Method Development and Validation of Sustained Release Tablets of Propranolol Hydrochloride

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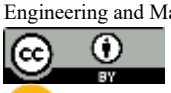

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Abstract: The present study reports the development and comprehensive ICH Q2(R1)-compliant validation of a UV spectrophotometric analytical method for Propranolol Hydrochloride (Propranolol HCl), combined with the design and evaluation of sustained release (SR) hydrophilic matrix tablets. Propranolol HCl is a BCS Class I, non-selective β-adrenergic receptor blocker with a short biological half-life (3–6 hours) and extensive first-pass hepatic metabolism, necessitating multiple daily dosing and causing peak-to-trough plasma fluctuations. Seven SR matrix tablet formulations (F1–F7) containing 80 mg Propranolol HCl were prepared by wet granulation using varying ratios of HPMC K4M and HPMC K15M as rate-controlling polymers. The validated UV method (λmax = 220 nm, 0.1N HCl) demonstrated excellent linearity over 2–24 µg/mL (r^2 = 0.9999), accuracy (% recovery 99.6–100.1%), and precision (%RSD < 1%). All formulations achieved sustained drug release over 12 hours; the Korsmeyer-Peppas model best described release kinetics (r^2 > 0.9951), with n values of 0.48–0.78 indicating anomalous diffusion-erosion transport. Formulation F4 (HPMC K4M:K15M = 50:50) was identified as optimal, achieving 88.5% cumulative drug release at 12 hours with near-zero-order kinetics. Accelerated stability studies at 40°C/75% RH for 3 months confirmed drug content ≥ 98.9% and consistent dissolution performance. The study demonstrates that integrated analytical validation and HPMC matrix optimization provide a reproducible, clinically relevant SR platform for improved cardiovascular pharmacotherapy.

Keywords: *Propranolol Hydrochloride, Sustained Release, HPMC K4M, HPMC K15M, ICH Q2(R1), UV Spectrophotometry, Matrix Tablets, Korsmeyer-Peppas, Wet Granulation.*

1. Introduction

The evolution of pharmaceutical science has increasingly shifted from focusing primarily on 'drug discovery' to optimizing 'drug delivery'. While the intrinsic efficacy of an active pharmaceutical ingredient (API) depends heavily on its molecular potency and receptor affinity, its ultimate clinical utility is strictly governed by the delivery system. Conventional immediate-release (IR) dosage forms, while foundational to modern medicine, present several severe pharmacokinetic limitations that impede the management of chronic diseases such as hypertension, angina pectoris, and cardiac arrhythmias.

These limitations include the 'peak-to-trough' phenomenon, wherein plasma drug concentrations rise to potentially toxic levels shortly after ingestion and abruptly fall to sub-therapeutic levels long before the subsequent dose is administered. This requires multiple daily dosing regimens which significantly increase the rate of patient non-compliance. First-pass metabolism is another barrier; for many orally administered drugs, rapid delivery of a bolus to the liver leads to extensive presystemic degradation and consequently low bioavailability. To circumvent these issues, modified release technologies—specifically Sustained Release (SR) matrix tablets—have been extensively engineered. By precisely controlling the rate of API release over an extended period, these systems optimize the therapeutic index, maximize patient convenience, and ensure consistent therapeutic outcomes without dangerous fluctuations in drug blood levels.

Propranolol Hydrochloride (Propranolol HCl) is a non-selective beta-adrenergic receptor blocking agent that has been in clinical use for over 50 years and remains one of the most extensively prescribed antihypertensive agents globally. It competitively blocks both beta-1 (cardiac) and beta-2 (bronchial, vascular, metabolic) adrenergic receptors, reducing heart rate, myocardial contractility, and systolic blood pressure. Despite its well-established clinical efficacy, conventional IR formulations of Propranolol HCl suffer from severe pharmacokinetic drawbacks. The drug exhibits a very short biological half-life ranging from 3 to 6 hours, mandating administration two to four times daily. Such regimens predictably result in poor patient compliance, particularly among the elderly managing complex polypharmacy. Moreover, while its gastrointestinal absorption is nearly 90%, its oral bioavailability is heavily compromised (only 25-35%) due to massive first-pass extraction by the liver via the cytochrome P450 enzymes CYP2D6 and CYP1A2. The IR tablets produce marked peak-to-trough plasma fluctuations where peak concentrations cause symptomatic bradycardia and hypotension, while trough concentrations risk rebound hypertension and breakthrough angina.

Hydrophilic matrix systems, particularly those utilizing Hydroxypropyl Methylcellulose (HPMC), represent the most commercially successful platform for resolving these issues. When a hydrophilic matrix tablet contacts gastrointestinal fluids, the polymer rapidly hydrates, swells, and forms a viscous gel layer. This layer serves as a physical barrier regulating water ingress and dissolved drug egress. The relative contributions of Fickian diffusion and polymer matrix erosion dictate the overall release kinetics. By manipulating HPMC viscosity grades (such as K4M and K15M) and polymer concentrations, pharmaceutical formulators can engineer the release profile to target a constant (zero-order) release over 12 to 24 hours. Formulating Propranolol HCl as an SR matrix tablet not only ensures patient compliance through once- or twice-daily dosing but also dampens inter-patient variability and mitigates dose-dependent adverse effects.

Equally critical to formulation development is the establishment of a robust analytical methodology. An unvalidated or poorly validated analytical method can generate unreliable data, leading to incorrect conclusions regarding drug content, release kinetics, and long-term stability. The International Council for Harmonisation (ICH) guideline Q2(R1) provides the strict regulatory framework for analytical method validation. The present investigation was specifically designed with dual objectives: (1) to systematically develop and comprehensively

validate a UV-Visible spectrophotometric method for the quantitative determination of Propranolol HCl in strict compliance with ICH Q2(R1), and (2) to design, optimize, and thoroughly evaluate HPMC-based sustained release matrix tablets of Propranolol HCl. The research encompasses preformulation profiling, in-vitro dissolution kinetic modeling, and accelerated stability assessments.

2. Review of Literature

The development of sustained-release drug delivery systems for Propranolol Hydrochloride is a well-documented domain in pharmaceutical research. A comprehensive review of historical milestones and contemporary research establishes the state-of-the-art in both analytical methodologies and formulation technologies, enabling the identification of critical research gaps and opportunities for optimization.

In the realm of analytical method development, the precision of pharmaceutical research is contingent upon the reliability of quantification techniques. Wankhede et al. (2011) successfully developed a simple UV spectrophotometric method for the simultaneous estimation of Propranolol HCl, observing linearity in the 5–30 µg/mL range with a correlation coefficient of 0.9999. Their method validated accuracy, precision, and robustness per ICH guidelines, confirming its suitability for routine quality control. Similarly, Reddy and Rao (2012) optimized a cost-effective UV method utilizing distilled water as the primary solvent, recording an absorption maximum at 290 nm and validating parameters within specified limits. More complex techniques have also been explored; Sharma et al. (2013) developed an RP-HPLC method for simultaneous determination of Propranolol HCl and Hydrochlorothiazide, while Patel et al. (2016) reported a robust stability-indicating HPLC method capable of resolving the drug from various forced degradation products. These studies collectively confirm that while HPLC provides excellent specificity for stability testing, highly optimized and validated UV spectrophotometry remains a highly practical, cost-effective, and sufficiently sensitive technique for routine formulation assay and in-vitro dissolution profiling.

Parallel to analytical advancements, extensive research has been conducted on the formulation dynamics of Propranolol SR systems. Khan et al. (2010) established the cornerstone for hydrophilic matrix approaches, demonstrating that drug release decreases progressively with increasing HPMC concentration and higher viscosity grades. Their study of wet-granulated tablets revealed that a 40% HPMC K15M formulation could achieve near-zero-order release over 12 hours, with release kinetics fitting the Korsmeyer-Peppas model via anomalous non-Fickian diffusion. Kumar and Mishra (2012) later investigated hybrid matrices, combining hydrophilic (HPMC K100M) and hydrophobic (Ethyl Cellulose) polymers. They proved that blending these polymers creates a synergistic effect that tempers water penetration, pushing the release profile closer to zero-order kinetics. Focusing on process engineering, Jain et al. (2015) identified that granulation parameters—specifically granule size and compression force—are as critical as polymer composition in controlling SR performance. Smaller granules provided a larger surface area accelerating release, while higher compression forces reduced tablet porosity and increased the tortuosity of diffusion pathways, effectively retarding release.

The implementation of Quality by Design (QbD) has also shaped modern SR development. Rao and Murthy (2017) utilized Box-Behnken designs to define a design space for Propranolol SR tablets, identifying granulation end-point and compression force as Critical Process Parameters (CPPs) impacting drug release. Furthermore, Mishra et al. (2020) highlighted the industrial shift toward direct compression to reduce the manufacturing footprint associated with wet granulation, relying heavily on specific excipient grades like Avicel PH 102. To establish predictive performance, Gao et al. (2014) developed a Level A In Vitro-In Vivo Correlation (IVIVC) for Propranolol extended-release capsules, proving that robust in-vitro dissolution data can act as a reliable surrogate for in-vivo bioequivalence, given the drug's BCS Class I status.

Despite these extensive investigations, a synthesis of the literature reveals a significant integration gap: the vast majority of studies focus exclusively on either analytical validation or formulation design in isolation. There is a marked scarcity of research that treats ICH-compliant analytical method development as a parallel, heavily

integrated pillar of the SR formulation lifecycle. The present study addresses this gap by simultaneously establishing a rigorously validated UV method and applying it to systematically evaluate the transition from HPMC K4M to HPMC K15M polymer matrices via wet granulation, rigorously applying kinetic modeling to elucidate the underlying mass transport mechanisms.

3. Materials and Methods

3.1 Materials

Propranolol Hydrochloride (IP/USP) was procured as the Active Pharmaceutical Ingredient (API) with a verified purity of ≥ 99.0%. Hydroxypropyl Methylcellulose grades HPMC K4M (viscosity ~4,000 mPa·s) and HPMC K15M (viscosity ~15,000 mPa·s) were utilized as the primary hydrophilic rate-controlling polymers. Microcrystalline Cellulose (Avicel PH 102) and Lactose Monohydrate were used as diluents and dry binders. Polyvinylpyrrolidone (PVP K30) was employed as a polymeric binder for wet granulation. Magnesium Stearate was selected as a boundary lubricant, while Talc and Colloidal Silicon Dioxide (Aerosil) served as glidants. All reagents, including Hydrochloric Acid and Phosphate buffer components, were of analytical grade.

3.2 Preformulation Studies

Preformulation assessments were systematically conducted to determine the physicochemical behavior and stability of the API. Organoleptic characterization evaluated physical state, color, odor, and taste against pharmacopoeial monographs. Solubility was determined via the saturation shake-flask method at 25 ± 0.5°C across various physiologically relevant media (Water, 0.1N HCl, pH 4.5, 6.8, and 7.4 buffers) to predict gastrointestinal behavior. Melting point was assessed using the digital capillary method (n=3) to confirm drug purity and crystalline integrity.

Ultraviolet (UV) spectrophotometric scanning of a 10 µg/mL API solution in 0.1N HCl was performed across the 200–400 nm range to determine the wavelength of maximum absorption (λmax). Drug-excipient compatibility was rigorously evaluated using Fourier Transform Infrared (FTIR) spectroscopy via the KBr pellet technique, analyzing both the pure drug and 1:1 binary physical mixtures to detect any deleterious chemical interactions. Micromeritic properties of the powder blends—specifically Bulk Density, Tapped Density, Carr's Compressibility Index, Hausner's Ratio, and Angle of Repose—were calculated to establish flowability and validate the requirement for wet granulation.

3.3 Analytical Method Development and Validation (ICH Q2(R1))

An analytical method was developed and strictly validated according to the International Council for Harmonisation (ICH) Q2(R1) guidelines. A standard stock solution of 1000 µg/mL was prepared by dissolving 100 mg of Propranolol HCl in 0.1N HCl, subsequently diluted to create working standards. Absorbance was measured at the identified λmax of 220 nm.

The validation protocol encompassed several parameters. Specificity was verified by analyzing a placebo solution containing all excipients to ensure zero absorbance interference at 220 nm. Linearity was assessed over six concentration levels (4, 8, 12, 16, 20, 24 µg/mL) to construct a calibration curve and determine the correlation coefficient (r^2). Accuracy was evaluated using the spike-and-recovery (standard addition) method at 80%, 100%, and 120% of the target analytical concentration (12 µg/mL). Precision was determined via Intraday (repeatability) and Interday (intermediate precision) studies, calculating the Relative Standard Deviation (%RSD). Sensitivity was defined by calculating the Limit of Detection (LOD) and Limit of Quantitation (LOQ) using standard deviation of intercepts (σ) and mean slopes (S). Finally, robustness was confirmed by deliberately varying analytical parameters such as wavelength (±2 nm) and solvent normality.

3.4 Formulation Design and Matrix Engineering

Seven distinct sustained release matrix tablet formulations (F1–F7) were engineered. Each tablet was designed to weigh 400 mg and contain exactly 80 mg of Propranolol HCl. To evaluate the impact of polymer viscosity and density on drug release, the total HPMC concentration was maintained at a constant 120 mg (30% w/w) per tablet, but the ratio of HPMC K4M to HPMC K15M was systematically shifted from 100:0 in formulation F1 to 0:100 in formulation F7. The detailed composition of these batches is delineated in Table 1.

Table 1: Formulation Composition of SR Tablets of Propranolol HCl (mg/tablet)

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7
Propranolol HCl	80	80	80	80	80	80	80
HPMC K4M	120	100	80	60	40	20	0
HPMC K15M	0	20	40	60	80	100	120
MCC (Avicel PH 102)	120	120	120	120	120	120	120
Lactose Monohydrate	60	60	60	60	60	60	60
PVP K30 (Binder)	8	8	8	8	8	8	8
Magnesium Stearate	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4
Colloidal SiO_2	4	4	4	4	4	4	4
Total Weight (mg)	**400**	**400**	**400**	**400**	**400**	**400**	**400**
K4M : K15M Ratio	**100:0**	**83:17**	**67:33**	**50:50**	**33:67**	**17:83**	**0:100**

3.5 Manufacturing Process

Tablet manufacturing was executed via a standardized wet granulation process to ensure optimal binder distribution and mechanical inter-particulate bonding. Initially, Propranolol HCl, HPMC K4M, HPMC K15M, MCC, and a portion of lactose were passed through a 40-mesh sieve and dry-blended in a planetary mixer for 10 minutes. A 10% w/v binder solution of PVP K30 in isopropyl alcohol (IPA) was incrementally added to form a coherent wet mass. The mass was sized and subsequently dried in a hot air oven at 50 ± 5°C for 2–3 hours until a Loss on Drying (LOD) of ≤ 2% was achieved. The dried granules were sized through a 20-mesh sieve. In the final blending step, the remaining MCC and lactose were incorporated, followed by the addition of pre-sifted (60-mesh) lubricants (Magnesium Stearate) and glidants (Talc, Colloidal SiO_2). The lubricated blend was compressed into tablets on a multi-station rotary press utilizing 10 mm flat-faced round punches, with compression force calibrated to yield a target hardness of 7–9 kg/cm².

3.6 Post-Compression Performance Evaluation

Post-compression quality control assessments were rigorously applied. Tablets were visually inspected for defects. Thickness and diameter were evaluated using digital Vernier calipers (n=10). Tablet hardness, representing mechanical crushing strength, was tested using a Monsanto hardness tester (n=10). Friability was analyzed utilizing a Roche friabilator at 25 rpm for 4 minutes (100 rotations), with a maximum acceptable weight loss of 1.0%. Uniformity of weight was checked according to USP monographs (n=20). The resistance to initial disintegration was validated in a USP disintegration apparatus using 0.1N HCl. Drug content uniformity was

assayed by powdering ten tablets, extracting the equivalent of 80 mg API in 0.1N HCl via sonication, filtering, and measuring UV absorbance at 220 nm, requiring results between 95–105% of the theoretical claim.

3.7 In-Vitro Dissolution Studies and Kinetic Modeling

In-vitro drug release profiles were established using a USP Type II (Paddle) dissolution apparatus. The testing medium consisted of 900 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5°C with a paddle rotation speed of 50 rpm. Testing was conducted over a 12-hour period (n=6). Aliquots were withdrawn at predetermined intervals (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours), filtered, diluted appropriately, and analyzed using the validated UV spectrophotometric method. To maintain sink conditions, an equal volume of fresh, pre-warmed medium was immediately replaced into the vessel after each sampling.

To elucidate the underlying mass transport mechanisms, the cumulative dissolution data were mathematically fitted into multiple kinetic models: Zero-Order (concentration independent), First-Order (concentration dependent), Higuchi (square-root of time Fickian diffusion), and the Korsmeyer-Peppas power law equation ($Mt/M\infty = kt^n$). In the Korsmeyer-Peppas model, the release exponent 'n' serves as the primary indicator of the release mechanism: $n \leq 0.45$ signifies pure Fickian diffusion; $0.45 < n < 0.89$ signifies anomalous (non-Fickian) transport driven by both diffusion and polymer relaxation; and $n \geq 0.89$ signifies Case-II zero-order transport driven strictly by polymer erosion.

3.8 Accelerated Stability Studies

To ensure product shelf-life and confirm matrix resilience against environmental stress, the optimized formulation (F4) was subjected to short-term accelerated stability testing in strict adherence to ICH Q1A(R2) guidelines. Tablets were packaged in high-density polyethylene (HDPE) bottles with desiccants and stored in a stability chamber maintained at 40°C ± 2°C and 75% ± 5% Relative Humidity (RH). Samples were withdrawn at 0, 1, 2, and 3 months and re-evaluated for physical appearance, hardness, residual drug content, and 12-hour cumulative dissolution performance.

4. Results and Discussion

4.1 Preformulation Studies

The preformulation phase successfully established the foundational physical properties of Propranolol HCl. Organoleptic analysis confirmed a white, odorless, bitter-tasting crystalline powder that strictly aligned with standard pharmacopoeial monographs. The melting point was recorded sharply between 163–165°C, matching the official 161–165°C range and confirming the absence of substantial polymorphic impurities or degradation. Solubility analyses revealed the drug was freely soluble (>100 mg/mL) in water, 0.1N HCl, and pH 6.8 and 7.4 buffers. This high aqueous solubility across physiological pH environments validates its BCS Class I classification, ensuring that drug dissolution is not a rate-limiting step; rather, release is governed almost entirely by the integrity of the HPMC matrix.

The UV spectrophotometric scan of the API in 0.1N HCl yielded a distinct maximum absorption peak (λmax) at 220 nm, which was selected for all quantitative assays due to its high molar absorptivity and sensitivity. The FTIR spectrum of pure Propranolol HCl displayed characteristic functional group peaks: a broad peak at 3380 cm^{-1} corresponding to N–H and secondary O–H stretching vibrations, aliphatic C–H stretching at 2980 cm^{-1}, aromatic ring C=C stretching at 1630 cm^{-1}, and C–O–C aryl ether stretching at 1250 cm^{-1}. Crucially, FTIR spectra of 1:1 physical mixtures of the drug with HPMC and other excipients revealed no significant peak shifts or disappearance of functional group signatures, definitively confirming chemical compatibility throughout the matrix formulation.

Micromeritic evaluation of the bulk API powder yielded a Bulk Density of 0.46 ± 0.02 g/cm³ and a Tapped Density of 0.60 ± 0.02 g/cm³. These parameters translated to a Carr's Compressibility Index of 23.3% and a Hausner's Ratio of 1.30, while the Angle of Repose was calculated at 29.6°. These indices classify the powder as having 'passable' to 'fair' flow properties. Since direct compression typically demands excellent flow dynamics to ensure rapid, uniform die-filling during high-speed manufacturing, these results firmly justified the adoption of the wet granulation technique to improve inter-particulate cohesion and overall powder flow. The summary of preformulation results is presented in Table 2.

Table 2: Summary of Preformulation Study Results

S.No.	Parameter	Observed Result	Interpretation
1	**Appearance**	White crystalline powder	Complies with IP/USP
2	**Melting Point**	163–165°C	Matches IP/USP
3	**Solubility (Water)**	Freely soluble (>100 mg/mL)	Suitable for SR matrix
4	**Solubility (pH 6.8)**	Freely soluble	Stable in intestinal pH
5	**UV λmax (0.1N HCl)**	220 nm	Selected for assay
6	**FTIR Peaks**	3380, 2980, 1630, 1250 cm^{-1}	Confirms drug identity
7	**Drug-Excipient Compat.**	No significant peak shifts	Highly compatible
8	**Carr's Index**	23.3 ± 0.8 %	Passable flow
9	**Hausner's Ratio**	1.30 ± 0.02	Passable compressibility
10	**Angle of Repose**	29.6 ± 0.8 °	Good to fair flow

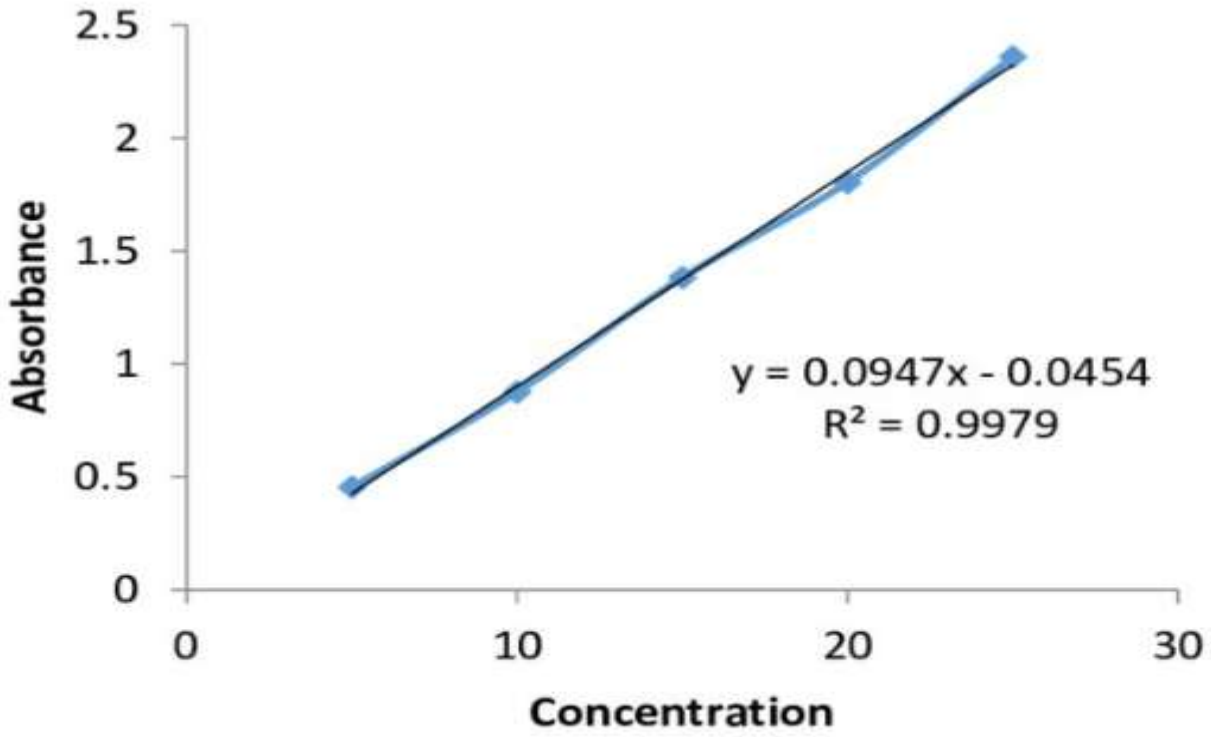
4.2 Analytical Method Validation (ICH Q2(R1))

The proposed UV spectrophotometric method was meticulously validated. The calibration curve constructed from six standard concentrations (2, 4, 8, 12, 16, 20, 24 µg/mL) demonstrated exceptional linearity. The regression analysis yielded the equation $y = 0.0315x + 0.0002$ with a correlation coefficient (r^2) of 0.9999. The robust r^2 value indicates a virtually perfect linear relationship adhering to the Beer-Lambert law, while the near-zero intercept (0.0002) confirms the absence of systematic instrumental bias or baseline drift.

Specificity testing revealed that the placebo formulation exhibited negligible absorbance (<0.005) at 220 nm, ensuring that HPMC and other excipients do not optically interfere with API quantification. Accuracy, evaluated via spike-and-recovery, returned mean percentage recoveries of 99.8%, 100.1%, and 99.6% at the 80%, 100%, and 120% target levels, respectively. These values fall strictly within the 98–102% acceptance criterion, proving the method's capability to measure the exact true value without bias. Precision was equally robust; intraday repeatability showed a relative standard deviation (%RSD) of 0.61%, and interday intermediate precision yielded an %RSD of 0.78%—both well below the stringent 2.0% ICH limit. Method sensitivity was mathematically established with a Limit of Detection (LOD) of 0.14 µg/mL and a Limit of Quantitation (LOQ) of 0.43 µg/mL, granting the capability to accurately track early-stage dissolution traces. Finally, robustness testing involving deliberate minor fluctuations in wavelength (±2 nm) and solvent normality resulted in %RSDs below 1.1%, validating the method's resilience in practical laboratory environments. These validation parameters are summarized in Table 3.

Table 3: ICH Q2(R1) Validation Parameters for UV Method (λmax = 220 nm)

Validation Parameter	Result	Acceptance Criterion	Status
Specificity	Placebo < 0.005 AU	No interference at 220 nm	**Pass**
Linearity (r^2)	0.9999	≥ 0.999	**Pass**
Linearity Range	2 – 24 µg/mL	Spans 80–120% of target	**Pass**
Regression Equation	y = 0.0315x + 0.0002	Near-zero intercept	**Pass**
Accuracy (80% level)	99.8 ± 0.42 %	Recovery between 98–102%	**Pass**
Accuracy (100% level)	100.1 ± 0.38 %	Recovery between 98–102%	**Pass**
Accuracy (120% level)	99.6 ± 0.45 %	Recovery between 98–102%	**Pass**
Intraday Precision	0.61 % RSD	≤ 2.0 %	**Pass**
Interday Precision	0.78 % RSD	≤ 2.0 %	**Pass**
LOD / LOQ	0.14 / 0.43 µg/mL	Reported Value	**Pass**
Robustness (Wavelength)	0.92 % RSD	≤ 2.0 %	**Pass**



4.3 Post-Compression Tablet Evaluation

The formulated wet granules exhibited excellent flow properties, facilitating smooth operation on the rotary press. All seven matrix formulations (F1–F7) produced physically robust, visually impeccable white, biconvex tablets completely free of lamination, capping, or picking defects. Dimensional analysis revealed a slight, systematic increase in tablet thickness from formulation F1 (4.12 ± 0.06 mm) to formulation F7 (4.24 ± 0.06

mm). This incremental expansion directly correlates with the increasing mass fraction of HPMC K15M, a polymer known to possess a slightly higher bulk volume compared to the lower molecular weight K4M grade. The tablet diameter remained highly consistent across all batches (10.01 – 10.03 mm), validating the uniformity of die-filling dynamics.

Mechanical integrity is a vital prerequisite for matrix tablets, as excessive friability or insufficient hardness can precipitate premature matrix erosion and catastrophic 'dose dumping'. Hardness values were calibrated and maintained within the target operational range of 7.3 to 8.3 kg/cm², ensuring an optimal balance between structural rigidity and the necessary matrix porosity required for fluid ingress. Friability testing underscored this mechanical resilience; all batches experienced a minute weight loss ranging strictly from 0.35% to 0.48%, dramatically outperforming the standard 1.0% pharmacopoeial threshold and confirming the tablets' ability to withstand post-production handling, packaging, and transit shocks. Uniformity of weight complied effortlessly with USP monographs, with no tablet deviating beyond ±5% of the theoretical average weight (400 mg). Similarly, UV-based drug content uniformity assays confirmed exceptionally homogenous distribution of the API within the polymeric network, returning values tightly clustered between 98.9% and 99.8%. Furthermore, in strict alignment with sustained release design parameters, all seven formulations completely resisted immediate disintegration in acidic media for well beyond 12 hours, relying instead on continuous surface gelation. These comprehensive post-compression metrics are delineated in Table 4.

Table 4: Post-Compression Evaluation Parameters of SR Tablets F1–F7 (Mean ± SD)

Parameter	F1	F2	F3	F4	F5	F6	F7
Thickness (mm)	4.12	4.14	4.16	4.18	4.20	4.22	4.24
Hardness (kg/cm²)	7.3	7.5	7.6	7.8	8.0	8.1	8.3
Friability (%)	0.48	0.45	0.42	0.41	0.39	0.37	0.35
Avg. Weight (mg)	400.2	399.8	400.5	400.1	399.6	400.3	399.9
Drug Content (%)	98.9	99.2	99.4	99.5	99.6	99.8	99.7

4.4 In-Vitro Drug Release Studies

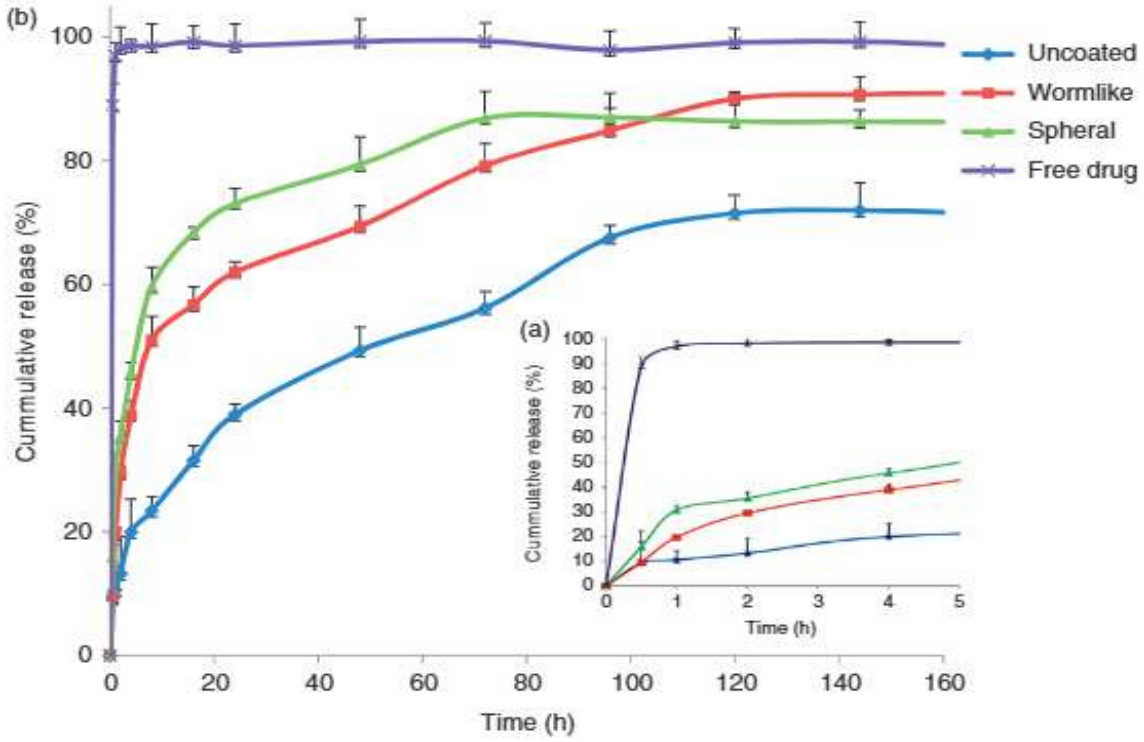
In-vitro dissolution profiles form the crux of SR formulation evaluation, serving as a primary surrogate for in-vivo pharmacokinetic behavior. The USP Type II paddle tests conducted in pH 6.8 phosphate buffer over 12 hours unmasked a profound, highly systemic relationship between the ratio of HPMC viscosity grades and the resulting drug release kinetics. At the beginning of the dissolution cycle (0–1 hour), a minor but consistent 'burst effect' was noted across all formulations (ranging from 18.5% in F1 to 10.7% in F7). This initial release is a well-documented phenomenon in hydrophilic matrices, caused by the rapid dissolution of drug particles situated at the immediate surface of the tablet before the full continuous gel layer has the physical time to properly hydrate and coalesce. However, this burst was effectively muted and remained within therapeutically safe boundaries, averting the risk of initial cardiovascular toxicity.

As continuous hydration progressed, the distinct properties of the HPMC grades dominated the transport process. Formulation F1, engineered entirely with HPMC K4M, exhibited the most rapid release trajectory, discharging 96.2% of its drug load by the 12-hour mark. Because K4M possesses a relatively low molecular weight and

viscosity (4,000 mPa·s), it generates a highly porous, physically looser gel layer that presents minimal diffusional resistance to the highly soluble Propranolol HCl. Conversely, as the mass fraction of the high-viscosity HPMC K15M was progressively escalated from F2 through F7, a dramatic retardation in the release rate was logged. HPMC K15M (15,000 mPa·s) is characterized by significantly longer cellulose chains that experience extensive physical entanglement upon hydration. This entanglement breeds a drastically thicker, more robust, and less permeable gel barrier that aggressively resists both water ingress and drug outward diffusion. Consequently, formulation F7, containing exclusively HPMC K15M, demonstrated the slowest profile, releasing a mere 73.2% of the API at 12 hours. The intermediate blends achieved a highly predictable titration of release rates. The detailed cumulative percentage drug release trajectory for all batches is captured in Table 5.

Table 5: Cumulative Percentage Drug Release Profile over 12 Hours (n=6, Mean ± SD)

Time (h)	F1	F2	F3	F4	F5	F6	F7
0.5	10.2	9.5	8.8	8.1	7.4	6.8	6.2
1	18.5	17.2	15.8	14.6	13.2	11.9	10.7
2	30.4	28.6	26.3	24.1	21.9	19.8	17.5
4	52.3	49.4	46.0	42.8	38.9	35.1	31.0
6	68.5	65.1	61.2	57.4	52.8	47.6	42.3
8	80.4	77.3	73.5	69.8	64.8	59.2	53.6
10	89.6	87.1	83.8	80.2	75.4	70.1	63.8
12	96.2	93.8	91.4	88.5	84.2	79.6	73.2



4.5 Drug Release Kinetics and Modeling

To decode the exact mass transport mechanisms governing the release of Propranolol HCl from the matrices, the empirical dissolution data were subjected to rigorous mathematical modeling. Across the board, all seven formulations exhibited their highest correlation coefficients (r^2) when fitted to the Korsmeyer-Peppas power law model (r^2 values uniformly ranging from 0.9951 to 0.9988). This strongly confirms that release is driven by a complex interplay of diffusion and polymer swelling, which is the hallmark of HPMC matrix systems.

A critical evaluation of the Korsmeyer-Peppas release exponent 'n' provided profound insight into the physical state of the hydrating tablets. The 'n' values escalated systematically from 0.48 in F1 to 0.78 in F7. In formulation F1 (100% K4M), the n value of 0.48 indicates that drug transport is heavily skewed toward near-Fickian diffusion; the drug rapidly diffuses out through the relatively loose gel network before the polymer itself undergoes significant structural relaxation or erosion. Conversely, as K15M is heavily incorporated, the 'n' value climbs into the anomalous (non-Fickian) transport regime ($0.45 < n < 0.89$). In formulation F7 ($n = 0.78$), the thicker, more rigid K15M gel layer violently restricts diffusion, forcing the release mechanism to become increasingly dependent on the physical swelling, relaxation, and eventual erosive sloughing of the polymer chains themselves (approaching Case-II transport).

Among the tested ratios, Formulation F4 (comprising an exact 50:50 ratio of HPMC K4M to K15M, translating to 60 mg of each per tablet) was unequivocally identified as the optimized formulation. It delivered an ideal 88.5% cumulative drug release perfectly spread across the 12-hour window. Crucially, kinetic analysis of F4 revealed an 'n' value of 0.61 coupled with a remarkably high Zero-Order regression coefficient ($r^2 = 0.9762$). This signifies that the blending of the fast-diffusing K4M and the erosion-resistant K15M created a perfectly synchronized matrix where the rate of diffusion precisely matched the rate of matrix swelling. The result is a near-linear, zero-order release profile capable of maintaining exceptionally constant plasma drug concentrations in vivo, thereby fulfilling the ultimate objective of the SR design. The comprehensive kinetic parameters are cataloged in Table 6.

Table 6: Drug Release Kinetics Modeling Parameters (Correlation Coefficients and Exponents)

Batch	Zero Order	First Order	Higuchi	K-P (r^2)	Best Fit	n value	Mechanism
F1	0.9612	0.9782	0.9924	0.9951	K-Peppas	**0.48**	Near-Fickian
F2	0.9654	0.9801	0.9918	0.9963	K-Peppas	**0.52**	Anomalous
F3	0.9708	0.9834	0.9911	0.9971	K-Peppas	**0.56**	Anomalous
F4*	0.9762	0.9861	0.9903	0.9978	K-Peppas	**0.61**	Anomalous / Zero
F5	0.9824	0.9889	0.9894	0.9983	K-Peppas	**0.66**	Anomalous
F6	0.9878	0.9912	0.9882	0.9986	K-Peppas	**0.72**	Anomalous
F7	0.9921	0.9934	0.9871	0.9988	K-Peppas	**0.78**	Near Case-II

4.6 Accelerated Stability Studies

The clinical and commercial viability of any pharmaceutical formulation hinges fundamentally on its long-term stability. The optimized formulation (F4) was subjected to rigorous short-term accelerated stability testing inside an environmental chamber programmed to 40°C ± 2°C and 75% ± 5% Relative Humidity for a continuous duration of 3 months, in accordance with the ICH Q1A(R2) regulatory standards. This high heat and humidity environment acts as an aggressive stress test, designed to drastically accelerate chemical degradation (like hydrolysis) or physical matrix failures (such as premature polymer cross-linking or moisture-induced plasticization).

The data generated over the 3-month observation window overwhelmingly confirmed the resilience of the F4 formulation. Visual and tactile inspections revealed zero alterations in the physical appearance of the tablets; they remained intact, bright white, and exhibited no signs of mottling, sticking, or structural deformation. Tablet hardness experienced a clinically negligible decline from an initial 7.8 kg/cm² to 7.6 kg/cm², a shift that remains well within the strict standard operating parameters and does not compromise the tablet's mechanical defenses. Chemical stability was impeccably maintained; the residual drug content assay dipped only slightly from 99.5% at baseline to 98.9% at the 3-month mark. This variance is statistically insignificant and remains safely bracketed within the 95–105% pharmacopoeial acceptance limits, categorically proving that Propranolol HCl is chemically stable when nested inside the HPMC and MCC excipient matrix, even under harsh thermal stress.

Crucially, the functional stability of the SR system—its ability to release the drug at the intended, controlled rate—was entirely preserved. The cumulative drug release over 12 hours shifted marginally from an initial 88.5% down to 87.4% by the third month. This proves that the hydrophilic HPMC polymers did not undergo deleterious moisture-induced glass transition or structural hardening during storage, maintaining their critical capacity to form the specific viscosity gel layer required for anomalous transport. The complete stability metrics are documented in Table 7.

Table 7: Accelerated Stability Metrics for Optimized Formulation F4 (40°C / 75% RH)

Evaluated Parameter	Initial Baseline	End of 1 Month	End of 2 Months	End of 3 Months
Physical Appearance	White, intact	No change	No change	No change
Tablet Hardness (kg/cm²)	7.8 ± 0.21	7.7 ± 0.19	7.7 ± 0.22	7.6 ± 0.24
Drug Content Assay (%)	99.5 ± 0.42	99.3 ± 0.38	99.1 ± 0.40	98.9 ± 0.44
Cum. % Release (12 hrs)	88.5 ± 2.5	88.2 ± 2.6	87.8 ± 2.7	87.4 ± 2.8

5. Future Prospects

The successful development and analytical validation of this HPMC-based matrix tablet open multiple advanced translational pathways. Given the well-documented circadian rhythm of cardiovascular emergencies—specifically the dangerous spike in blood pressure and myocardial infarctions during the early morning hours—future research could pivot this SR formulation toward Chronotherapeutic Drug Delivery. By modifying the outer polymer coatings, the system could be engineered as a delayed-pulsatile release tablet taken at bedtime, programmed to release its maximum Propranolol load just prior to awakening. Furthermore, transitioning from traditional wet granulation to advanced Quality by Design (QbD) optimization, combined with continuous

manufacturing paradigms or 3D pharmaceutical printing, could allow for highly personalized dosing modifications. Most immediately, the robust in-vitro kinetic data acquired here sets the foundational baseline required to establish a Level A In Vitro-In Vivo Correlation (IVIVC), paving the way for targeted human pharmacokinetic trials and regulatory bioequivalence submissions.

6. Summary and Conclusion

This comprehensive investigation successfully converged the rigorous demands of analytical method validation with the complex materials science required to engineer a sustained-release drug delivery system. The research accomplished two primary directives: (1) the creation of a highly sensitive, universally accessible UV-Visible spectrophotometric assay for Propranolol Hydrochloride, and (2) the formulation and kinetic optimization of HPMC-driven hydrophilic matrix tablets designed to mitigate the severe pharmacokinetic limitations inherent to conventional IR beta-blocker therapy.

The developed analytical method (utilizing 0.1N HCl at 220 nm) was subjected to an exhaustive validation protocol matching the strict ICH Q2(R1) international standards. Demonstrating flawless linearity ($r^2 = 0.9999$), remarkable precision (%RSD < 1.0%), unquestionable accuracy (98–102% recovery), and excellent robustness, the assay proves perfectly suited for highly reliable, routine quality control and complex in-vitro dissolution tracking. Preformulation assessments confidently corroborated the API's compatibility with the selected excipient array, showing zero deleterious interactions via FTIR spectral screening and confirming that wet granulation was the most appropriate industrial process to manage the powder's fair flow metrics.

The formulation phase highlighted the immense regulatory and therapeutic potential of blended hydrophilic polymer systems. By systematically adjusting the ratio of medium-viscosity HPMC K4M to high-viscosity HPMC K15M, the drug release velocity was successfully customized. Mathematical kinetic modeling conclusively proved that higher ratios of K15M shift the mass transport mechanism away from simple Fickian diffusion and toward an anomalous, polymer-relaxation dependent pathway. Ultimately, Formulation F4—composed of an exact 1:1 synergistic blend of K4M and K15M—emerged as the superior candidate. It delivered an idealized, near-zero-order release profile, discharging 88.5% of its active payload gradually and evenly across a 12-hour physiological window. Furthermore, F4 demonstrated exceptional physical integrity and remained totally chemically inert and functionally stable under 3 months of severe accelerated environmental stress testing (40°C / 75% RH).

In clinical application, this optimized sustained-release tablet holds immense promise. By flattening the dangerous peak-to-trough plasma fluctuations caused by standard Propranolol tablets, formulation F4 can theoretically minimize the incidence of symptomatic bradycardia while completely preventing trough-triggered rebound hypertension. Most importantly, by extending the therapeutic dosing interval to 12 or 24 hours, this formulation directly tackles the most prominent barrier in chronic cardiovascular management: patient non-compliance. Ultimately, this research provides a highly reproducible, scientifically validated, and industrially scalable framework that is fully primed for subsequent in-vivo pharmacokinetic evaluation and eventual commercial pharmaceutical deployment.

7. References

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