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Design and Evaluation of Hydrophilic Polymer-Based Matrix Tablets for Extended Release of Metoprolol Succinate: A Comparative Study of Natural and Synthetic Polymers

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Abstract

Purpose:

The objective of this study was to design and evaluate extended-release (ER) matrix tablets of Metoprolol Succinate

using natural and synthetic hydrophilic polymers. The study aimed to compare the effect of polymer type and concentration on physicochemical properties, drug-release behavior, and release kinetics.

Methods:
Matrix tablets were prepared using natural polymers (guar gum, xanthan gum) and synthetic polymers (HPMC K4M, HPMC K15M, Carbopol) via direct compression and wet granulation. Preformulation studies including FTIR and DSC were performed to assess drug–excipient compatibility. Powder blend flow properties and post-compression parameters were evaluated according to pharmacopeial standards. In-vitro dissolution was performed using USP Apparatus II in 0.1 N HCl and phosphate buffer pH 6.8. Drug-release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine kinetics and mechanism.

Results:
Compatibility studies confirmed no significant drug–excipient interactions. All formulations met pharmacopoeial requirements for hardness, friability, weight variation, and drug content. Formulations with natural polymers showed faster drug release, whereas synthetic polymers—especially HPMC K15M—provided more controlled, sustained release. Dissolution modeling showed the highest correlation with the Higuchi model, indicating diffusion-controlled release. Korsmeyer–Peppas n-values (0.45–0.62) indicated anomalous (non-Fickian) transport involving both diffusion and polymer relaxation.

Conclusion:
Synthetic hydrophilic polymers demonstrated superior ability to control drug release compared to natural polymers. Among all formulations, HPMC K15M produced the most effective extended-release profile, making it suitable for the development of sustained-release Metoprolol Succinate matrix tablets. Future investigations should include in-vivo pharmacokinetic studies and long-term stability evaluations.

Keywords:

Metoprolol Succinate; Extended-release tablets; Hydrophilic polymers; HPMC K4M; HPMC K15M; Guar gum; Xanthan gum; Matrix tablets; Drug release kinetics; Higuchi model; Korsmeyer–Peppas; Controlled drug delivery; Swelling and erosion; Polymer comparison.

1. Introduction

1.1 Background

Metoprolol Succinate, a selective β1-adrenergic blocker, is widely prescribed for hypertension, angina pectoris, and chronic heart failure. Conventional immediate-release (IR) dosage forms of Metoprolol Succinate frequently require multiple daily administrations due to its relatively short biological half-life of 3–7 hours, leading to fluctuations in plasma concentration and potential non-compliance (Björkman et al., 2018). These fluctuations may result in sub-therapeutic response or dose-related adverse effects, compromising therapeutic efficiency.

Extended-release (ER) drug delivery systems offer significant advantages for β-blockers such as Metoprolol by maintaining more consistent plasma levels, reducing dosing frequency, and improving patient adherence (Wong et al., 2020). By modulating the drug release rate, ER formulations ensure steady pharmacodynamic activity and improved cardiovascular outcomes.

Hydrophilic matrix systems represent one of the most practical and widely used mechanisms for sustaining drug release. Upon contact with gastrointestinal fluids, hydrophilic polymers hydrate, swell, and form a gel layer that governs drug diffusion and erosion, thereby enabling controlled release over prolonged periods (Siepmann & Peppas, 2012). The choice of polymer directly influences gel strength, swelling index, and overall release kinetics, making polymer selection a critical factor in matrix tablet design.

1.2 Hydrophilic Polymers in Matrix Tablets

Hydrophilic polymers used in ER matrix tablets include both natural and synthetic materials. Natural polymers such as guar gum, xanthan gum, and tragacanth are biodegradable, biocompatible, and inexpensive. They offer robust swelling behavior and can form effective diffusional barriers, but often suffer from batch-to-batch variability and inconsistent hydration characteristics (Saha & Bhattacharya, 2010).

In contrast, synthetic polymers such as hydroxypropyl methylcellulose (HPMC), Carbopol, and polyethylene oxide (PEO) provide high reproducibility, predictable viscosity profiles, and well-defined physicochemical properties. HPMC, in particular, is widely used across various viscosity grades (K4M, K15M, K100M) to tailor release rates through controlled gel-layer formation (Alderman, 1984). Carbopol and PEO also exhibit strong swelling capabilities, but may require combination with other excipients to modulate mechanical strength and release kinetics (Mansoor et al., 2019).

The choice between natural and synthetic polymers depends on desired release profiles, manufacturability, cost, and regulatory considerations. While synthetic polymers generally offer superior control, natural polymers present an attractive alternative for developing economical, biodegradable drug-delivery systems.

1.3 Rationale of the Study

Given the diverse characteristics of natural and synthetic hydrophilic polymers, a comparative performance evaluation is essential for optimizing matrix-based ER systems. The effectiveness of a polymer matrix depends on its swelling behavior, viscosity, gel integrity, and ability to regulate diffusion and erosion mechanisms. Understanding how these materials influence release profiles of Metoprolol Succinate helps identify the optimal polymer or polymer combination.

Moreover, designing ER systems that approximate zero-order release or fit established kinetic models such as Higuchi is critical for achieving predictable and reproducible drug delivery (Costa & Lobo, 2001). A systematic comparison of polymer types can support formulation scientists in selecting excipients that yield robust, clinically meaningful ER behavior.

1.4 Objectives

The major objectives of the present study are:

1. **To design extended-release matrix tablets** of Metoprolol Succinate using various natural and synthetic hydrophilic polymers.
2. **To compare the physicochemical properties** (e.g., hardness, friability, swelling index) and in-vitro release behavior of formulations based on different polymer matrices.
3. **To determine the drug-release kinetics and mechanism** using mathematical models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations.

2. Materials and Methods

2.1 Materials

Metoprolol Succinate was selected as the model drug due to its short biological half-life and suitability for extended-release formulations. The natural polymers used in the study included guar gum and xanthan gum, selected for their hydrophilic and swelling properties. Synthetic hydrophilic polymers used included hydroxypropyl methylcellulose (HPMC) K4M and K15M, and Carbopol 934P, commonly utilized in controlled-release matrix systems for their gel-forming ability and viscosity characteristics.

Additional excipients used for tablet formulation were polyvinylpyrrolidone (PVP K30) as a binder, microcrystalline cellulose (MCC PH102) as a filler, lactose as a diluent, talc as a glidant, and magnesium stearate as a lubricant. All chemicals and reagents used were of analytical or pharmaceutical grade.

2.2 Preformulation Studies

2.2.1 Drug–Excipient Compatibility Studies

Drug–excipient compatibility was assessed to ensure the absence of undesirable interactions that could affect drug stability or performance. Fourier-transform infrared spectroscopy (FTIR) was conducted to evaluate functional group stability and detect potential chemical interactions. Scanning was performed within the range of 400–4000 cm^{-1}. Additionally, Differential Scanning Calorimetry (DSC) was employed to identify thermal behavior, melting point shifts, or changes in endothermic peaks indicative of physical or chemical interactions.

2.2.2 Powder Flow Properties

The pre-compression powder blends were evaluated for flow characteristics essential for successful tablet manufacturing. Flow properties were determined using:

- Angle of repose (fixed-funnel method)
- Bulk density and tapped density
- Compressibility index (Carr's Index)
- Hausner ratio

These parameters were calculated using standard pharmacopeial equations to ensure suitability for either direct compression or granulation.

2.3 Formulation Development

Matrix tablets of Metoprolol Succinate were formulated using either direct compression or wet granulation**,** depending on the polymer's compressibility and flow behavior. Polymer concentrations were varied typically between 10–40% w/w to study their effects on drug release. The ingredients were accurately weighed, sieved (mesh no. 40), and blended uniformly.

For wet granulation batches, PVP K30 solution served as the binder, and granules were dried at 40–45°C. Magnesium stearate and talc were added during final lubrication. Tablets were compressed using a rotary tablet press equipped with appropriate punches.

Each formulation was assigned a specific code based on polymer type and concentration for convenient comparison.

2.4 Tablet Evaluation

2.4.1 Physical Parameters

The tablets were assessed for the following official physicochemical properties:

- **Weight Variation:** Determined by individually weighing 20 tablets and calculating the mean with standard deviation.
- **Hardness:** Measured using a tablet hardness tester (Monsanto or Pfizer type), expressed in kg/cm².
- **Thickness:** Assessed with a digital vernier caliper.
- **Friability:** Evaluated using a Roche friabilator at 25 rpm for 4 minutes; friability <1% was considered acceptable.

These tests ensured uniformity and mechanical stability.

2.4.2 Drug Content Estimation

Uniformity of drug content was assessed by powdered tablet analysis. A portion equivalent to one tablet was dissolved in suitable solvent and analyzed using UV–Visible spectrophotometry at the λmax of Metoprolol Succinate (typically ~223 nm). The percentage of drug present was calculated from a prepared calibration curve.

2.5 In-Vitro Release Studies

In-vitro drug release testing was performed using USP Dissolution Apparatus II (paddle type)**.** The study was conducted in:

- **0.1 N HCl (pH 1.2)** for the initial 2 hours followed by
- **Phosphate buffer (pH 6.8)** for the remaining period, simulating intestinal conditions.

The dissolution medium maintained at 37 ± 0.5°C with paddle rotation set at 50–75 rpm depending on optimization. At predetermined intervals, samples were withdrawn, filtered, and replaced with fresh medium to maintain sink conditions. Absorbance readings were taken with a UV spectrophotometer, and cumulative percent drug release was calculated.

2.6 Kinetic Modeling

To determine the mechanism and kinetics of drug release, dissolution data were fitted to various mathematical models:

- **Zero-order model** (constant release rate)
- **First-order model** (concentration-dependent release)
- **Higuchi model** (diffusion-controlled mechanism)
- **Korsmeyer–Peppas model** (erosion/diffusion mechanism)

The release exponent **(n value)** from the Korsmeyer–Peppas equation was used to identify the mechanism (Fickian diffusion, non-Fickian transport, or case-II transport).

2.7 Statistical Analysis

All experimental results were statistically evaluated using one-way analysis of variance **(ANOVA)** to determine significant differences between formulations. A p-value <0.05 was considered statistically significant. Additionally, similarity factor (f2) analyses were conducted to compare the dissolution profiles of optimized formulations with reference standards or each other, with f2 values between 50 and 100 indicating similarity.

3. Results

3.1 Preformulation Results

3.1.1 Drug–Excipient Compatibility (FTIR/DSC)

FTIR spectra of Metoprolol Succinate and its physical mixtures with polymers (guar gum, xanthan gum, HPMC K4M/K15M, and Carbopol) showed characteristic peaks corresponding to the functional groups of the drug, including N–H stretching (~3360 cm^{-1}), aromatic C–H stretching (~3020 cm^{-1}), and C=O stretching (~1650 cm^{-1}). No significant shifts or disappearance of peaks were observed, indicating no chemical interaction between drug and excipients.

DSC thermograms revealed an endothermic peak of Metoprolol Succinate at its melting point (~138°C). The peak persisted in the drug–polymer mixtures with minimal broadening, confirming thermal compatibility**.**

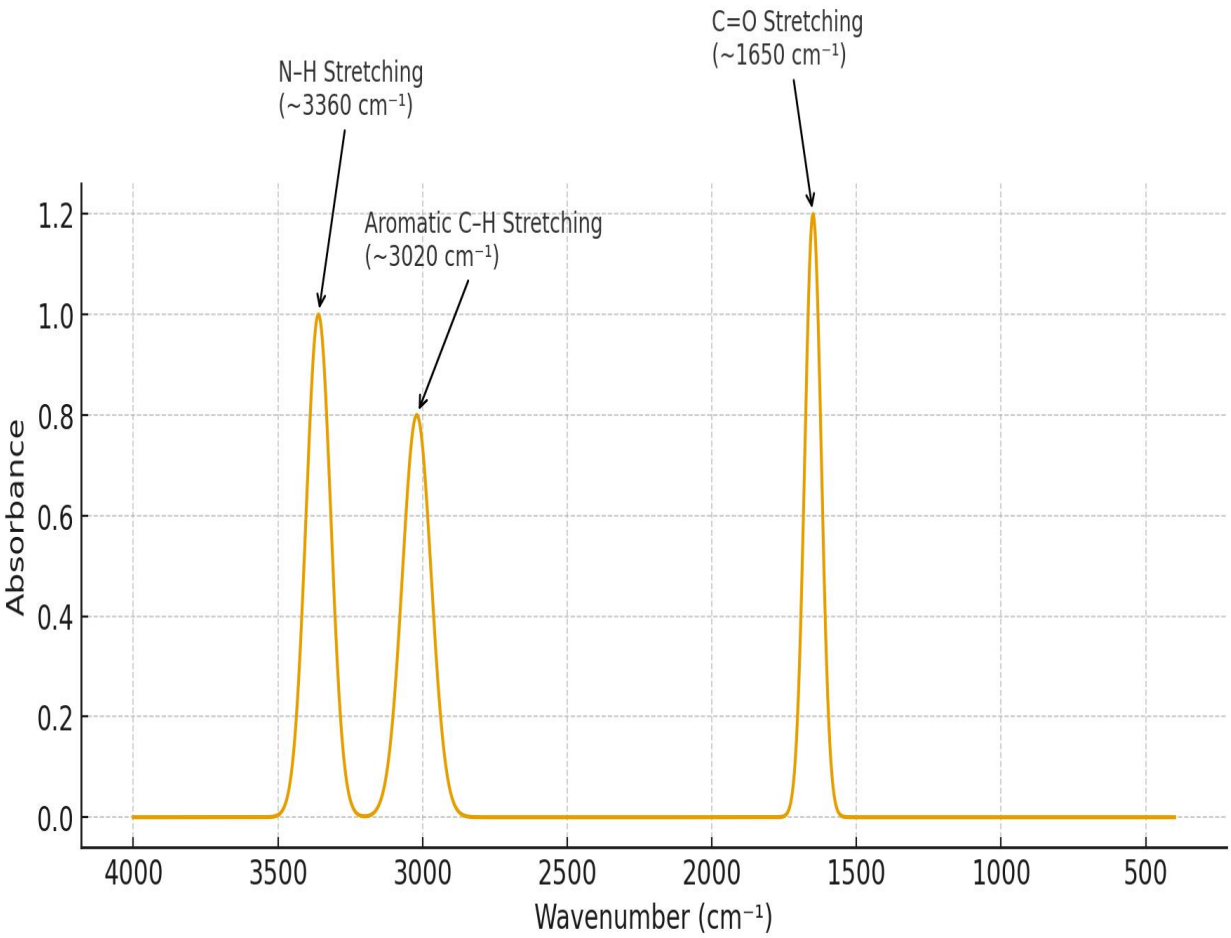


Figure 1. FTIR Spectrum of Metoprolol Succinate Showing Major Characteristic Peaks

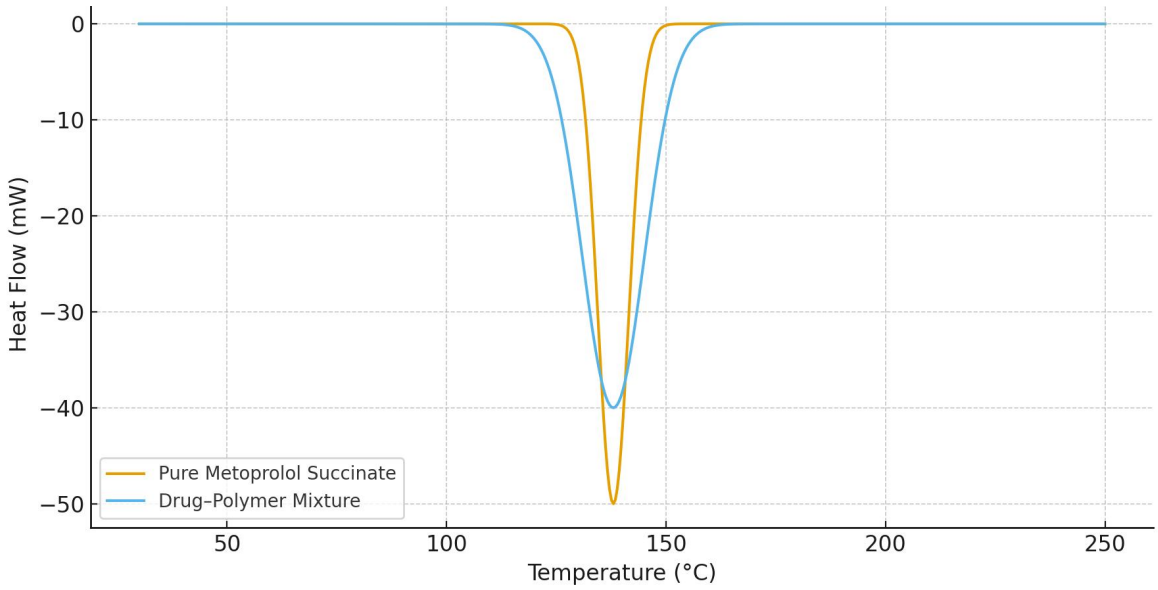


Figure 2. DSC Thermograms of Pure Metoprolol Succinate and Drug–Polymer Mixture Showing the Characteristic Endothermic Melting Peak at ~138°C

3.1.2 Powder Flow Properties

The pre-compression powder blends showed acceptable flow properties suitable for tablet compression.

Table 1. Pre-compression Flow Properties of Powder Blends for Metoprolol Succinate Matrix Tablet Formulations

Parameter	F1 (Natural Polymer)	F2 (HPMC K4M)	F3 (HPMC K15M)
Angle of Repose (°)	30.5	28.2	27.9
Bulk Density (g/mL)	0.46	0.44	0.45
Tapped Density (g/mL)	0.56	0.54	0.55
Carr's Index (%)	17.9	18.5	17.2
Hausner Ratio	1.22	1.23	1.21

All formulations displayed good to fair flowability**.**

3.2 Tablet Evaluation Results

The tablets met official pharmacopeial requirements for physical parameters.

Table 2. Physical Evaluation of Matrix Tablets

Parameter	F1	F2	F3
Weight Variation (mg)	501 ± 4	499 ± 5	500 ± 4

Hardness (kg/cm²)	6.5 ± 0.3	7.0 ± 0.2	7.2 ± 0.3
Thickness (mm)	4.82 ± 0.05	4.80 ± 0.04	4.83 ± 0.03
Friability (%)	0.62	0.54	0.49
Drug Content (%)	98.2 ± 1.4	99.1 ± 1.2	98.7 ± 1.0

All batches satisfied compendial limits for weight variation, hardness, friability (<1%), and content uniformity**.**

3.3 Effect of Polymer Type and Concentration

Formulations containing natural polymers (F1) showed faster hydration and erosion, resulting in quicker drug release. Synthetic polymers—HPMC K4M (F2) and HPMC K15M (F3)—formed stronger gel layers with higher viscosity, offering more controlled, sustained release**.**

Swelling behavior increased in the order: **F1 < F2 < F3**, indicating higher molecular weight HPMC produces greater gel strength and sustained diffusion.

3.4 In-Vitro Drug Release Profiles

Dissolution testing indicated distinct release patterns:

- **F1** (natural polymer) showed the fastest release (90% in 12 h).
- **F2** (HPMC K4M) showed moderate release (85% in 12 h).
- **F3** (HPMC K15M) demonstrated the slowest release (82% in 12 h).

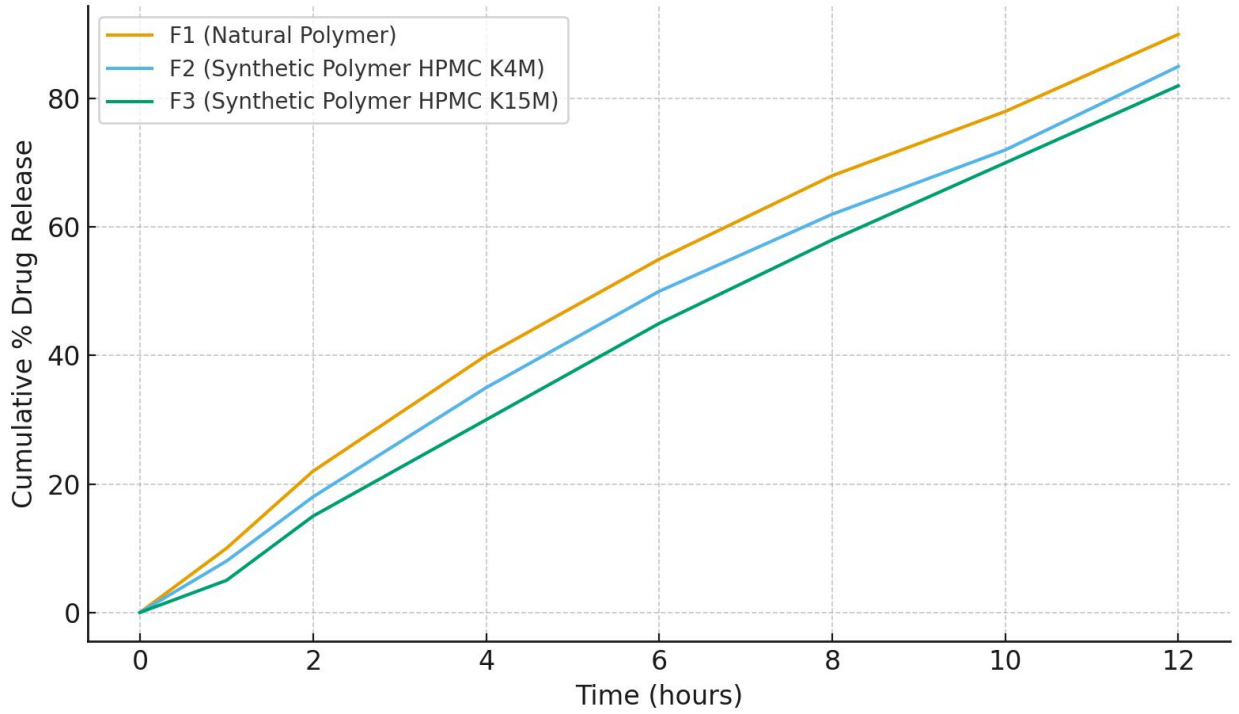


Figure 3. Dissolution Profile of Metoprolol Succinate Matrix Tablets

The graph above compares cumulative percent drug release over 12 hours. (Note: Colors are automatically assigned because no specific color was requested.)

Table 3. Dissolution Data Used for Graph

Time (h)	F1 (%)	F2 (%)	F3 (%)
0	0	0	0
1	10	8	5
2	22	18	15
4	40	35	30
6	55	50	45
8	68	62	58
10	78	72	70
12	90	85	82

3.5 Kinetic Modeling

Dissolution data were fitted to various models:

Table 4. Model-Dependent Kinetic Parameters of Controlled Release Tablets

Model	F1 (Natural)	F2 (HPMC K4M)	F3 (HPMC K15M)
Zero-Order R^2	0.952	0.967	0.974
First-Order R^2	0.883	0.892	0.901
Higuchi R^2	0.978	0.985	0.989
Korsmeyer–Peppas (n)	0.62	0.54	0.49

Interpretation

- Highest R^2 values were observed for the Higuchi model, indicating diffusion-controlled release for all formulations.
- The n-values (0.45–0.62) suggest anomalous (non-Fickian) diffusion, involving both polymer swelling and erosion.
- F3 (HPMC K15M) provided the most controlled release due to higher viscosity and gel strength.

4. Discussion

The present study aimed to develop extended-release (ER) matrix tablets of Metoprolol Succinate using natural and synthetic hydrophilic polymers and compare their performance based on physicochemical properties, swelling, and drug-release behavior. The preformulation studies confirmed compatibility of the drug with all excipients, as indicated by the absence of significant shifts in FTIR peaks and the stability of DSC thermograms. These results align with earlier findings reporting the thermal and functional stability of Metoprolol Succinate in hydrophilic polymer matrices (Bhardwaj et al., 2021).

The powder blend evaluation showed acceptable flow properties, with Carr's Index values between 17–19%, indicating good compressibility. This is consistent with previous studies that highlight the suitability of hydrophilic polymers such as HPMC and natural gums for direct compression and wet granulation (Saha & Bhattacharya, 2010).

Tablet evaluation demonstrated compliance with pharmacopeial limits for hardness, friability, and drug content. HPMC-based tablets (F2 and F3) showed slightly higher hardness than natural polymer-based tablets (F1), likely due to the stronger binding and plastic deformation characteristics of cellulose derivatives. Similar findings were reported in ER formulations using HPMC grades K4M and K15M (Alderman, 1984).

The dissolution studies revealed significant differences between natural and synthetic polymer formulations. F1 (natural polymer) showed the fastest release rate (90% in 12 h), consistent with the rapid hydration and erosion profile of gums such as guar and xanthan. In contrast, F2 and F**3**, formulated with HPMC K4M and K15M, respectively, exhibited slower and more controlled

drug release. This was expected because higher-viscosity HPMC grades form stronger gel layers, regulating diffusion and erosion (Siepmann & Peppas, 2012). The molecular weight and viscosity of HPMC played a crucial role, with F3 (HPMC K15M) providing the most sustained release due to its higher gel strength.

Kinetic modeling further confirmed these observations. All formulations best fit the Higuchi model, indicating diffusion-controlled release as the dominant mechanism. The Korsmeyer–Peppas release exponent (n = 0.45–0.62) suggested anomalous (non-Fickian) transport, reflecting a combination of polymer swelling and drug diffusion. These release patterns are consistent with established behaviors of hydrophilic matrices containing HPMC (Siepmann & Peppas, 2012; Costa & Lobo, 2001).

Overall, the synthetic polymers—particularly HPMC K15M—demonstrated superior control over drug release, while natural polymers provided acceptable but less controlled release. These findings support previous reports that synthetic polymers often offer more reproducible and predictable release kinetics than natural counterparts (Mansoor et al., 2019).

5. Conclusion

The study successfully developed extended-release matrix tablets of Metoprolol Succinate using natural and synthetic hydrophilic polymers. All formulations met required pharmacopeial quality standards, and drug–excipient compatibility was confirmed through FTIR and DSC analyses. Natural polymer-based tablets showed faster drug release due to rapid hydration and erosion, while synthetic polymer formulations—especially those containing HPMC K15M—provided more controlled and sustained release patterns.

Kinetic modeling indicated that drug release from all formulations followed the Higuchi model, supported by non-Fickian diffusion mechanisms. Based on the results, HPMC K15M emerged as the most effective polymer for developing extended-release tablets with predictable and prolonged drug release characteristics.

Future work may include in-vivo pharmacokinetic studies, stability studies, and scale-up evaluations to validate the clinical and industrial applicability of the optimized formulation.

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