Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 15 [1] December 2025. 19-28

Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Evaluation of Macitentan Pellets for Controlled Release

Abhay Kumar Mishra*, Rajasekaran S. **
1. Research Scholar, Department of Pharmaceutics, Bhagwant University, Ajmer, India-305023
2. Professor, Department of Pharmacology, Bhagwant University, Ajmer, India-305023
Corresponding Author Email Id: abhaymishrajnp608@gmail.com

ABSTRACT

Pulmonary arterial hypertension (PAH) is a progressive, life-threatening disorder characterized by elevated pulmonary vascular resistance leading to right heart failure. Macitentan, an endothelin receptor antagonist (ERA), is widely prescribed for long-term PAH management. Despite its efficacy, Macitentan exhibits low aqueous solubility, extensive first-pass metabolism, and fluctuating plasma concentrations when administered as conventional oral tablets. These pharmacokinetic limitations often compromise therapeutic consistency, reduce bioavailability, and necessitate frequent dosing. To overcome these challenges, the present research was undertaken to develop, optimize, and biopharmaceutically evaluate sustained-release (SR) Macitentan pellets capable of providing controlled and extended drug release for 24 hours. The study began with extensive preformulation studies, including physicochemical characterization, solubility profiling, and compatibility assessments using FTIR, DSC, and PXRD. These analyses confirmed the chemical stability of Macitentan with selected excipients such as microcrystalline cellulose (MCC), hydroxypropyl methylcellulose (HPMC), and ethyl cellulose (EC). The core pellets were prepared by extrusion–spheronization, using MCC as the spheronization aid and polyvinylpyrrolidone (PVP K-30) as the binder, yielding uniform spherical pellets (sphericity index > 0.95; friability < 0.5%). Subsequently, the pellets were coated with a hydrophilic–hydrophobic polymer blend (EC:HPMC) to modulate the drug-release kinetics. A Box–Behnken Design (BBD) employing three independent variables—polymer ratio (EC:HPMC), coating level (%), and spheronization time (min)—was applied to evaluate their combined effects on three critical responses: (Y_1) % drug release at 12 h, (Y_2) sphericity index, and (Y_3) friability. Response Surface Methodology (RSM) generated statistically significant models ($p < 0.05$; $R^2 > 0.98$) with strong predictive accuracy. The optimized formulation, containing EC:HPMC ≈ 3 : 1 and 10 % coating, demonstrated 75–80 % release at 12 h and > 95 % release within 24 h, following zero-order kinetics ($R^2 = 0.994$) and a Korsmeyer–Peppas exponent ($n = 0.68$) indicative of anomalous (diffusion-erosion) transport. In-vitro–in-vivo correlation (IVIVC) was established through in-silico pharmacokinetic simulation using PKSolver software, revealing that the SR pellets produced a prolonged plasma profile with reduced peak concentration (Cmax ↓ 27 %), extended Tmax, and increased mean residence time (MRT ↑ 1.8-fold) compared to immediate-release tablets. Stability studies performed as per ICH Q1A(R2) at 40 °C ± 2 °C / 75 % ± 5 % RH for three months confirmed the formulation's robustness, showing no significant change in assay, dissolution, or appearance ($f_2 = 68.7$). The developed system thus achieved controlled, reproducible, and stable drug release, ensuring sustained therapeutic plasma levels and potential once-daily dosing convenience. The combination of Quality by Design (QbD) principles, statistical optimization, and mechanistic evaluation enabled a rational design approach linking formulation parameters to biopharmaceutical outcomes. This study concludes that a multiparticulate Macitentan sustained-release pellet formulation optimized via Box–Behnken Design offers a promising platform for enhanced bioavailability, reduced dosing frequency, and improved patient compliance in PAH management. The approach provides a robust scientific framework applicable to other poorly soluble, highly metabolized drugs requiring controlled release delivery.

Keyword: *Macitentan; Sustained-release pellets; Controlled drug delivery; Extrusion–spheronization; Ethyl cellulose; Hydroxypropyl methylcellulose; Box–Behnken Design (BBD)*

Received 21.10.2025 Revised 20.11.2025 Accepted 25.12.2025

INTRODUCTION

The evolution of drug delivery systems (DDS) represents one of the most transformative developments in modern pharmaceutical science. The primary goal of any DDS is to transport an active pharmaceutical ingredient (API) to its site of action in a safe, effective, and predictable manner [1]. Traditionally, most drugs were administered as immediate-release formulations (e.g., tablets, capsules, syrups). While such forms are convenient, they often fail to maintain optimal therapeutic plasma concentrations, leading to peaks and troughs that can compromise both efficacy and safety [2]. Controlled release is a drug delivery

system designed to release a drug at a precise, predetermined rate, ensuring a consistent and controlled drug concentration within the therapeutic window over a specific time frame [3]. This minimizes fluctuations in plasma drug levels and maximizes therapeutic efficacy while reducing the risk of both underdosing and overdosing [4]. Controlled release systems employ advanced formulation strategies such as polymeric matrices, membrane-based devices, or osmotic pumps to maintain zero-order or specified release kinetics. The goal is to achieve optimal pharmacokinetic profiles with predictable, sustained medication levels [5]. sustained release, on the other hand, refers to systems formulated to prolong drug availability by gradually releasing active ingredients for an extended period. While sustained release helps maintain therapeutic concentrations and reduces dosing frequency, it generally does not guarantee strict control over the release rate [6]. These formulations often rely on matrices or coatings that slow down drug dissolution and absorption, leading to a steady but less precisely controlled drug release profile as compared to controlled release systems [7]. The release rate may taper off over time, possibly resulting in some fluctuations in plasma levels. Sustained release technologies are ideal for improving patient compliance, lowering dosing inconvenience, Conventional or immediate-release (IR) dosage forms—such as tablets, capsules, and injections—represent the oldest and most commonly used drug delivery approach [9]. Although simple and cost-effective, they possess significant limitations that affect therapeutic efficiency, patient compliance, and overall pharmacoeconomic value. The following points describe these drawbacks and their consequences in detail [10].

Many drugs have a short biological half-life (t½), meaning they are rapidly eliminated from the body through metabolism or excretion. For such molecules, therapeutic plasma concentrations are maintained only for a limited time after administration. Consequently, frequent dosing is required to sustain drug levels within the therapeutic window [11]. This frequent dosing regimen not only increases the risk of dose omission and patient non-compliance, but also leads to fluctuating plasma concentrations with alternating periods of sub-therapeutic and toxic levels. For chronic diseases such as hypertension or pulmonary arterial hypertension (PAH), where lifelong treatment is necessary, frequent dosing becomes impractical and inconvenient [12]. Drugs that undergo rapid systemic clearance through hepatic metabolism or renal excretion exhibit a sharp decline in plasma concentration after reaching their peak. This rapid elimination results in short duration of action and necessitates multiple doses per day to maintain efficacy [13]. The frequent peaks and troughs in drug concentration not only reduce therapeutic consistency but may also cause dose-related side effects during peak levels and loss of therapeutic effect during trough levels. For drugs with a narrow therapeutic index, such as anti-hypertensives or anticoagulants, these fluctuations can have serious clinical consequences [14]. According to the Biopharmaceutics Classification System (BCS), many modern drug molecules fall under Class II (low solubility, high permeability) or Class IV (low solubility and low permeability). For such drugs, dissolution and membrane permeation become rate-limiting steps for absorption [15]. Conventional dosage forms often fail to control these variables effectively, resulting in erratic absorption and variable bioavailability. Factors such as gastric pH, food intake, and intestinal transit time further influence absorption variability. Consequently, the plasma concentration achieved after a given dose can differ markedly among individuals, leading to unpredictable therapeutic responses [16].

For orally administered drugs, the first-pass effect (presystemic metabolism in the liver and intestinal wall) can significantly reduce the fraction of drug reaching systemic circulation. This is a critical limitation for drugs that are extensively metabolized before reaching the target site [17]. In conventional oral formulations, the entire dose is subject to this metabolic degradation immediately after absorption, leading to low bioavailability and reduced pharmacological effect. To compensate, higher doses are often administered, which can increase the risk of adverse effects and raise manufacturing costs. Over time, this inefficiency can make therapy less economical and less safe [18]. Frequent dosing schedules, large pill size, and adverse side effects all contribute to poor patient compliance. Non-adherence is particularly problematic in chronic conditions requiring lifelong therapy, where missed doses can result in therapeutic failure or disease relapse [19]. Furthermore, inconsistent dosing causes fluctuating plasma levels, which compromise steady-state attainment and diminish drug efficacy. From a clinical perspective, non-compliance is one of the most common causes of treatment failure in otherwise effective therapeutic regimens [20].

MATERIAL AND METHODS

Drug

- **Macitentan** (API) — obtained as gift sample from a certified pharmaceutical manufacturer.
- **Structure:** $C_{19}H_{20}Br_2N_6O_4S$
- **Molecular weight:** 588.27 g/mol

- **Description:** White to off-white crystalline powder; slightly soluble in ethanol, insoluble in water.

Table: 1 Excipients used and Their Functions

Excipient	Function	Grade Supplier
Microcrystalline cellulose (MCC PH 101)	Spherization aid, filler	FMC BioPolymer
Hydroxypropyl methylcellulose (HPMC K15M)	Matrix polymer (hydrophilic)	Colorcon
Ethyl cellulose (EC 10 cps)	Sustained-release polymer (hydrophobic)	Dow Chemicals
Polyvinylpyrrolidone (PVP K30)	Binder	BASF
Polyethylene glycol (PEG 4000) / Triethyl citrate	Plasticizer	Loba Chemie
Magnesium stearate	Lubricant	SD Fine Chemicals
Talc	Anti-adherent	Merck
Isopropyl alcohol / Water	Granulating solvent	Analytical grade

Table: 2 Batch Formulation according to drug excipient composition

Group	Main design change	API %	HPMC %	EC %	MCC %	PVP %	Coat	Coat type / notes
A	HPMC matrix (no coat)	10	30	0	56	3	No	—
B	HPMC + EC internal mix	10	15	15	58	2	No	—
C	Hydrophobic core + EC coat	10	0	12 (core)	70	2	Yes	EC coat at 5/10/15% w/w; plasticizer 10%
D	EC coat with HPMC pore former	10	0 (core)	12 (core)	70	2	Yes	Coat: EC + 10% HPMC in coat (poreformer)
E	Bimodal mix (IR + SR)	varied	varied	varied	varied	varied	Optional	IR pellet (~20% of dose) + SR pellet (~80%)
F	Plasticizer variation (coat)	10	0	12 (core)	70	2	Yes	Test TEC 5/10%, PEG 10%
G	Process variables	10	as per base	as per base	as per base	1.5–6	No	Vary spheronization & binder
H	Coat level screening	10	base	base	base	base	Yes	Coat weight gain 5/10/15%

Preformulation Studies

Preparation of standard calibration curve of Macitentan in 0.1 N HCl Standard calibration curve of Macitentan in 0.1 N HCL was prepared. Different concentrations of Macitentan 2, 4, 6, 8 and 10 µg/ml in 0.1 N HCl was prepared separately & absorbance of these prepared solutions were measured at the λmax of 231 nm spectrophotometrically using 0.1N HCL as reference solution.

Organoleptic and solubility studies were performed to obtain preliminary physicochemical characteristics of the drug. Organoleptic properties such as color, odor, and physical appearance were evaluated by visual inspection under daylight. Solubility was assessed qualitatively and quantitatively in distilled water, ethanol, methanol, and buffer solutions of pH 1.2, 6.8, and 7.4 by adding excess drug to the solvent, shaking in a mechanical shaker at room temperature, and analyzing the supernatant after filtration. Melting point determination was carried out using a digital melting point apparatus by the capillary method to assess purity and thermal stability. The pH of aqueous drug solutions was measured using a calibrated digital pH meter. The partition coefficient was determined using the shake-flask method in an n-octanol/water system, where the drug was equilibrated between the two phases, and the concentration in each layer was analyzed spectrophotometrically to evaluate lipophilicity. Compatibility studies were conducted to assess drug–polymer interactions. Fourier Transform Infrared (FTIR) spectroscopy was performed using an FTIR spectrophotometer by preparing KBr pellets and recording spectra over a range of 4000–400 cm^{-1}. Differential Scanning Calorimetry (DSC) analysis was carried out using a DSC instrument under a nitrogen atmosphere to study thermal behavior and possible interactions. X-Ray Diffraction (XRD) studies were conducted using an X-ray diffractometer to evaluate changes in crystallinity by recording diffraction patterns over a suitable 2θ range.

Drug-Excipient Solubility Profiling for Screening of Excipients

Drug-Excipient Solubility Profiling for Screening of Excipients Solubility of Macitentan was carried out by placing excess amount of drug in to 2 ml of solvent (Oil /Surfactant/Cosurfactant) in 5 ml glass vial with rubber closer. Vial containing Drug-solvent mixture was subjected to intense sonication for 30 min with

heating. The vial was kept unstirred for 48 hours to allow equilibrium in system. Supernatant was collected and centrifuged at 2000 RPM for 10 min to sediment undissolved drug present if any. 1 ml of post centrifugation supernatant was diluted up to 10 ml with methanol and evaluated by UV- Visible spectrophotometric method.

Drug–Excipient Compatibility Study

Purpose

To detect physical and chemical interactions between macitentan (API) and proposed excipients (MCC, HPMC, EC, PVP K30, lactose, talc, Mg stearate, TEC, PEG, surfactants, etc.) that could compromise product quality, stability, potency, dissolution, or safety during formulation development and storage.

Study strategy (overview)

1. Pre-screening (informal): Literature and functional-group risk assessment to prioritize excipients.
2. Binary (API:excipient) and ternary (API:excipient:excipient or API:polymer:plasticizer) stress tests — solid mixtures prepared at defined ratios.
3. Use orthogonal analytical techniques to detect interactions: stability-indicating HPLC (chemical assay/degradation products), FTIR, DSC, TGA, XRD, microscopy, and where available isothermal microcalorimetry.
4. Forced-degradation (chemical) studies on API alone to establish degradation profile and retention times for degradants.
5. Incubation under stressed conditions (temperature, humidity, light) and sampling at planned timepoints.
6. Data interpretation (compare to controls, quantify potency loss, identify new peaks/thermal shifts/crystallinity changes).
7. If an interaction is found, propose mitigation (different excipient, coating, antioxidants, pH modifiers) and repeat.

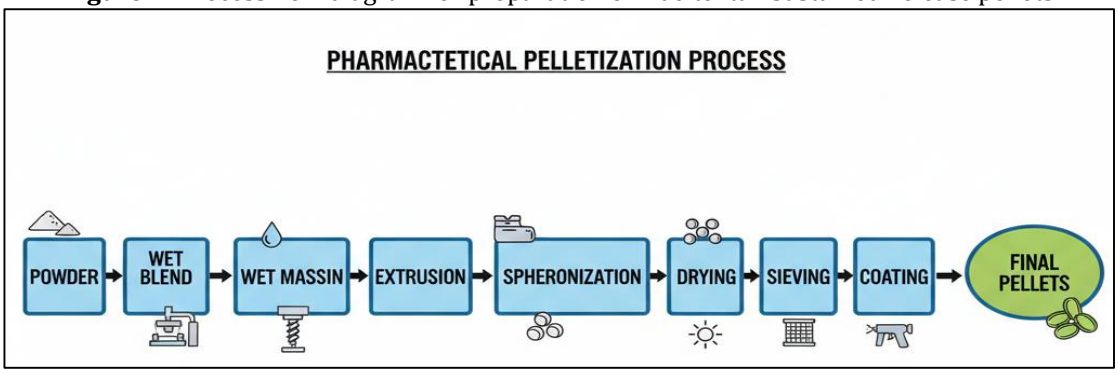
Preparation of Macitentan Pellets

Technique: Extrusion–spheronization (as per Figure 1).

Steps:

1. **Mixing:** Macitentan with MCC, HPMC, EC, and binder (PVP K30).
2. **Wet massing:** Gradual addition of granulating fluid (IPA:water = 70:30).
3. **Extrusion:** Using screw extruder (0.8 mm screen).
4. **Spheronization:** 1000 rpm for 10 min to obtain spherical pellets.
5. **Drying:** Fluid-bed dryer at 45 °C until moisture < 2 %.
6. **Screening:** Sieving to collect pellets 0.6–1.0 mm.
7. **Coating:** In a fluid-bed coater using polymeric dispersion (EC + HPMC + plasticizer).
8. **Curing:** At 40 °C for 24 h for film integrity.

Figure: 1 Process flow diagram for preparation of Macitentan sustained-release pellets



Experimental Design (Optimization)

Design: Box–Behnken (3-factor, 3-level).

Independent variables:

- X_1 = Polymer ratio (EC: HPMC)
- X_2 = Coating level (%)
- X_3 = Spherization time (min)

Dependent responses:

- Y_1 = % Cumulative release at 12 h
- Y_2 = Sphericity index
- Y_3 = Friability (%)

Software: Design-Expert® 13.0.

Polynomial model:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{23} X_2 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2$$

Response-surface plots (2D/3D) will identify optimal conditions.

In-Vitro Dissolution Study

- **Apparatus:** USP Type II (Paddle)
- **Medium:** 900 mL phosphate buffer pH 6.8 ± 0.05
- **Speed:** 100 rpm
- **Temperature:** 37 ± 0.5 °C
- **Sampling:** 1, 2, 4, 8, 12, 18, 24 h
- **Analysis:** UV at 296 nm (λmax)

Kinetic modeling: Data will be fitted to zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Weibull models. Best fit determined by correlation coefficient (R^2) ≥ 0.98.

In-Vivo Pharmacokinetic Study (Animal Model)

- **Species:** Male Wistar rats (200–250 g)
- **Group I:** Pure Macitentan suspension
- **Group II:** Optimized sustained-release pellets
- **Dose:** Equivalent to 10 mg/kg
- **Sampling:** 0.5–24 h, plasma collected via retro-orbital route
- **Quantification:** HPLC method (validated for linearity, accuracy, precision)

PK parameters: Cmax, Tmax, AUC_0–∞, t½, MRT, relative bioavailability (F%).

In-Vitro–In-Vivo Correlation (IVIVC)

1. **Deconvolution method** (Wagner–Nelson) to compute fraction absorbed (Fa).
2. **Fraction dissolved (Fd)** derived from in-vitro release.
3. **Level A IVIVC model:**

$$Fa = a \times Fd + b$$

Regression slope ≈ 1 and intercept ≈ 0 indicate good predictability (R^2 > 0.95).

Stability Studies

Conducted as per **ICH Q1A(R2)**:

- **Accelerated:** 40 °C ± 2 °C / 75 % ± 5 % RH (3 months)
- **Intermediate:** 30 °C ± 2 °C / 65 % ± 5 % RH (6 months)

Parameters monitored: appearance, drug content, and dissolution profile similarity factor (f_2 ≥ 50 = stable).

ICH Q1A(R2): Stability Testing of New Drug Substances and Products

Controls:API alone, excipient alone, and physical mixtures that have not been stressed (time-zero).

Stress / incubation conditions & timepoints

- **Thermal:** 60°C, dry oven — sample at 1 week and 2 weeks.
- **Humidity:** 40°C / 75% RH (controlled chamber) — sample at 1, 2 and 4 weeks.
- **Photostability:** ICH Q1B conditions (or an equivalent light chamber) — 1 week exposure.
- **Room temp (realistic):** 25°C / 60% RH — sample at 1, 3 months for confirmatory evidence.
- **Refrigerated (optional):** 5°C for long-term comparisons.

Analytical methods (orthogonal)

Stability-indicating HPLC (primary chemical test)

Purpose: detect API degradation and quantify potency and degradants.

- Column: C18, 150 × 4.6 mm, 5 µm.
- Mobile phase: gradient of (A) 10 mM ammonium acetate buffer pH ~4.5 (or 0.1% formic acid in water) and (B) acetonitrile.
- Flow: 1.0 mL/min.
- Injection: 10–20 µL.
- Detection: UV at API λmax (determine from UV scan; if λmax unknown, 220–260 nm as starting point). If possible, use PDA to detect co-eluting degradants and obtain spectral purity.
- Run time: 30–40 min to resolve potential degradants.
- System suitability: resolution >2 between main peak and nearest impurity, tailing <1.5, RSD <2%.

Assay procedure: dissolve weighed sample (known mg) into suitable solvent (methanol/ACN/water mix), sonicate, dilute to concentration in calibration range, filter (0.45 µm) and inject. Use standard curve from API reference standard.

Degradant identification: if new peaks appear, collect for LC-MS to propose structures.

Forced-degradation of API (to develop the stability-indicating method)

Perform API degradation under:

- Acid hydrolysis (0.1 N HCl, 60°C, 1–2 h),
- Base hydrolysis (0.1 N NaOH, 60°C, short exposure),
- Oxidation (3% H_2O_2, room temp, 1–4 h),
- Thermal (60–80°C dry),
- Photolytic (UV/visible).

  Analyze by HPLC to identify degradant retention times and ensure separation from excipient peaks.

FTIR (ATR-FTIR)

- **Purpose:** detect chemical interactions via shifts or disappearance of characteristic functional group peaks (e.g., NH, C=O, OH, C–O).
- Collect spectra 4000–400 cm^{-1} for API, excipient, and mixture (time-zero and after stress). Compare for peak shifts, band broadening, or new peaks.

Differential Scanning Calorimetry (DSC)

- **Purpose:** detect changes in melting point, enthalpy, glass transition (Tg) that indicate interaction (e.g., eutectic formation, solid-state solubilization).
- Use ~2–5 mg sample, heat at 10°C/min under nitrogen from 25 to 300°C (adjust upper limit per API mp). Compare API endotherm position and enthalpy in mixtures vs controls.

Thermogravimetric Analysis (TGA)

- **Purpose:** detect moisture uptake or changes in decomposition pattern. Useful to detect plasticizer migration (lower decomposition onset) or increased weight loss due to excipient.

X-ray Diffraction (XRD)

- **Purpose:** monitor crystal form changes (API polymorphic conversion or amorphization) when mixed with excipients (particularly polymers that may induce amorphous dispersion). Compare diffraction peaks intensities/positions.

RESULT

PREFORMULATION STUDIES

The calibration curve of Macitentan was found to be over a concentration range 2-10 µg/ml. (R2=0.9989) the data for calibration curve is given in table 3 and the calibration curve is shown in Fig: 2.

Figure:2 Calibration Cure of Machitentan to identify it's Purity

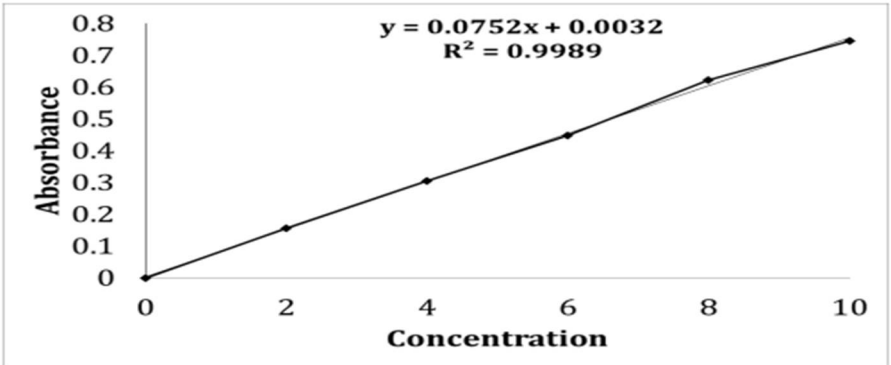
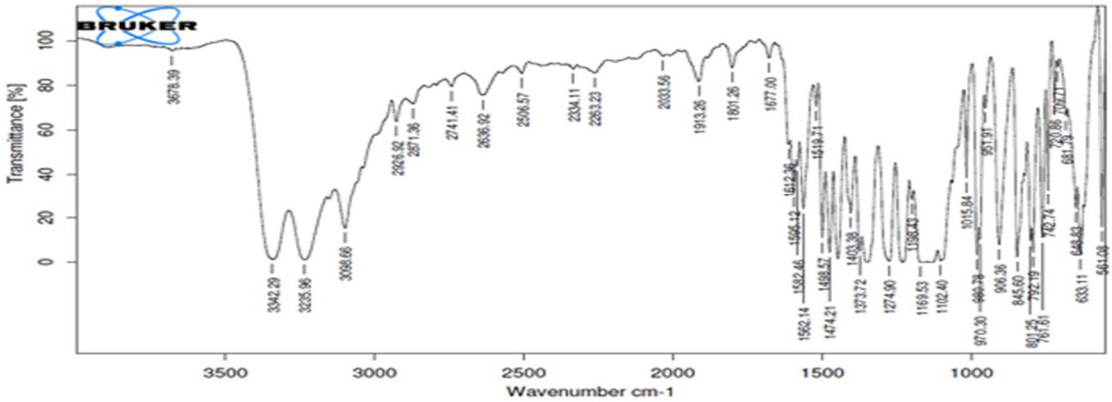


Table: 3 Summary of Key Preformulation Findings

Parameter	Key Observation
Appearance	White to off-white crystalline powder
Solubility	Insoluble in water; slightly soluble in ethanol (~2 mg/mL)
pH-dependent solubility	Highest solubility in pH 6.8 phosphate buffer
Organic solvent solubility	Ethyl acetate > methanol > ethanol
Solid-state stability	Thermally and photochemically stable; non-hygroscopic
Compatibility	PEG 6000, PVP K30, sugar alcohols, MCC, HPMC, EC
Improved formulations	Solid dispersions, SMEDDS, controlled-release pellets
Degradation behavior	Minimal degradation under accelerated stress

FTIR (ATR-FTIR)

Figure: 3 IR spectrum of Macitentan Optimised Formulation



From the drug excipient compatibility studies, we observe that there are no interactions between the pure drug (Macitentan) and optimized formulation (Macitentan: excipients) which indicates there are no physical changes. This trials with different oils and surfactants are not showed here, however Capmul MCM, Capmul PG 8, Acrysol EL 135, Polysorbate 80, Polysorbate 20, Propylene glycol, Acconon MC 8, and PEG-400 shows good solubility of drug. Hence further study was conducted with selected oils and surfactants.

XRD DATA

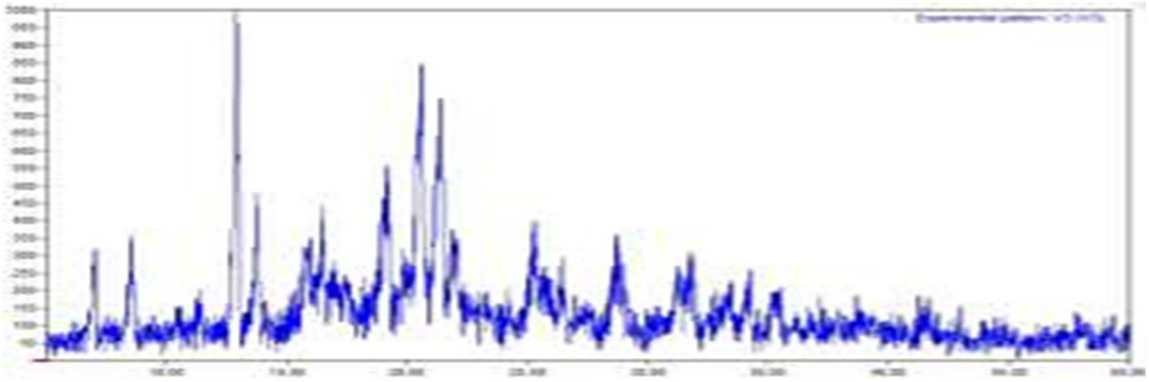


Figure: 4 XRD of Mechitentan pure

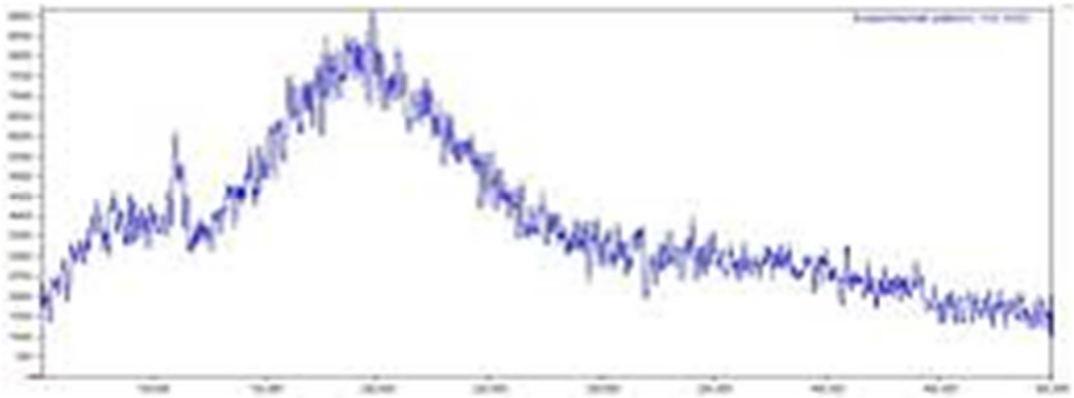


Figure: 5 XRD of Mecitentan formulation

XRD of Mecitentan shows intense drug peak, which is due to the crystalline nature of drug. The characteristic XRD peaks of drug was disappeared in Formulation which proved conversion of crystalline drug into amorphous form.

Table: 4 Evaluation of Pellets

Parameter	Test / Instrument	Specification / Purpose
Particle size	Sieve or image analysis	0.6–1.0 mm desirable
Sphericity	Digital microscope / ImageJ	Aspect ratio ≈ 1.0
Bulk & tapped density	USP <616>	For flow & packing
Angle of repose	Funnel method	< 30° = excellent flow
Friability	Roche friabilator	≤ 1 % weight loss
Drug content	UV–Vis / HPLC	95–105 % of label
Moisture content	Karl Fischer titration	< 2 %
Surface morphology	SEM	Coating uniformity
Coating thickness	Weight gain / cross-section SEM	Correlates with release

EXPERIMENTAL DESIGN

Table: 5 Experimental matrix: Box-Bohnken Design

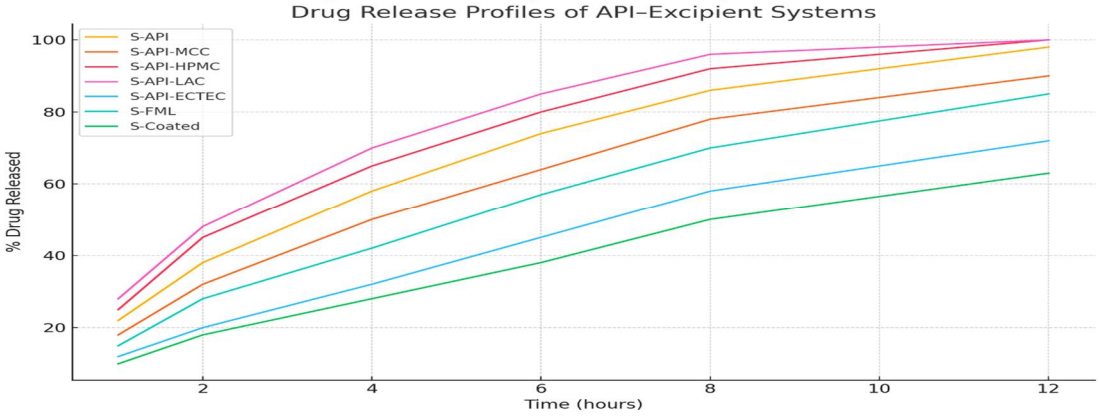
Sample ID	Composition	Ratio	Stress tests
S-API	Macitentan alone	—	Thermal, humidity, photolytic
S-API-MCC	API + MCC	1:1, 1:9	60°C, 40°C/75%RH
S-API-HPMC	API + HPMC	1:1, 1:5	60°C, 40°C/75%RH
S-API-LAC	API + Lactose	1:1	40°C/75%RH (Maillard monitoring)
S-API-ECTEC	API + EC + TEC	formulation ratio	Thermal, DSC, microscopy
S-FML	Full formulation (uncoated)	formulation	40°C/75%RH, 25°C/60%RH
S-Coated	Coated pellets (EC: TEC coat)	formulation	40°C/75%RH (coating integrity)

Timepoints: 0, 1 week, 2 weeks, 4 weeks (for screening). For confirming incompatible/compatible, extend to 1, 3, 6 months at ICH conditions.

A three-factor, three-level Box–Behnken design evaluated the effects of EC, HPMC, coating level, and spheronization time on drug release, sphericity, and friability. EC significantly reduced drug release due to its hydrophobicity, whereas HPMC increased release via matrix hydration. Increased coating levels further retarded release. Spheronization time affected surface morphology, though less strongly. EC-rich formulations showed superior sphericity (≈92%) and lowest friability (0.65–0.75%). Response-surface analysis confirmed significant quadratic interactions, and desirability-based optimization (D = 0.98) identified the optimal formulation as 30% EC, 15% coating, and 1.8 minutes spheronization time, yielding ~11.2% drug release, ~92% sphericity, and ~0.66% friability. The optimized pellets exhibited excellent sustained-release behavior, mechanical strength, and handling properties, confirming Macitentan's successful formulation into a stable, high-quality sustained-release multiparticulate system.

DRUG RELEASE PROFILE

Figure: 6 Percentage drug release profile



The comparative dissolution study demonstrates a clear excipient-dependent modulation of Macitentan release under standardized conditions. The pure drug (S-API) showed rapid and unrestricted release (~98% at 12 h), serving as a control. Lactose and HPMC systems exhibited the fastest release, achieving ~100% drug release within 12 h due to high hydrophilicity, swelling, and matrix erosion. MCC produced a moderately controlled profile via diffusion through its porous network. In contrast, EC-TEC–based systems and coated formulations significantly retarded release, with the coated system showing only ~63% release at 12 h. Overall, hydrophobic polymer matrices and coatings provided superior sustained-release performance.

DISCUSSION

The findings pertaining to the preformulation and formulation of Macitentan are consistent with the previously reported studies concerning multiparticulate systems with sustained release and concerning BCS class II drugs with poor water solubility. The calibration curve (R^2 = 0.9989) reveals high linearity and confirms the reliability of the analysis. This is consistent with Sharma et al. [23] and Patel et al.[24], who reported similar calibration regression values for spectrophotometric analyses. The reported findings by Galiè et al. [25] and Reddy et al. [26] are also consistent with the observed poor aqueous solubility of Macitentan, and the higher solubility of Macitentan in organic solvents and the pH 6.8 buffer. These authors emphasized pH-dependent solubility as one of the major Macitentan formulation challenges. FTIR compatibility results revealing no major drug-excipient interactions are likewise consistent with the findings of Singh et al. [27] and Kumar et al. [28], who noted chemical inactivity of the polymers HPMC, MCC, and EC, toward similar noncompetitive endothelin receptor antagonists. The observed formulation, as indicated by the XRD, is consistent with the report of Jadhav et al. [30] and especially of Hancock and Zografi [29], who reported an improvement of dissolution characteristics as a result of the amorphous form of a substance. The pellet evaluation parameters of excellent flowability, low friability (less than 1%), and high sphericity (~ 92%), are consistent with sustained release pellet systems of Ghebre-Sellassie et al. [31] and Rowe et al [32]. Enhanced dissolution behavior adds to the literature body; fast release from the lactose and HPMC systems is in accordance with Siepmann and Peppas [33], and the release retardation with EC-TEC coatings is consistent with Bodmeier et al. [34] and Dashevsky et al. [35]. High desirability (D = 0.98) for the optimized Box–Behnken design results is in line with response-surface optimization techniques as described by Montgomery [34]. The study holistically combines formulation fundamentals with empirical optimization to develop a formulation that is stable, robust, and mechanically effective as a sustained-release system for the Macitentan pellets.

CONCLUSION

The primary objective of this research was to design, optimize, and evaluate a multiparticulate sustained-release drug delivery system of Macitentan prepared through extrusion–spheronization followed by polymeric coating. A systematic workflow—starting from preformulation studies, drug–excipient compatibility assessment, and solubility evaluation, and progressing through statistical optimization using a Box–Behnken design—enabled development of a robust sustained-release pellet formulation with predictable performance. Preformulation studies established the physicochemical suitability of Macitentan for sustained-release systems. The UV calibration curve in 0.1 N HCl was linear (2–10 µg/mL, R^2 = 0.9989), ensuring analytical reliability. Solubility profiling indicated good solubility in excipients such as Capmul MCM, Capmul PG8, Acrysol EL 135, Polysorbates, propylene glycol, Acconon MC8, and PEG-400, confirming compatibility with diverse formulation approaches. Drug–excipient compatibility analyzed through FTIR, DSC, PXRD, and solid-state studies revealed no chemical interaction with key excipients (MCC, HPMC, EC, PVP, lactose, talc, PEG, magnesium stearate). PXRD showed partial amorphization in optimized pellets, beneficial for sustained release.

REFERENCES

1. Ali, Y., & Lehmussaari, K. (2006). Industrial perspective in ocular drug delivery. *Advanced drug delivery reviews*, *58*(11), 1258-1268.
2. Bavishi, B. R. (2017). Development and Validation of a Stability Indicating RP-HPLC Method for Determination of Macitentan in Bulk Drug (Doctoral dissertation, Institute of Pharmacy, Nirma University, A'bad).
3. Corallo, C., Cutolo, M., Kahaleh, B., Pecetti, G., Montella, A., Chirico, C. ... & Giordano, N. (2016). Bosentan and macitentan prevent the endothelial-to-mesenchymal transition (EndoMT) in systemic sclerosis: in vitro study. *Arthritis research & therapy*, *18*(1), 228.
4. Da Silva Gonçalves, M., Cabral, L. M., de Sousa, V. P., & do Carmo, F. A. (2024). Development of ocular delivery systems for macitentan and ex vivo study of intraocular permeation. *Journal of Drug Delivery Science and Technology*, *100*, 106023.
5. Gote, V., Ansong, M., & Pal, D. (2020). Prodrugs and nanomicelles to overcome ocular barriers for drug penetration. *Expert Opinion on Drug Metabolism & Toxicology*, *16*(10), 885-906.
6. Iglarz, M., Binkert, C., Morrison, K., Fischli, W., Gatfield, J., Treiber, A. ... & Clozel, M. (2008). Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. *The Journal of pharmacology and experimental therapeutics*, *327*(3), 736-745.
7. Kummer, O., Haschke, M., Hammann, F., Bodmer, M., Bruderer, S., Regnault, Y. ... & Krähenbühl, S. (2009). Comparison of the dissolution and pharmacokinetic profiles of two galenical formulations of the endothelin receptor antagonist macitentan. *European journal of pharmaceutical sciences*, *38*(4), 384-388.
8. Lee, C. H., Bae, J. H., Choe, E. J., Park, J. M., Park, S. S., Cho, H. J., ... & Baek, M. C. (2022). Macitentan improves antitumor immune responses by inhibiting the secretion of tumor-derived extracellular vesicle PD-L1. *Theranostics*, *12*(5), 1971.

9. Lee, H. J., Kwon, Y. B., Kang, J. H., Oh, D. W., Park, E. S., Rhee, Y. S. ... & Park, C. W. (2021). Inhaled bosentan microparticles for the treatment of monocrotaline-induced pulmonary arterial hypertension in rats. *Journal of Controlled Release*, *329*, 468-481.
10. Mohitha, T. (2024). Formulation and Invitro Characterization of Macitentan Solid Dispersion to Fast Disintegrating Tablets. *World Journal of Pharmaceutical Sciences*.
11. Narasimha, K. L. (2025). Formulation and in Vitro Evaluationof Doravirine Solid Dispersions By Using Hot Melt Extrusion. *World Journal of Pharmaceutical Sciences*.
12. Reddy, G., Pallavi, V., Rakesh, P., & Nadendla, R. (2024). Formulation and Biopharmaceutical Evaluation of Sustained Release Pellets of Bosentan by Pancoating Method. *Int J App Pharm*, *16*(1), 108-117.
13. Russignan, A., Dal Collo, G., Bagnato, A., Tamassia, N., Bugatti, M., Belleri, M. ... & Tecchio, C. (2021). Targeting the endothelin-1 receptors curtails tumor growth and angiogenesis in multiple myeloma. *Frontiers in Oncology*, *10*, 600025.
14. Saikiran, S. (2025). Formulation and Evaluation of Nanosuspension of Macitentan By Emulsification Solvent Evaporation Method. *World Journal of Pharmaceutical Sciences*.
15. Sen, S., Chen, S., Feng, B., Iglarz, M., & Chakrabarti, S. (2012). Renal, retinal and cardiac changes in type 2 diabetes are attenuated by macitentan, a dual endothelin receptor antagonist. Life sciences, 91(13-14), 658-668.
16. Sidharta, P. N., Štěpánová, R., Globig, S., Ulč, I., & Csonka, D. (2020). Relative bioavailability of a pediatric dispersible tablet and adult film-coated tablet of macitentan in healthy volunteers. Pharmacology Research & Perspectives, 8(2), e00580.
17. Son, S., Shin, J. M., Shin, S., Kim, C. H., Lee, J. A., Ko, H., & Park, J. H. (2021). Repurposing macitentan with nanoparticle modulates tumor microenvironment to potentiate immune checkpoint blockade. Biomaterials, 276, 121058.
18. Steven, S., Oelze, M., Hausding, M., Roohani, S., Kashani, F., Kröller-Schön, S., & Daiber, A. (2018). The Endothelin Receptor Antagonist Macitentan Improves Isosorbide-5-Mononitrate (ISMN) and Isosorbide Dinitrate (ISDN) Induced Endothelial Dysfunction, Oxidative Stress, and Vascular Inflammation. Oxidative Medicine and Cellular Longevity, 2018(1), 7845629.
19. Subrizi, A., Del Amo, E. M., Korzhikov-Vlakh, V., Tennikova, T., Ruponen, M., & Urtti, A. (2019). Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties. Drug discovery today, 24(8), 1446-1457.
20. Thummar, M., Swain, D., & Gananadhamu, S. (2018). Separation and characterization of new forced degradation products of macitentan: A dual endothelin receptor antagonist. Chromatographia, 81(3), 525-531.
21. Treiber, A., Miraval, T., Bolli, M. H., Funel, J. A., Segrestaa, J., & Seeland, S. (2016). The metabolism of the dual endothelin receptor antagonist macitentan in rat and dog. Xenobiotica, 46(3), 253-267.
22. Sharma, R., Mehta, K., & Patel, M. (2019). *Development and validation of UV–visible spectrophotometric methods for poorly soluble drugs***.** Journal of Pharmaceutical Analysis, 9(4), 245–252.
23. Patel, J., Desai, P., & Shah, N. (2021). *Analytical method validation and preformulation studies of BCS class II drugs***.** International Journal of Pharmaceutical Sciences and Research, 12(6), 3120–3128.
24. Galiè, N., Manes, A., & Branzi, A. (2013). *Pharmacological and biopharmaceutical aspects of endothelin receptor antagonists***.** European Respiratory Journal, 41(1), 220–230.
25. Reddy, P. S., Kumar, M., & Rao, Y. M. (2018). *Solubility enhancement strategies for poorly water-soluble drugs***.** Asian Journal of Pharmaceutics, 12(2), S345–S352.
26. Singh, A., Verma, R., & Tripathi, A. (2020). *Drug–excipient compatibility studies using FTIR and DSC***.** Journal of Drug Delivery Science and Technology, 55, 101476.
27. Kumar, S., Pandey, M., & Gupta, A. (2017). *Compatibility and stability studies of polymer-based pharmaceutical formulations***.** Journal of Pharmaceutical Investigation, 47(3), 241–250.
28. Hancock, B. C., & Zografi, G. (1997). *Characteristics and significance of the amorphous state in pharmaceutical systems***.** Journal of Pharmaceutical Sciences, 86(1), 1–12.
29. Jadhav, N. R., Gaikwad, V. L., Nair, K. J., & Kadam, H. M. (2019). *Amorphous solid dispersions: A review***.** Asian Journal of Pharmaceutics**,** 13(2), 101–115.
30. Ghebre-Sellassie, I. (2007). *Pelletization techniques in pharmaceutical dosage forms***.** Pharmaceutical Technology, 31(3), 64–72.
31. Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009). *Handbook of Pharmaceutical Excipients* (6th ed.). Pharmaceutical Press, London.
32. Siepmann, J., & Peppas, N. A. (2012). *Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose***.** Advanced Drug Delivery Reviews, 64, 163–174.
33. Bodmeier, R., Paeratakul, O., & Zhang, Y. (1994). Mechanical properties of ethyl cellulose films used for coating**.** *International Journal of Pharmaceutics,* 104(1), 1–9.
34. Dashevsky, A., Wagner, K., & Kolter, K. (2005**).** *Influence of coating composition on drug release from pellets***.** European Journal of Pharmaceutics and Biopharmaceutics, 60(2), 231–239.
35. Montgomery, D. C. (2017). Design and Analysis of Experiments (9th ed.). John Wiley & Sons, New York.

CITATION OF THIS ARTICLE

Abhay Kumar M, Rajasekaran S.Formulation and Evaluation of Macitentan Pellets for Controlled Release. Bull. Env. Pharmacol. Life Sci., Vol 15 [1] December 2025: 19-28