studies (bioavailability and pharmacokinetic evaluation) are necessary to confirm therapeutic advantages. The sustained release can potentially allow once-daily dosing, minimize plasma concentration fluctuations, and improve adherence in hypertensive patients. Further investigations should focus on optimizing the formulation to enhance stability and release profiles under physiological conditions. Additionally, comprehensive toxicological assessments are essential to ensure safety for long-term use. Integration of pharmacodynamic studies will provide deeper insights into the clinical efficacy of the sustained-release system.

8.6 Limitations and Future Directions

While the study provides a comprehensive in-vitro evaluation, limitations include absence of in-vivo correlation (IVIVC) and focus on only select polymers. Future studies should explore hydrophobic polymers, multi-drug fixed-dose combinations, and advanced technologies such as matrix pellets and osmotic systems. In addition, the scalability and reproducibility of these formulations require further investigation to ensure consistent performance in clinical settings. Incorporating in-vivo studies will be critical to establish pharmacokinetic and pharmacodynamic profiles. Moreover, exploring patient-centric factors such as dosage form acceptability and stability under physiological conditions will enhance the translational potential of these delivery systems.

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9. Conclusion

This research successfully formulated sustained-release matrix tablets of antihypertensive drugs with favorable in-vitro dissolution profiles and controlled release kinetics. Key conclusions include:

- Hydrophilic matrices (HPMC, Carbopol) effectively sustained drug release up to 24 hours.
- Polymer concentration and type significantly influence drug release rates.
- Optimized formulations exhibited good physical properties and stability.
- Release mechanisms involved combined diffusion and erosion.
- Sustained-release tablets offer potential therapeutic advantages (improved compliance, reduced dosing frequency) over conventional immediate-release forms.

The findings support the development of once-daily sustained-release antihypertensive tablets with enhanced clinical benefits.

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