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RESEARCH ARTICLE

Chronotherapeutic Film-Coated Pulsatile Drug Delivery System of Resveratrol for the Management of Rheumatoid Arthritis

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Abstract: Circadian fluctuations in inflammatory cytokine production exacerbate joint pain, stiffness, and clinical pathology during early morning hours in rheumatoid arthritis patients. Standard immediate-release drug formulations fail to provide targeted drug availability during these peak symptomatic windows. Synchronizing therapeutic drug delivery with biological rhythms offers a targeted approach to mitigate nocturnal inflammatory cascades. A chronotherapeutic pulsatile dosage form was developed using a polymer-coated tablet core containing resveratrol to achieve time-controlled release after a predetermined delay period. Preformulation characterization confirmed the lipophilic nature (log P = 3.12 ± 0.05), melting point range (254 ± 0.62 °C), and spectroscopic absorption maximum (λ_{max} = 303 nm) of resveratrol. Fourier-transform infrared spectroscopy revealed no chemical interaction between the drug and formulation excipients. Core tablets prepared via direct compression were evaluated for mechanical integrity, mass variation, friability, and disintegration time. The optimized core tablet (F4) exhibited superior mechanical strength (4.1 ± 0.3 kg/cm²), acceptable friability (0.91%), and rapid core disintegration. Application of a hydrophobic film coating comprising ethyl cellulose (95%) and dibutyl phthalate (5%) established a functional polymeric barrier that delayed initial fluid ingress. Coated tablets displayed enhanced hardness (5.2 ± 0.3 kg/cm²), low friability (0.57%), and an extended disintegration lag phase (31.2 ± 0.9 min). *In-vitro* dissolution showed a defined lag period followed by rapid drug release, attaining 88.4% cumulative release within 60 minutes. The system successfully delays drug release while providing targeted anti-inflammatory action aligned with early morning arthritic exacerbations.

Keywords: Pulsatile drug delivery systems; Resveratrol; Chronotherapeutics; Partition coefficient; Lag phase.

1. Introduction

Optimal clinical outcomes in pharmacotherapy depend on delivering active therapeutic agents to target sites at concentrations matched to the temporal pattern of disease symptoms [1]. Conventional immediate-release dosage forms frequently generate fluctuating systemic drug concentrations, necessitating repeated daily administration and increasing the incidence of concentration-dependent adverse effects [2]. Controlled-release formulations mitigate peak-to-trough fluctuations; however, continuous drug input remains sub-optimal for medical conditions characterized by circadian variation in symptom severity [3].

Chronotherapeutics aligns drug administration with endogenous biological rhythms to optimize clinical efficacy and minimize adverse reactions [4]. Pulsatile drug delivery systems (PDDS) are engineered to release active ingredients rapidly and completely after an initial lag phase [5]. This temporal release profile contrasts with zero-order delivery systems by providing a rapid drug pulse precisely when pathological activity peaks [6].

Rheumatoid arthritis exhibits pronounced circadian variations in pain intensity, morning joint stiffness, and functional impairment [7]. Physiological evidence attributes these morning flare-ups to nocturnal surges in pro-inflammatory cytokines, specifically interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), alongside a relative deficiency in early morning endogenous cortisol secretion [8]. Standard anti-inflammatory formulations taken at bedtime often fail to maintain effective therapeutic plasma levels until the early morning hours, resulting in uncontrolled stiffness and discomfort upon waking [9].

Engineering a chronotherapeutic delivery vehicle that maintains structural integrity throughout the nocturnal period and rapidly discharges the drug during peak symptom manifestation resolves this temporal mismatch [10]. Delivering anti-inflammatory agents in alignment with diurnal cytokine rhythms improves morning mobility and overall patient compliance [11].

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Resveratrol (3,5,4'-trihydroxystilbene) is a natural polyphenolic compound that displays potent anti-inflammatory, antioxidant, and immunomodulatory properties [12]. It inhibits cyclooxygenase-2 (COX-2), downregulates nuclear factor kappa B (NF-ϰB) signaling pathways, and reduces pro-inflammatory cytokine expression, making it a promising candidate for arthritic therapy [13]. However, resveratrol exhibits poor aqueous solubility, rapid hepatic metabolism, and limited systemic bioavailability following conventional oral administration [14]. Formulating resveratrol into a chronomodulated delivery system protects the active compound during initial gastrointestinal transit and triggers rapid release at the designated therapeutic window [15].

Among available pulsatile delivery designs, reservoir film-coated core systems offer precise control over lag time and drug release kinetics [16]. A core tablet engineered for rapid disintegration is surrounded by a functional polymeric barrier layer that delays water penetration [17]. The present work focused on the design, optimization, and evaluation of a reservoir film-coated pulsatile tablet of resveratrol to achieve time-controlled release aligned with the circadian rhythms of arthritic pathology.

2. Materials And Methods

2.1. Materials

Resveratrol was obtained from M/s Sami-Sabinsa Group Limited (Bengaluru, India). Microcrystalline cellulose (MCC, Avicel PH-102), anhydrous lactose, sodium starch glycolate (SSG), magnesium stearate, hydroxypropyl methylcellulose (HPMC E5 LV Premium), and ethyl cellulose (10 cP) were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). Eudragit L100 was supplied by Evonik Industries (Essen, Germany). Absolute ethanol (99.9%), acetone, and propan-2-ol were sourced from Molychem Pvt Ltd. (Mumbai, India). Dibutyl phthalate was supplied by Loba Chemie Pvt. Ltd. All chemical reagents and buffer salts were of analytical grade and used as received.

2.2. Preformulation Studies

2.2.1. Solubility Studies

The solubility of resveratrol was determined using a standardized shake-flask method. An excess quantity of resveratrol was added to screw-capped glass vials containing 10 mL of various solvent media, including purified water, methanol, ethanol, chloroform, dichloromethane, dimethyl sulfoxide (DMSO), and phosphate buffer solutions adjusted to pH 1.2, pH 6.8, and pH 7.4. The mixtures were agitated at 25 ± 1 °C for 24 hours in a mechanical shaker bath to achieve thermodynamic equilibrium. Samples were centrifuged at 3000 rpm for 15 minutes, filtered through 0.45 μm membrane filters, and analyzed spectrophotometrically to evaluate qualitative and equilibrium solubility behavior [18].

2.2.2. Determination of Melting Point

The melting point range of resveratrol was determined using a calibrated capillary melting point apparatus (Model 931). Resveratrol powder was dried over silica gel, packed tightly into a glass capillary tube sealed at one end, and heated at a controlled rate of 1°C/min. The temperatures corresponding to the initiation and completion of melting were recorded in triplicate [19].

2.2.3. Determination of Partition Coefficient (log P)

The n-octanol/water partition coefficient of resveratrol was determined using the shake-flask method. Prior to testing, the organic phase (n-octanol) and aqueous phase (phosphate buffer, pH 6.8) were mutually saturated by shaking for 24 hours at 25°C. An accurately weighed mass of resveratrol (15 mg) was added to a mixture containing 15 mL of pre-saturated n-octanol and 15 mL of pre-saturated buffer in a separating funnel. The mixture was shaken vigorously for 30 minutes and allowed to stand for 24 hours to achieve phase equilibrium. The biphasic system was separated, centrifuged at 2000 rpm for 10 minutes, and the drug concentration in the aqueous phase was measured spectrophotometrically at λ_{max} = 303 nm. The concentration in the organic phase was derived by mass balance. The partition coefficient (P) and log P were calculated using the following equations:

$$P = \frac{C_{\text{octanol}}}{C_{\text{aqueous}}} \log P = \log_{10}\left(\frac{C_{\text{octanol}}}{C_{\text{aqueous}}}\right)$$

where C_{octanol} and C_{aqueous} represent equilibrium concentrations in the n-octanol and aqueous buffer phases, respectively [20].

2.2.4. Fourier-Transform Infrared (FTIR) Spectroscopy

Chemical compatibility between resveratrol and formulation excipients was evaluated by FTIR spectroscopy (PerkinElmer Spectrum Two). Samples of pure resveratrol, individual excipients, and binary physical mixtures (1:1 w/w) were ground with spectroscopic-grade potassium bromide (KBr) and compressed into translucent pellets using a hydraulic press. Spectra were collected over the wave number range of 4000 cm^{-1} to 400 cm^{-1} at a resolution of 2 cm^{-1} to identify characteristic functional group frequencies and monitor structural interactions [21].

2.2.5. UV-Visible Spectrophotometric Assay and Calibration

A primary stock solution (1000 µg/mL) was prepared by dissolving 10 mg of resveratrol in 10 mL of phosphate buffer (pH 6.8). A working stock solution (100 µg/mL) was obtained by diluting 1 mL of primary stock to 10 mL with buffer. The working solution was scanned over the wavelength spectrum of 200 nm to 400 nm using a UV-Visible spectrophotometer (Shimadzu UV-1780) against a buffer blank to establish the maximum absorbance wavelength (λ_{max}).

Calibration standards ranging from 2 µg/mL to 20 µg/mL were prepared by serial dilution of the working solution with phosphate buffer (pH 6.8). Absorbance values were recorded at λ_{max} = 303 nm in triplicate. A linear calibration curve was constructed by plotting absorbance against concentration, and regression analysis was applied to assess linearity [22].

2.3. Formulation and Preparation of Core Tablets

2.3.1. Compression

Core tablets containing 40 mg of resveratrol were formulated via direct compression. Six batch variations (F1–F6) were prepared to evaluate the influence of superdisintegrant and polymeric binder proportions on tablet characteristics. The precise composition per tablet is detailed in Table 1.

Resveratrol, microcrystalline cellulose, lactose, ethyl cellulose, HPMC E5, Eudragit L100, and sodium starch glycolate were passed through a #40 mesh sieve (425 µm) and blended homogeneously for 20 minutes in a mortar. Magnesium stearate was sieved through a #60 mesh (250 µm), added to the blend, and mixed for an additional 5 minutes. The final powder blend was compressed into 360 mg tablets using a single-station rotary tablet machine fitted with round concave punches [23].

Table 1. Composition of Resveratrol Core Tablet Formulations (F1–F6)

Component (mg/tablet)	F1	F2	F3	F4	F5	F6
Resveratrol	40	40	40	40	40	40
Microcrystalline Cellulose	130	130	130	130	—	—
Lactose Anhydrous	110	110	110	110	110	110
Ethyl Cellulose	80	70	60	50	—	—
HPMC E5	—	—	—	—	40	30
Eudragit L100	—	—	—	—	15	25
Sodium Starch Glycolate	10	20	30	40	50	60
Magnesium Stearate	5	5	5	5	5	5
Total Weight (mg)	360	360	360	360	360	360

2.3.2. Optimization and Selection for Core Tablets

Core tablets were screened based on physical integrity, hardness, disintegration rate, and friability. Formulation F4 indicated balanced mechanical strength, rapid core disintegration, and low friability, making it the optimal core substrate for subsequent functional film coating [24].

2.4. Polymeric Film Coating

2.4.1. Preparation of Coating Solution

The functional film-coating solution was prepared by dissolving ethyl cellulose (95 w/w%) and dibutyl phthalate (5 w/w%) in a organic solvent mixture consisting of acetone and propan-2-ol (1:1 v/v) to achieve a total polymer concentration of 6 % w/v. Dibutyl phthalate acted as a plasticizer to ensure film flexibility and prevent crack formation during fluid contact [25].

2.4.2. Coating Process

Core tablets from formulation F4 were coated using a conventional pan-coating apparatus equipped with a manual spray gun. Operating variables were maintained as follows: inlet air temperature (30-35 °C), tablet bed temperature (30 °C), pan speed (25 rpm), atomization air pressure (1.0 bar), spray rate (2.0-2.5 g/min), and nozzle orifice diameter (1.0 mm). Coating was continued incrementally to obtain weight gains of 5%, 10%, and 15 % w/w. Coated tablets were dried under warm air circulation for 24 hours to remove residual solvent traces [26].

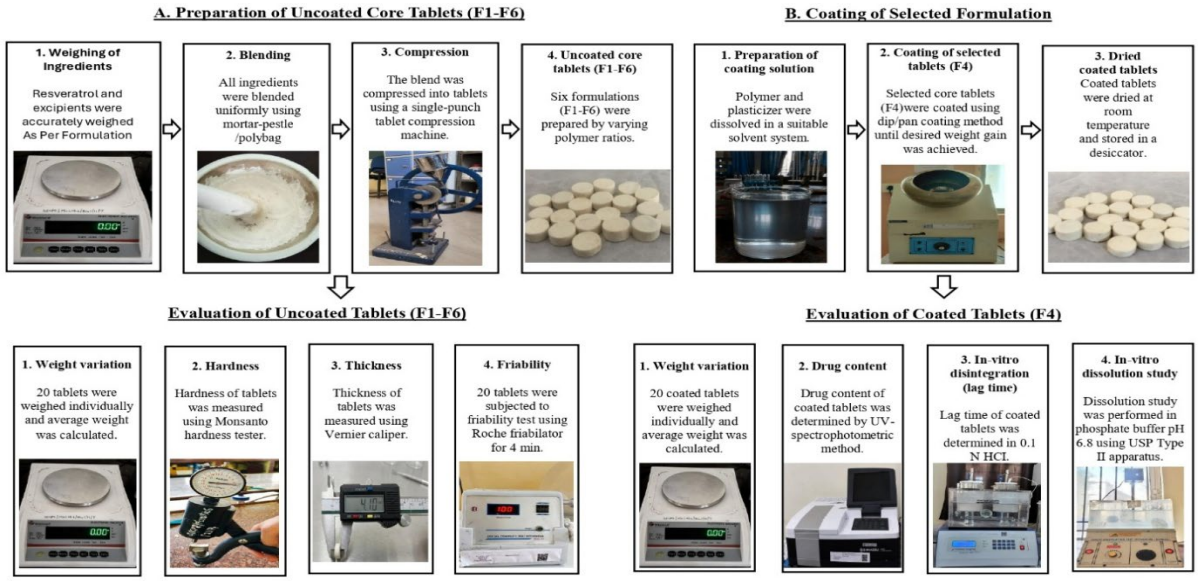

Figure 1. Preparation of uncoated core tablets (F1–F6), coating of the optimized formulation (F4), and evaluation of uncoated and coated tablets

2.5. Physicochemical and *In-Vitro* Characterization

2.5.1. Weight Variation Assessment

Twenty tablets from each batch were selected randomly and weighed individually on an analytical balance. Average tablet weight and percentage deviations were calculated using the standard formula:

$$\text{Weight Variation (\%)} = \left(\frac{W_i - W_{\text{avg}}}{W_{\text{avg}}}\right) \times 100$$

where W_i is the weight of an individual tablet and W_{avg} is the average mass of the evaluated sample [27].

2.5.2. Mechanical Hardness Testing

Crushing strength was determined using a Monsanto hardness tester. Ten tablets per batch were tested individually, and results were expressed in kg/cm² as mean values with standard deviations [28].

2.5.3. Tablet Thickness

Individual thickness values for ten tablets per batch were recorded using a digital Vernier caliper (0.01 mm resolution). Mean dimensions and standard deviations were documented [29].

2.5.4. Friability

Pre-weighed samples of 20 tablets ($W_{initial}$) were rotated in a Roche friabilator at 25 rpm for 4 minutes (100 total revolutions). Tablets were dedusted, inspected for physical defects, and reweighed (W_{final}). Percentage friability was calculated as:

$$\text{Friability (\%)} = \left(\frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}}\right) \times 100$$

Values below 1.0 % without tablet breakage were considered acceptable [30].

2.5.5. Disintegration and Lag Time

In-vitro disintegration times were evaluated using a USP disintegration apparatus (Electrolab, Model 1901). Six tablets per formulation were placed in individual glass tubes fitted with mesh screens at the base. The immersion medium consisted of distilled water maintained at 37.0 ± 0.5°C. The time required for total tablet disintegration and passage through the mesh screen was recorded. For film-coated tablets, lag time was defined as the time required for complete rupture or erosion of the outer polymer coating [31].

2.5.6. Assay

Ten core or coated tablets were pulverized in a mortar. A sample equivalent to 10 mg of resveratrol was accurately weighed, transferred into a 100 mL volumetric flask, dissolved in 20 mL of methanol, and diluted to volume with phosphate buffer (pH 6.8). The solution was filtered through 0.45 μm filter paper, diluted appropriately, and measured at λ_{max} = 303 nm using a UV-Visible spectrophotometer. Active content was determined using the calibration equation [32].

2.5.7. In-Vitro Dissolution Studies

In-vitro drug release profiles were determined using a USP Type II paddle apparatus (Adarsh International) running at 50 rpm. The dissolution vessel was filled with 900 mL of phosphate buffer (pH 6.8) maintained at 37.0 ± 0.5 °C. Tablet samples were added to the vessels, and 5 mL aliquots were withdrawn at predetermined time intervals (5, 10, 15, 30, 45, and 60 min). Media volumes were replenished immediately with equal amounts of fresh buffer maintained at 37°C. Samples were filtered, diluted, and assayed spectrophotometrically at 303 nm. Cumulative percentage drug release was calculated and plotted against time [33].

3. Results

3.1. Preformulation Characterization

3.1.1. Solubility

Qualitative and quantitative solubility studies showed that resveratrol possesses low aqueous solubility while displaying high solubility in organic systems. The compound was practically insoluble in pure water (0.03 mg/mL) and displayed limited solubility across physiological pH environments, including pH 1.2 (0.04 mg/mL), pH 6.8 (0.06 mg/mL), and pH 7.4 (0.07 mg/mL). Resveratrol exhibited high solubility in organic media, including methanol (125 mg/mL), ethanol (85 mg/mL), chloroform (18 mg/mL), dichloromethane (22 mg/mL), and DMSO (>200 mg/mL). These data confirm the lipophilic nature of the active pharmaceutical ingredient.

3.1.2. Melting Point Range

The experimental melting point of resveratrol was determined as 254 ± 0.62°C. This narrow melting range closely matches reported reference values (253-255 °C), confirming the chemical purity and crystalline stability of the starting material.

3.1.3. Octanol-Water Partition Coefficient (log P)

Quantitative equilibrium partitioning between n-octanol and phosphate buffer (pH 6.8) yielded a residual aqueous phase concentration of 11.37 μg/mL. The calculated partition coefficient (P) was 1318.2, corresponding to an experimental log P value of 3.12 ± 0.05. This positive log P confirms high lipophilicity, consistent with the low aqueous solubility profile of resveratrol.

3.1.4. Drug Excipient Compatibility by FTIR

The FTIR spectrum of pure resveratrol showed characteristic absorption at 3280 cm^{-1} (O-H stretching vibration), 1606 cm^{-1} (aromatic C=C stretching), 1588 cm^{-1} (trans-olefinic C=C stretching), 1382 cm^{-1} (phenol O–H bending), and 965 cm^{-1} (trans-olefinic C–H out-of-plane bending) (shown in Figure 2).

Spectra of individual excipients showed expected functional group bands: lactose exhibited O–H stretching (3300-3500 cm^{-1}) and C–O stretching (1030 cm^{-1}); microcrystalline cellulose showed O–H stretching (3350 cm^{-1}) and C–H stretching (2895 cm^{-1}); HPMC exhibited hydroxyl bands (3450 cm^{-1}) and ether linkages (1060 cm^{-1}); sodium starch glycolate displayed carboxylate groups (1600 cm^{-1}); Eudragit L100 exhibited ester carbonyl stretching (1730 cm^{-1}); magnesium stearate showed aliphatic C–H stretching (2850-2920 cm^{-1}) and carboxylate bands (1575 cm^{-1}); and ethyl cellulose showed ether link bands (1050-1100 cm^{-1}).

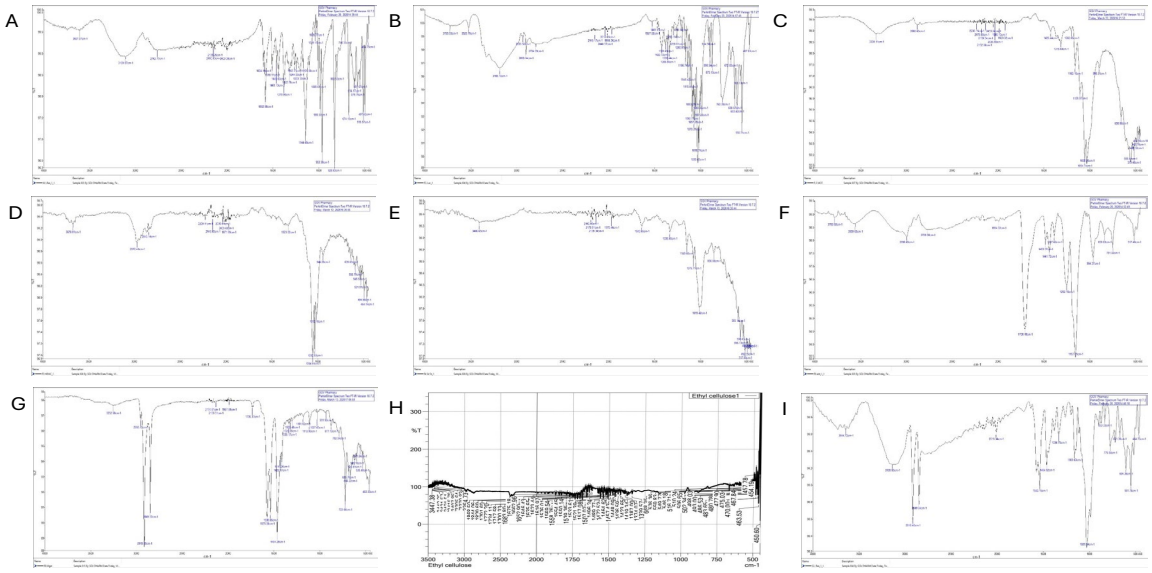

Figure 2. FTIR spectra of (A) Resveratrol, (B) Lactose, (C) Microcrystalline Cellulose (MCC), (D) HPMC, (E) Sodium Starch Glycolate (SSG), (F) Eudragit, (G) Magnesium Stearate, (H) Ethyl Cellulose, and (I) Physical Mixture of Resveratrol with Excipients

The physical mixture spectrum containing resveratrol and all formulation excipients retained the principal absorption peaks of the active drug without peak shifts, peak disappearances, or new absorption band appearances. These results confirm the absence of chemical degradation or structural incompatibility between resveratrol and the selected excipients.

3.1.5. UV Spectrophotometry and Linearity

Scanning resveratrol in phosphate buffer (pH 6.8) over 200-400 nm revealed a sharp, distinct absorbance peak at λ_{max} = 303 nm. This peak corresponds to π to π* electronic transitions within the conjugated stilbene ring structure. The calibration curve generated across concentrations of 2-20 µg/mL at 303 nm indicated linear behavior (Figure 3). The linear regression equation was y = 0.0408 x + 0.0012 where y indicates absorbance and x represents concentration in µg/mL. The coefficient of determination (R^2 = 0.9978) confirmed strict adherence to Beer–Lambert's law within the evaluated concentration range.

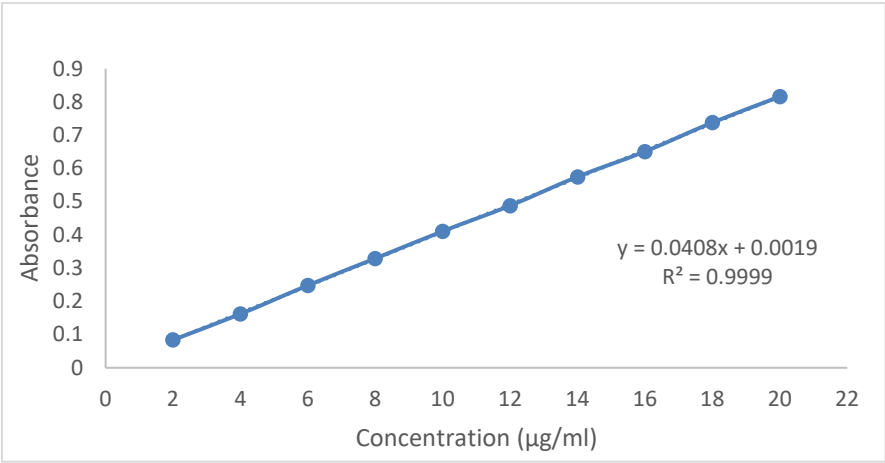

Figure 3. Calibration Curve of Resveratrol in PBS 6.8

3.2. Physicochemical Characterization of Core and Coated Formulations

3.2.1. Core Tablet Physical Properties (F1–F6)

Core tablet formulations (F1–F6) showed acceptable mechanical properties during compression. Increasing ethyl cellulose concentration in formulations F1 through F4 produced a steady increase in crushing strength from 3.0 ± 0.2 kg/cm² to 4.1 ± 0.3 kg/cm². Friability decreased correspondingly from 1.32% in F1 to 0.91% in F4. Formulations F5 and F6, containing HPMC and Eudragit mixtures, displayed hardness values of 4.5 ± 0.2 kg/cm² and 4.8 ± 0.2 kg/cm², with friability values of 0.78% and 0.65%, respectively. Tablet thickness remained consistent across all batches (4.06 ± 0.05 mm to 4.14 ± 0.03 mm). Physical parameters for core formulations F1–F6 are summarized in Table 2.

Table 2. Physicochemical Characteristics of Uncoated Resveratrol Core Tablets (F1–F6)

Formulation	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Disintegration Time (min)
F1	3.0 ± 0.2	4.06 ± 0.05	1.32	2.1 ± 0.3
F2	3.4 ± 0.3	4.09 ± 0.04	1.10	3.4 ± 0.4
F3	4.8 ± 0.2	4.12 ± 0.05	0.98	5.2 ± 0.5
F4	4.1 ± 0.3	4.10 ± 0.04	0.91	1.8 ± 0.2
F5	4.5 ± 0.2	4.14 ± 0.03	0.78	8.5 ± 0.6
F6	4.8 ± 0.2	4.13 ± 0.04	0.65	11.2 ± 0.8

Formulation F4 was selected as the optimal core composition because it combined rapid disintegration (1.8 ± 0.2 min), driven by 40 mg of sodium starch glycolate, with low friability (0.91%) and sufficient mechanical strength (4.1 ± 0.3 kg/cm²).

3.2.2. Characterization of Polymeric Coated Tablets (Optimized F4)

Application of the ethyl cellulose coating onto optimized F4 cores produced a uniform film layer. Coating increased tablet hardness from 4.1 ± 0.3 kg/cm² to 5.2 ± 0.3 kg/cm² and mean thickness from 4.10 ± 0.04 mm to 4.46 ± 0.05 mm. Friability dropped to 0.57%, indicating enhanced resistance to mechanical abrasion.

3.2.3. Weight Uniformity

Uncoated F4 core tablets exhibited an average weight of 358 ± 4.3 mg. Following polymeric coating to a target 10 % w/w weight gain, coated F4 tablets displayed an average mass of 392 ± 5.0 mg. Both uncoated and coated batches satisfied pharmacopoeial standards, showing mass deviations well within the permitted ± 5% limit.

3.2.4. Disintegration Lag Time

Uncoated F4 core tablets disintegrate rapidly within 1.8 ± 0.2 minutes due to the swelling action of sodium starch glycolate. In contrast, ethyl cellulose film-coated F4 tablets exhibited a mean disintegration lag time of 31.2 ± 0.9 minutes in aqueous medium. The hydrophobic ethyl cellulose layer resists immediate water penetration, establishing an initial lag period prior to core exposure.

3.2.5. Content Uniformity

Assay of individual coated F4 tablets yielded resveratrol contents ranging from 96.9 % to 99.1 % of the labeled dose (40 mg). Mean drug content was calculated as 97.3 ± 0.9 %, confirming uniform drug distribution throughout the manufacturing process. Individual assay results are detailed in Table 3.

Table 3: Drug Content Uniformity Assay for Coated F4 Tablets

Sample	Measured Absorbance (303 nm)	Calculated Drug Content (%)
Tablet 1	0.407	97.6
Tablet 2	0.414	98.4
Tablet 3	0.401	96.9
Tablet 4	0.419	99.1
Tablet 5	0.409	97.8
Tablet 6	0.416	98.6
Mean ± SD		97.3 ± 0.9

3.2.6. Dissolution Kinetics and Drug Release

In-vitro dissolution testing of coated F4 tablets in phosphate buffer (pH 6.8) revealed a clear pulsatile release profile. Drug release was suppressed during the initial period, reaching 19.9 ± 1.1 % at 5 minutes and 27.3 ± 1.4 % at 10 minutes. Once water permeated the semi-permeable film and reached the core, the superdisintegrant swelled rapidly, causing coating rupture and fast drug release. Cumulative drug release reached 51.5 ± 2.1 % at 30 minutes, 79.6 ± 2.8 % at 45 minutes, and 88.4 ± 2.5 % at 60 minutes. Dissolution kinetics data are presented in Table 4.

Table 4. *In-Vitro* Cumulative Dissolution for Polymer-Coated F4 Tablets

Time (min)	Absorbance (303 nm)	Cumulative Drug Release (%)
5	0.198	19.9 ± 1.1
10	0.271	27.3 ± 1.4
15	0.346	34.8 ± 1.8
30	0.512	51.5 ± 2.1
45	0.789	79.6 ± 2.8
60	0.876	88.4 ± 2.5

4. Discussion

Chronotherapeutic management of rheumatoid arthritis aims to synchronize drug availability with peak diurnal inflammatory cycles [34]. Because pro-inflammatory mediators such as IL-6 peak during nocturnal hours, patients routinely experience severe morning joint stiffness and pain [35]. Developing a film-coated pulsatile system provides a timed delay that prevents premature drug release during early GI transit, releasing the therapeutic dose when morning symptoms peak [36].

Preformulation studies confirmed the physicochemical suitability of resveratrol. The observed experimental melting point (254 ± 0.62 °C) and UV λ_{max} (303 nm) match reported literature values [37]. The experimental partition coefficient (log P = 3.12 ± 0.05) confirms high lipophilicity, which accounts for the low aqueous solubility observed across physiological pH ranges [38]. FTIR spectroscopy indicated that mixing resveratrol with chosen polymers and excipients produced no structural modifications or chemical incompatibilities [39].

Direct compression yielded core tablet matrices with low friability and good weight uniformity. In core formulations F1 through F4, increasing the level of sodium starch glycolate accelerated disintegrant action. Formulation F4 achieved rapid core disintegration (1.8 min) while maintaining adequate mechanical hardness (4.1 kg/cm^2).

Applying an insoluble polymer film coating composed of ethyl cellulose plasticized with dibutyl phthalate modified fluid ingress kinetics [40]. Ethyl cellulose forms a hydrophobic barrier around the tablet core. As dissolution medium slowly permeates the film, water reaches the tablet core and hydrates the sodium starch glycolate. Rapid swelling of the superdisintegrant generates internal hydrostatic pressure, rupturing the outer coating and releasing the active payload [41]. The disintegration lag phase of 31.2 minutes observed in coated F4 tablets shows how the polymeric film delays fluid ingress. *In-vitro* dissolution assays confirmed this lag behavior, showing minimal drug release early in the study followed by rapid release that reached 88.4% at 60 minutes. This temporal release confirms that polymer-coated core tablets can prevent immediate drug release and provide timed anti-inflammatory release aligned with circadian arthritic symptoms [42].

5. Conclusion

A film-coated reservoir pulsatile drug delivery system of resveratrol was successfully engineered for the chronotherapeutic management of rheumatoid arthritis. Preformulation characterization validated the purity, lipophilicity (log P = 3.12 ± 0.05), spectroscopic profile (λ_{max} = 303 nm), and excipient compatibility of the active payload. Direct compression yielded rapid-disintegrating core tablets, among which formulation F4 showed superior mechanical stability and disintegration performance. Coating the F4 core with an ethyl cellulose functional membrane established a time-controlled diffusion barrier, achieving a pronounced disintegration lag phase (31.2 ± 0.9 min) followed by rapid drug liberation (88.4% within 60 min). This pulsatile drug delivery matches nocturnal inflammatory rhythms and holds strong clinical potential to suppress early morning arthritic exacerbations, thereby improving the therapeutic efficacy and patient adherence.

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