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Research Article

Development and Evaluation of Prolonged Release Carvedilol Matrix Tablets Using Hydrophilic–Hydrophobic Polymer Blends

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Abstract

Objective: The present work was aimed at designing and optimizing a prolonged-release matrix tablet of carvedilol (12.5 mg) employing binary polymer combinations to achieve sustained antihypertensive and cardioprotective action over 24 hours and improve patient compliance through once-daily dosing.

Methods: Nine formulations (F1–F9) were developed via wet granulation using varying proportions of hydroxypropyl methylcellulose (HPMC) K100M and ethyl cellulose (EC) N50 as rate-controlling polymers. Preformulation studies including Fourier-transform infrared (FTIR) spectroscopy were conducted to evaluate drug–excipient compatibility. The micromeritic properties of granules and physicomechanical characteristics of compressed tablets were assessed. *In vitro* drug release was performed in pH 6.8 phosphate buffer using a USP Type II dissolution apparatus at 37 ± 0.5 °C and 50 rpm. Dissolution kinetics were analyzed by zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models. Accelerated stability studies were conducted as per ICH Q1A(R2) guidelines.

Results: Compatibility studies confirmed the absence of physicochemical interactions between carvedilol and the selected excipients. Among all developed batches, formulation F5, containing 20% w/w HPMC K100M and 5% w/w ethyl cellulose N50, exhibited the most desirable dissolution profile, releasing 95.5 ± 1.1 % of the drug over a 24-hour period. The release followed near-zero-order kinetics (R^2 = 0.981) with an anomalous (non-Fickian) transport mechanism (release exponent, n = 0.52; R^2 = 0.991). All formulations complied with pharmacopeial limits for weight variation, hardness, friability, and content uniformity. Accelerated stability testing (40 ± 2 °C / 75 ± 5 % RH, 90 days) demonstrated no significant change in drug content or release behaviour; the similarity factor (f_2) remained above 83.

Conclusion: The optimized prolonged-release matrix tablet successfully sustained carvedilol release over 24 hours and displayed excellent physicochemical stability, presenting a viable platform for once-daily oral administration in the management of essential hypertension and chronic heart failure.

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1. INTRODUCTION

Essential hypertension and chronic heart failure remain among the most prevalent cardiovascular disorders globally, constituting major risk factors for ischemic stroke, myocardial infarction, and progressive left ventricular dysfunction. Effective long-term haemodynamic control is contingent upon sustained pharmacological intervention and high patient adherence to prescribed regimens. Beta-adrenergic blocking agents with ancillary vasodilatory properties, including carvedilol, occupy a cornerstone position in contemporary cardiovascular therapy owing to their proven efficacy in reducing morbidity and mortality across the heart-failure spectrum [1]. Carvedilol is a non-selective β-adrenergic antagonist with additional α_1-adrenergic blocking activity, producing balanced arterial and venous vasodilation alongside cardioprotective antioxidant effects. The drug is characterized by a relatively short plasma elimination half-life of approximately 6–10 hours; conventional immediate-release formulations of carvedilol (6.25–25 mg) are administered twice daily, yet are associated with pronounced peak–trough fluctuations and higher incidences of dose-dependent dizziness and orthostatic hypotension [2]. The development of a prolonged-release (PR) formulation delivering 12.5 mg over 24 hours offers the dual advantage of smoother plasma concentration–time profiles and comparable therapeutic efficacy with improved tolerability and adherence [3]. Carvedilol is categorized as a Biopharmaceutics Classification System (BCS) Class II compound, exhibiting low aqueous solubility and high intestinal permeability. The pH-dependent solubility profile-minimal solubility in neutral and weakly alkaline intestinal fluid—presents distinct formulation challenges for prolonged-release delivery. An excessively retardant matrix may suppress release below bioavailable thresholds, whereas an insufficiently robust gel barrier may yield premature release and loss of prolonged action [4]. Hydrophilic matrix systems based on hydroxypropyl methylcellulose (HPMC) represent the most extensively utilized platform for oral prolonged-release delivery. The viscosity grade of HPMC critically influences gel layer formation, diffusional path length, and matrix erosion kinetics. High-viscosity grades such as HPMC K100M generate dense, mechanically robust gel layers particularly effective for drugs exhibiting low aqueous solubility [5]. However, for BCS Class II compounds, HPMC alone may require high polymer loadings that can compromise tablet compactness and lead to incomplete release because of excessively slow matrix erosion. Ethyl cellulose (EC) N50, a water-insoluble, hydrophobic cellulosic ether, is widely employed as a release-retarding polymer in sustained-delivery systems. When combined with HPMC, EC can modulate gel layer permeability, enhance tortuosity of the diffusion path, and reduce matrix front hydration through the formation of a composite hydrophilic–hydrophobic network [6]. The resulting binary polymer barrier may confer superior and more reproducible retardation compared with either polymer in isolation, while preserving sufficient permeability for complete drug elution within the gastrointestinal transit window. The present study was undertaken to develop and optimize carvedilol-loaded prolonged-release matrix tablets (12.5 mg strength) employing HPMC K100M alone or in combination with ethyl cellulose N50. The work encompasses comprehensive preformulation assessment, systematic characterization of granule and tablet properties, *in vitro* dissolution profiling over 24 hours, rigorous kinetic modelling, and accelerated stability evaluation to establish a robust, reproducible once-daily formulation conforming to pharmacopoeial specifications.

2. MATERIALS AND METHODS

2.1 Materials

Carvedilol (BP grade) was obtained as a gift sample and used as received. HPMC K100M (Dow Chemical Company, USA) and ethyl cellulose N50 (Ethocel Std. 50 Premium; Dow Chemical Company, USA) were employed as hydrophilic and hydrophobic matrix-forming polymers, respectively. Microcrystalline cellulose (MCC PH 102; FMC Biopolymer, USA) served as the diluent, polyvinylpyrrolidone K30 (PVP K30; BASF, Germany) as the granulating binder, and magnesium stearate and purified talc as lubricants and glidants, respectively. All excipients were of pharmaceutical grade. Double-distilled water was used throughout the study, and all solvents and reagents were of analytical grade.

2.2 Preformulation and Compatibility Studies

Binary physical mixtures (1:1 w/w) of the drug with each polymer, and a ternary mixture representative of the optimized formulation, were prepared by geometric dilution and trituration in a mortar. The mixtures were sealed in amber glass vials and subjected to accelerated stress conditions at 40 ± 2 °C and 75 ± 5 % relative humidity for four weeks [7]. Fourier-Transform Infrared (FTIR) Spectroscopy: Spectra were recorded over a scanning range of 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1} using the potassium bromide pellet method on a Shimadzu IRAffinity-1S spectrophotometer (Kyoto, Japan).

2.3 Formulation Design and Preparation

Matrix tablets were designed to contain 12.5 mg of carvedilol per unit with a target total weight of 150 mg. Nine formulations were developed according to a systematic screening design to investigate the individual and combined effects of polymer concentration on drug release kinetics. The compositions of all batches are presented in **Table 1**. The target specifications for selection of the optimized batch were initial release below 20 % at 1 h to prevent dose dumping, 30–50 % release at 4 h, and greater than 85 % release at 24 h to ensure complete bioavailability over the dosing interval [8]. Tablets were manufactured by the conventional wet granulation technique. Intragranular components (drug, polymer, diluent) were blended uniformly in a V-cone blender (Erweka, Germany) for 15 min at 25 rpm. The weighed quantity of PVP K30 was dissolved in isopropyl alcohol and water (1:1, v/v) to prepare a 5 % w/v binder solution, which was added slowly to the dry

blend until a satisfactory wet mass was obtained. The mass was passed through a 22-mesh (0.71 mm) sieve, dried in a fluidized bed dryer (Gansons, India) at 50 °C to a moisture content below 2.5 % (determined by loss on drying at 105 °C), and sized through a 30-mesh (0.60 mm) screen. Extra-granular lubricants were blended for 5 min, and the resulting mixture was compressed into tablets using 7.5 mm round, standard concave punches on a 16-station rotary tablet press (Cadmach, India). Compression parameters were adjusted to achieve a target hardness of 4.0 to 6.0 kg/cm².

Table 1: Composition of carvedilol prolonged-release matrix formulations (mg per tablet)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
HPMC K100M	22.5	30.0	37.5	22.5	30.0	37.5	22.5	30.0	37.5
Ethyl cellulose N50	-	-	-	7.5	7.5	7.5	15.0	15.0	15.0
PVP K30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Microcrystalline cellulose (MCC PH 102)	103.0	95.5	88.0	95.5	88.0	80.5	88.0	80.5	73.0
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total weight	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0	150.0

2.4 Micromeritic Evaluation of Granules

The flow properties of the lubricated granules for the optimized batch were characterized by the angle of repose (fixed-funnel method), bulk density, tapped density, Carr's compressibility index, and Hausner ratio using standard procedures [9].

2.5 Tablet Characterization

Weight Variation: Twenty tablets were weighed individually, and the mean and relative standard deviation (RSD) were calculated.

Dimensions: Thickness and diameter were measured using a digital Vernier caliper (n=10).

Hardness: Crushing strength was determined using a Monsanto-type hardness tester (n=6).

Friability: Evaluated using a Roche-type friabilator rotated at 25 rpm for 4 min (total 100 drops), and the percentage weight loss was calculated (n=20).

Content Uniformity: Ten tablets were assayed individually. Powder equivalent to 12.5 mg of carvedilol was extracted into methanol, diluted with pH 6.8 phosphate buffer, sonicated for 15 min, filtered through a 0.45 µm nylon membrane, and analyzed by UV spectrophotometry at 285 nm. The method was validated for linearity (R^2=0.9996) over a concentration range of 2–20 µg/mL, accuracy (recovery 98.4–101.2 %), intra-day precision (RSD < 1.5 %), and inter-day precision (RSD < 2.0 %) [10].

2.6 *In Vitro* Drug Release Studies

Dissolution testing was performed using a USP Type-II (paddle) apparatus (Lab India, India) in 900 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5 °C with a paddle rotation speed of 50 rpm. Aliquots (5 mL) were withdrawn at predetermined intervals (1, 2, 4, 6, 8, 12, 16, and 24 h), filtered through 0.45 µm membrane filters, appropriately diluted, and quantified at 285 nm. An equivalent volume of fresh, pre-warmed dissolution medium was replaced after each sampling. Cumulative percentage drug released was calculated (n=3).

2.7 Drug Release Kinetics and Mechanism

The dissolution data of the optimized formulation were fitted to five mathematical models using DDSolver (Microsoft Excel add-in): zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell. The coefficient of determination (R^2) and the release exponent (n) were computed. An n value of 0.45 or less indicates Fickian diffusion; 0.45 to 0.89 indicates anomalous (non-Fickian) transport; and 0.89 or greater corresponds to Case II transport [11, 12].

2.8 Stability Studies

The optimized formulation was packed in amber-coloured high-density polyethylene bottles with a cotton plug and silica gel desiccant, and subjected to accelerated stability conditions of 40 ± 2 °C and 75 ± 5 % relative humidity for 90 days per ICH Q1A(R2) guidelines. At 0, 30, 60, and 90 days, samples were evaluated for physical appearance, drug content, hardness, friability, and dissolution profile. The similarity factor (f_2) was calculated between the initial and storage dissolution profiles [13].

2.9 Statistical Analysis

All experiments were performed in triplicate unless otherwise specified. Data are expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post-hoc test was employed to determine significant differences between formulations. A p-value less than 0.05 was considered statistically significant [14].

3. RESULTS AND DISCUSSION

3.1 Preformulation and Compatibility Studies

FTIR analysis of pure carvedilol revealed characteristic absorption bands corresponding to O–H and N–H stretching (3380 cm^{-1}, 3305 cm^{-1}), aromatic C–H stretching (3065 cm^{-1}), aliphatic C–H stretching (2942 cm^{-1}, 2870 cm^{-1}), aromatic C=C stretching (1602 cm^{-1}, 1485 cm^{-1}), C–O–C asymmetric stretching (1242 cm^{-1}), and C–N stretching (1068 cm^{-1}). The FTIR spectrum of pure carvedilol is depicted in **Figure 1**. The

physical mixture and the ternary mixture representing the optimized formulation shown in **Figure 2** retained all principal peaks with negligible shifts (less than 4 cm^{-1}), and no new absorption bands or band disappearances were observed, suggesting the absence of chemical incompatibility between carvedilol and the selected excipients.

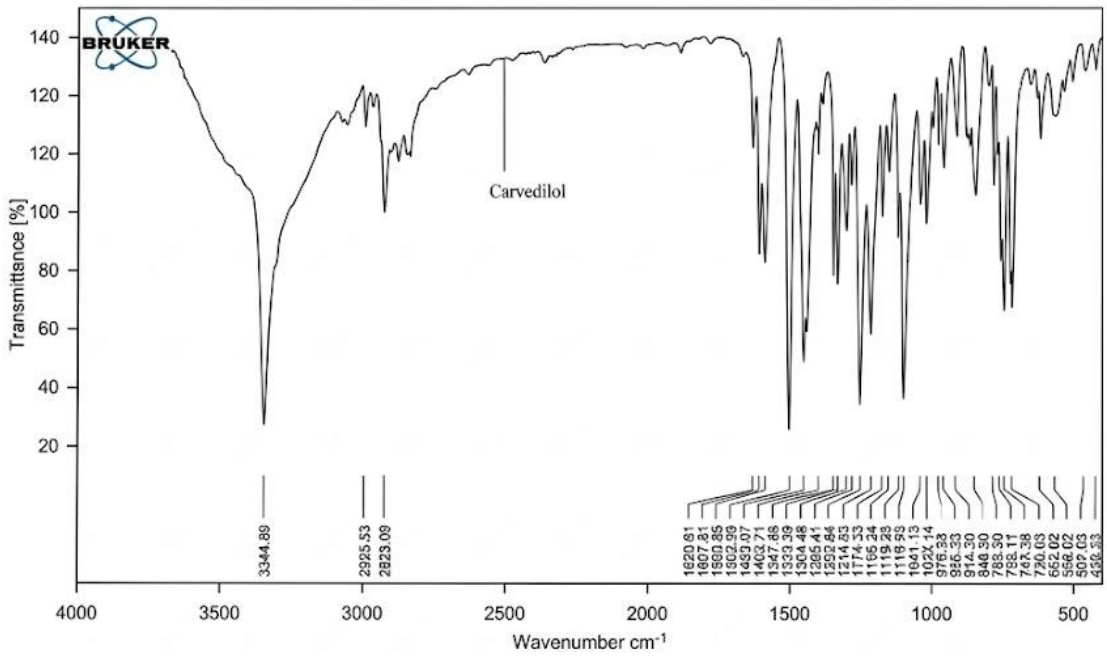

Figure 1: FTIR analysis of pure carvedilol.

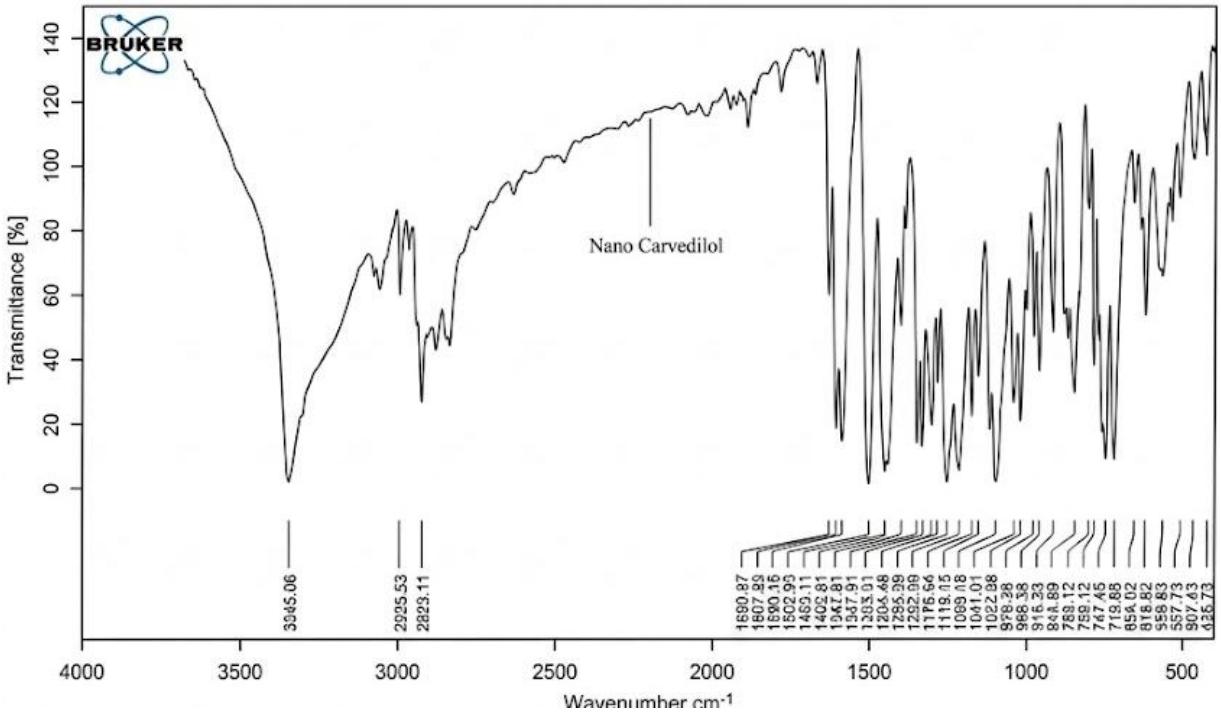

Figure 2: FTIR analysis of physical mixture

3.2 Micromeritic Properties

The lubricated granules intended for the optimized batch (F5) demonstrated an angle of repose of 25.8 ± 1.0°, a bulk density of 0.425 ± 0.007 g/mL, a tapped density of 0.498 ± 0.006 g/mL, a Carr's compressibility index of 14.7 ± 0.7 %, and a Hausner ratio of 1.17 ± 0.02. These values, summarized in **Table 2**, indicate satisfactory to excellent flow properties, suitable for high-speed rotary tablet compression. The favourable flow characteristics are attributed to the spherical granule morphology and narrow particle size distribution achieved during wet granulation with the PVP K30 binder solution.

3.3 Physicomechanical Characterization of Tablets

The post-compression parameters for all nine batches are given in **Table 2**. Mean tablet weights ranged from 149.2 to 150.8 mg with relative standard deviations below 1.5 %, complying with pharmacopoeial weight variation tolerances for tablets weighing less than 250 mg (±7.5 %). Thickness and diameter were consistent across all batches, reflecting uniform die fill and consistent compression force settings. Hardness values increased progressively with increasing total polymer content because of the superior binding and plastic deformation characteristics of HPMC and the rigid filler effect of ethyl cellulose. Friability for all formulations was well below 1.0 %, indicating acceptable mechanical robustness for subsequent handling and packaging operations. Drug content uniformity assays revealed that all batches contained between 98.5 % and 101.2 % of the labelled claim, with relative standard deviations below 2.5 %.

Table 2: Physicomechanical properties of carvedilol prolonged-release matrix tablets (mean ± SD, n = 6–20).

Formulation	Weight (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug Content (%)
F1	150.2 ± 1.8	3.32 ± 0.04	4.2 ± 0.3	0.60 ± 0.05	100.2 ± 1.3
F2	149.6 ± 1.5	3.35 ± 0.04	4.5 ± 0.3	0.54 ± 0.04	99.6 ± 1.1
F3	150.5 ± 1.6	3.38 ± 0.05	4.9 ± 0.4	0.48 ± 0.03	98.9 ± 1.4
F4	149.8 ± 1.7	3.34 ± 0.04	4.4 ± 0.3	0.56 ± 0.04	101.2 ± 1.0
F5	150.0 ± 1.5	3.37 ± 0.04	4.8 ± 0.3	0.50 ± 0.03	99.5 ± 1.0
F6	150.4 ± 1.4	3.40 ± 0.05	5.2 ± 0.4	0.44 ± 0.03	98.5 ± 1.2
F7	149.5 ± 1.6	3.36 ± 0.04	4.6 ± 0.3	0.52 ± 0.04	100.6 ± 1.1
F8	150.3 ± 1.5	3.39 ± 0.04	5.0 ± 0.4	0.46 ± 0.03	99.2 ± 1.3
F9	150.8 ± 1.5	3.42 ± 0.05	5.5 ± 0.4	0.40 ± 0.03	98.8 ± 1.5

3.4 *In Vitro* Drug Release Studies

The dissolution profiles for all formulations are presented in **Table 3** and illustrated in **Figure 3**. Formulations prepared with HPMC K100M alone (F1–F3) exhibited an inverse relationship between polymer concentration and drug release rate, as expected for a hydrophilic matrix system. F1, containing only 15 % HPMC K100M, released approximately 22.5 % at 1 hour and achieved 90.2 % by 12 hours, with near-complete release by 24 hours. The relatively rapid initial release is attributed to the insufficient gel layer thickness and limited diffusional resistance for this poorly soluble compound in pH 6.8 medium. At 25 % polymer loading (F3), the release was substantially retarded; however, only 86.4 % of the drug was released by 24 hours, suggesting a potential risk of incomplete bioavailability within the gastrointestinal transit window.

The inclusion of ethyl cellulose N50 in binary matrices (F4–F9) produced a marked synergistic retardation effect that was particularly pronounced during the middle and latter phases of the release profile. Formulation F5, comprising 20 % HPMC K100M and 5 % ethyl cellulose N50, demonstrated the most desirable profile (**Table 3**, **Figure 3**): an initial release of 14.5 ± 1.0 % at 1 hour (preventing dose dumping), progressive release of 38.5 ± 1.2 % at 4 hours, 60.5 ± 1.4 % at 8 hours, and near-complete release of 95.5 ± 1.1 % at 24 hours. The profile was significantly more sustained than F1 and F4 ($p < 0.05$) and more complete than F3 and F6 ($p < 0.05$). Formulations containing 10 % ethyl cellulose (F7–F9) showed excessive retardation, with F9 releasing only 74.2 % at 24 hours, indicating that higher EC loadings may establish a hydrophobic barrier too resistant for complete dissolution within the gastrointestinal transit time for this low-solubility active pharmaceutical ingredient.

Table 3: Cumulative % drug released from carvedilol prolonged-release matrix tablets (mean ± SD, n = 3).

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	22.5 ± 1.2	17.2 ± 0.9	12.4 ± 0.8	19.5 ± 1.0	14.5 ± 1.0	10.2 ± 0.8	18.2 ± 1.1	13.5 ± 0.9	9.5 ± 0.8
2	36.8 ± 1.5	28.5 ± 1.2	21.5 ± 1.0	31.2 ± 1.3	24.8 ± 1.1	18.5 ± 1.0	28.5 ± 1.2	22.4 ± 1.1	16.2 ± 1.0
4	54.2 ± 1.6	42.5 ± 1.4	32.8 ± 1.2	46.5 ± 1.5	38.5 ± 1.2	28.4 ± 1.2	42.2 ± 1.4	34.5 ± 1.3	25.5 ± 1.1
6	68.5 ± 1.5	52.4 ± 1.5	41.5 ± 1.4	56.8 ± 1.6	50.2 ± 1.3	38.2 ± 1.2	52.5 ± 1.5	44.2 ± 1.4	34.8 ± 1.2
8	78.4 ± 1.4	62.5 ± 1.5	50.2 ± 1.4	66.2 ± 1.5	60.5 ± 1.4	48.5 ± 1.3	62.4 ± 1.5	54.8 ± 1.4	44.5 ± 1.3
12	90.2 ± 1.2	76.4 ± 1.3	64.8 ± 1.4	80.5 ± 1.4	76.8 ± 1.3	62.5 ± 1.4	76.2 ± 1.4	68.5 ± 1.3	58.2 ± 1.3
16	96.5 ± 1.0	86.2 ± 1.2	75.5 ± 1.3	90.4 ± 1.1	86.2 ± 1.2	74.2 ± 1.2	86.5 ± 1.2	78.4 ± 1.2	68.5 ± 1.2
24	99.2 ± 0.8	94.6 ± 1.0	86.4 ± 1.1	97.2 ± 0.9	95.5 ± 1.1	88.5 ± 1.1	94.2 ± 1.0	88.5 ± 1.1	74.2 ± 1.2

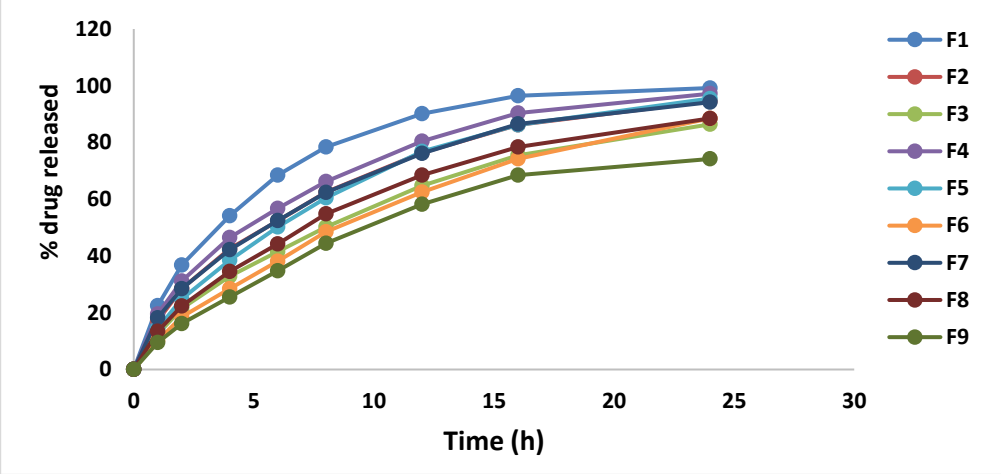

Figure 3: *In vitro* Dissolution Profiles of carvedilol formulations F1–F9

3.5 Drug Release Kinetics and Mechanism

The dissolution data for the optimized formulation F5 were fitted to established mathematical models to elucidate the release mechanism (Table 4). The Korsmeyer–Peppas model provided the highest coefficient of determination (R^2 = 0.991), followed by the zero-order model (R^2 = 0.981). The first-order and Hixson–Crowell models exhibited comparatively weaker correlations, indicating that drug release is not governed predominantly by concentration-dependent dissolution or surface-area reduction alone. The release exponent (n) calculated from the Korsmeyer–Peppas equation was 0.52. Since this value lies between 0.45 and 0.89, the dominant release mechanism is classified as anomalous (non-Fickian) transport, indicating a coupling of drug diffusion through the gel layer with polymer chain relaxation and matrix erosion. Such a mechanism is highly favourable for prolonged-release formulations because it typically yields a more consistent release rate compared to purely diffusion-controlled systems, which inherently exhibit a declining rate over time. The Higuchi model, representing Fickian diffusion from a planar matrix, yielded a moderate fit (R^2 = 0.968), further supporting the contribution of polymer relaxation kinetics and confirming that diffusion alone does not fully account for the observed release behaviour.

Table 4: Kinetic modelling parameters for optimised formulation F5.

Model	Equation Form	R^2	Rate Constant (k)
Zero-order	$Q_t = Q_0 + k_0 t$	0.981	3.985
First-order	$\log Q_t = \log Q_0 + k_1 t / 2.303$	0.918	0.006
Higuchi	$Q_t = k_H t^{0.5}$	0.968	16.850
Korsmeyer–Peppas	$M_t/M\infty = k_{KP} t^n$	0.991	6.428 (n = 0.520)
Hixson–Crowell	$(100 - Q_t)^{1/3} = (100 - Q_0)^{1/3} - k_{HC} t$	0.936	0.010

3.6 Accelerated Stability Studies

The optimized batch F5 demonstrated excellent physicochemical stability under accelerated stress conditions over a 90-day period (**Table 5**). No changes in physical appearance, odour, or colour were observed at any time point. The mean drug content remained within the acceptance criteria (97.5–99.5 %), and tablet hardness and friability did not deviate substantially from baseline values, indicating that the compressed matrix structure remained mechanically intact. The dissolution profile remained essentially unchanged, with the similarity factor (f_2) between the initial and 90-day profiles exceeding 83. These results indicate that the carvedilol matrix tablets are chemically stable and that the polymeric gel network maintains its physical integrity and functional performance under elevated temperature and humidity conditions.

Table 5: Accelerated stability data of optimised formulation F5 at 40 ± 2 °C / 75 ± 5 % RH.

Parameter	Initial (Day 0)	1 Month	2 Months	3 Months
Appearance	White, smooth	No change	No change	No change
Assay (%)	99.5 ± 1.0	98.8 ± 1.1	98.0 ± 1.0	97.5 ± 1.2
Hardness (kg/cm²)	4.8 ± 0.3	4.7 ± 0.3	4.6 ± 0.4	4.5 ± 0.3
Friability (%)	0.50 ± 0.03	0.52 ± 0.04	0.54 ± 0.03	0.57 ± 0.04
Release at 24 h (%)	95.5 ± 1.1	94.8 ± 1.2	93.2 ± 1.1	92.0 ± 1.3
f_2 versus Day 0	—	89.5	85.8	83.2

4. DISCUSSION

The central challenge in formulating a prolonged-release dosage form of carvedilol stems from its classification as a BCS Class II compound, characterized by low aqueous solubility across the physiological pH range and high intestinal permeability. Unlike highly soluble drugs where the primary formulation objective is to retard rapid efflux, the challenge with carvedilol lies in achieving a balanced release profile: sufficiently prolonged to maintain therapeutic plasma concentrations over 24 hours, yet sufficiently complete to ensure adequate bioavailability before gastrointestinal transit is complete. Hydrophilic matrix tablets rely on the formation of a hydrated gel layer at the tablet–fluid interface; the thickness, tortuosity, and mechanical strength of this layer dictate the release kinetics for poorly soluble actives.

The findings of this study demonstrate that while HPMC K100M alone can retard carvedilol release, concentrations exceeding 25 % w/w are required to approach the target 24-hour duration, and even then, the profile may be suboptimal or incomplete (F3 released only 86.4 % at 24 h). Incomplete release is a critical concern for BCS Class II drugs because any undissolved fraction represents a direct loss in systemic exposure. The incorporation of ethyl cellulose N50 synergistically augmented the retardation capacity of the HPMC matrix while preserving release completeness at moderate total polymer loadings. This effect is mechanistically attributed to the distinct hydration behaviour of ethyl cellulose, which does not swell or dissolve in aqueous media but rather forms a rigid, hydrophobic polymeric skeleton interspersed within the hydrating HPMC gel. Within the binary network, physical entanglement between the cellulosic chains of HPMC and the ethoxy-substituted cellulose backbone of EC is postulated to increase the local hydrophobicity of the gel layer, reduce the effective diffusion coefficient of dissolved drug molecules, and modulate the erosion rate of the polymer front. Consequently, a moderate total polymer load (25 % w/w) in F5 achieved superior prolonged release with near-complete dissolution compared to higher loads of HPMC alone.

The viscosity grade of HPMC emerged as a critical determinant of release kinetics. The high molecular weight and extended chain length of K100M facilitate the formation of a mechanically robust gel layer that resists both dissolution medium penetration and shear forces from the hydrodynamic environment of the gastrointestinal tract. In contrast, lower viscosity grades (e.g., K4M, K15M) would require proportionally higher concentrations to achieve equivalent gel layer thickness, potentially increasing tablet bulk beyond acceptable limits for a 12.5 mg dose. The contrast between the 15 %, 20 %, and 25 % K100M loadings clearly illustrated that chain entanglement density scales with polymer concentration, yielding progressively prolonged drug release.

The kinetic analysis of F5 (Table 4) confirmed anomalous (non-Fickian) transport, with the release exponent of 0.52 indicating comparable contributions from Fickian diffusion and polymer chain relaxation. This is mechanistically consistent with the behaviour of swellable hydrophilic matrices containing hydrophobic modifiers, wherein the velocity of the swelling front advancing into the glassy core is of the same order of magnitude as the velocity of the erosion front receding from the surface. The near-zero-order release kinetics observed between 4 and 16 hours are particularly clinically relevant, as they predict relatively constant plasma concentrations and reduced peak-to-trough fluctuations compared to immediate-release administration. Smoother plasma profiles are associated with reduced incidences of adrenergic-blockade-related adverse effects, including dizziness, fatigue, and symptomatic hypotension, which are frequently cited as reasons for beta-blocker discontinuation in clinical practice.

Accelerated stability data further reinforced the robustness of the optimized formulation. The absence of significant physical or chemical changes after 90 days at 40 °C and 75 % relative humidity suggests that carvedilol is chemically stable within the HPMC–ethyl cellulose matrix and that the composite polymeric structure does not undergo substantial thermal ageing, cross-linking, or phase separation during storage. The consistently high f_2 values (above 83, **Table 5**) provide strong assurance of batch-to-batch reproducibility and shelf-life viability, particularly important for a low-dose formulation where small variations in matrix composition can disproportionately affect release behaviour.

5. CONCLUSION

This study successfully developed a once-daily prolonged-release matrix tablet of carvedilol (12.5 mg) by systematically optimizing a binary hydrophilic–hydrophobic polymer system comprising HPMC K100M and ethyl cellulose N50. Formulation F5, containing 20 % w/w HPMC K100M and 5 % w/w ethyl cellulose N50, achieved the most desirable release profile, delivering approximately 95.5 % of the drug over 24 hours with near-zero-order kinetics governed by anomalous (non-Fickian) transport. The tablets met all pharmacopoeial quality specifications for weight variation, hardness, friability, and content uniformity, and demonstrated excellent physicochemical stability under accelerated ICH conditions. The developed formulation offers a clinically relevant advance over conventional immediate-release carvedilol by providing sustained 24-hour cardiovascular coverage with potentially improved tolerability and adherence. These findings support the further development and bioavailability assessment of the optimized formulation as a patient-friendly alternative in the long-term management of essential hypertension and chronic heart failure.

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