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# Formulation and Evaluation of a Press-Coated Pulsatile Drug Delivery System of Telmisartan for Chronotherapeutic Management of Hypertension

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**Abstract:** Hypertension exhibits a circadian rhythm, with blood pressure rising sharply during the early morning hours, thereby increasing the risk of cardiovascular events. Chronotherapeutic drug delivery systems are designed to release drugs in alignment with biological rhythms to improve therapeutic outcomes. The present study aimed to formulate and evaluate a press-coated pulsatile drug delivery system of Telmisartan using hydrophilic polymer HPMC K4M and hydrophobic polymer Ethyl Cellulose. Core tablets of Telmisartan were prepared by direct compression and optimized based on pre-compression and post-compression parameters. The optimized core tablet (C2) was further press-coated with varying concentrations of HPMC K4M and Ethyl Cellulose to achieve desired lag time. The prepared pulsatile tablets were evaluated for weight variation, hardness, thickness, friability, drug content, in-vitro dissolution, and stability studies. Among all formulations, batch F2 exhibited optimum lag time with 96.3% cumulative drug release at the end of 8 hours and satisfactory mechanical properties within pharmacopoeial limits. Accelerated stability studies conducted as per ICH guidelines revealed no significant changes in physical characteristics or drug release profile. The results indicate that the developed press-coated pulsatile drug delivery system of Telmisartan can effectively provide chronotherapeutic drug release and may improve therapeutic efficacy and patient compliance in hypertension management.

**Keywords:** Telmisartan, Pulsatile drug delivery, Chronotherapy, HPMC K4M, Ethyl Cellulose, Press-coated tablets.

## INTRODUCTION

Hypertension is a chronic cardiovascular disorder characterized by persistent elevation of arterial blood pressure. Blood pressure follows a circadian rhythm, typically rising in the early morning hours, which significantly increases the risk of myocardial infarction, stroke, and other cardiovascular complications. Conventional sustained release formulations release the drug continuously, which may not match the body's biological rhythm. Therefore, chronotherapeutic drug delivery systems have gained considerable attention.

Chronotherapy aims to synchronize drug release with the biological rhythm of the disease condition. Pulsatile drug delivery systems are designed to release the drug after a predetermined lag time, followed by rapid drug release. Such systems are particularly beneficial in diseases like hypertension, asthma, arthritis, and peptic ulcer where symptoms exhibit time-dependent variation.

Telmisartan is an angiotensin II receptor blocker (ARB) widely used in the treatment of hypertension. Due to its role in controlling morning blood pressure surge, it is an ideal candidate for pulsatile drug delivery. Delivering Telmisartan after a specific lag time may enhance its therapeutic effectiveness and reduce cardiovascular risk.

Press-coating is a simple and solvent-free technique used to develop pulsatile systems. In this approach, a rapidly disintegrating core tablet is coated with a polymeric barrier layer that controls the lag time. Hydrophilic polymers such as HPMC K4M swell upon hydration, whereas hydrophobic polymers like Ethyl Cellulose retard drug release by forming a barrier layer. By modifying the ratio of these polymers, the lag time and release profile can be effectively controlled.

The present study focuses on the formulation and evaluation of press-coated pulsatile tablets of Telmisartan using varying ratios of HPMC K4M and Ethyl Cellulose to achieve chronotherapeutic drug release suitable for hypertension management.

## MATERIALS AND METHODS

### Materials

Telmisartan was obtained as a gift sample from a reputed pharmaceutical manufacturer. Hydroxypropyl methylcellulose (HPMC K4M) and Ethyl Cellulose were used as hydrophilic and hydrophobic polymers, respectively. Croscarmellose sodium was used as super disintegrant. Microcrystalline cellulose (MCC) served as diluent, while magnesium stearate and talc were used as lubricant and glidant, respectively. All other reagents and chemicals used were of analytical grade.

### Preparation of Core Tablets

Core tablets containing Telmisartan (40 mg) were prepared by the direct compression method. All excipients were passed through sieve No. 30 prior to blending. The required quantities of Telmisartan, microcrystalline cellulose, and croscarmellose sodium were accurately weighed and mixed thoroughly. Talc and magnesium stearate were added to the blend and mixed for an additional 5 minutes to ensure uniform distribution.

The final blend was evaluated for micromeritic properties and compressed using an 8 mm flat-faced punch in a multi-station tablet compression machine. Each tablet was adjusted to a total weight of 150 mg.

**Table 1:** Composition of Telmisartan Core Tablets

| S. No | Ingredients | C1 (mg) | C2 (mg) | C3 (mg) | C4 (mg) |
|---|---|---|---|---|---|
| 1 | Telmisartan | 40 | 40 | 40 | 40 |
| 2 | Croscarmellose sodium | 3 | 4.5 | 6 | 5.5 |
| 3 | Magnesium stearate | 1.5 | 1.5 | 1.5 | 1.5 |
| 4 | Talc | 1.5 | 1.5 | 1.5 | 1.5 |
| 5 | Microcrystalline cellulose | 104 | 102.5 | 101 | 101.5 |
| | Total Weight (mg) | 150 | 150 | 150 | 150 |

### Pre-Compression Evaluation

The prepared powder blends were evaluated for bulk density, tapped density, angle of repose, compressibility index, and Hausner's ratio using standard procedures.

- **Bulk density and tapped density** were determined using a graduated measuring cylinder method.
- **Angle of repose** was measured using the fixed funnel method.
- **Compressibility index (Carr's index)** and **Hausner's ratio** were calculated using standard equations.

These parameters were evaluated to assess flow properties and compressibility of the powder blend.

**Post-Compression Evaluation of Core Tablets**

Core tablets were evaluated for the following parameters according to pharmacopoeial guidelines:

- **Weight variation:** Twenty tablets were weighed individually and the average weight was calculated.
- **Thickness:** Measured using a calibrated Vernier calliper (n = 10).
- **Hardness:** Determined using Monsanto hardness tester and expressed in kg/cm² (n = 10).
- **Friability:** Evaluated using a digital friabilator at 25 ± 1 rpm for 100 revolutions. Percentage friability was calculated using:

$$\text{Friability (\%)} = \frac{W_0 - W}{W_0} \times 100$$

where $W_0$is initial weight and $W$is final weight.

- **Drug content:** Determined by crushing tablets, dissolving an accurately weighed portion in phosphate buffer pH 7.4, filtering, suitably diluting, and analyzing spectrophotometrically at 296 nm using a UV–Visible spectrophotometer.

**Formulation of Press-Coated Pulsatile Tablets**

Press-coated tablets were prepared using the optimized core tablet (C2). Coating polymers (HPMC K4M and Ethyl Cellulose) were passed through sieve No. 70 and blended uniformly. Half of the polymer blend was placed in a 12 mm die cavity and lightly compressed to form a uniform bed. The core tablet was positioned centrally over this bed, and the remaining polymer blend was added to completely cover the core. The assembly was compressed using a 12 mm flat punch to obtain press-coated pulsatile tablets of total weight 350 mg. Different formulations (F1–F4) were prepared by varying the ratio of HPMC K4M and Ethyl Cellulose to modulate lag time and release behavior.

**Table 2:** Composition of Press-Coated Tablets

| S. No | Ingredients | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) |
|---|---|---|---|---|---|
| 1 | Core tablet | 150 | 150 | 150 | 150 |
| 2 | HPMC K4M | 200 | 125 | 105 | – |
| 3 | Ethyl cellulose | – | 75 | 95 | 200 |
| | Total Weight (mg) | 350 | 350 | 350 | 350 |

**Evaluation of Press-Coated Tablets**

The press-coated tablets were evaluated for various post-compression parameters including weight variation, thickness, hardness, friability, and drug content uniformity. Weight variation was assessed to ensure uniformity of tablet mass within the batch. Thickness was measured using a calibrated Vernier calliper to confirm consistency in tablet dimensions. Hardness testing was performed to determine the mechanical strength and ability of the tablets to withstand handling and transportation. Friability was evaluated using a friabilator to assess resistance to abrasion and mechanical stress, ensuring the percentage weight loss remained within acceptable limits. Drug content uniformity was determined to confirm the uniform distribution of Telmisartan within the formulation. All evaluation tests were conducted according to standard pharmacopoeial procedures to ensure compliance with quality specifications.

**In-Vitro Dissolution Studies**

In-vitro drug release studies were carried out using USP Dissolution Apparatus Type II (paddle method). The dissolution medium consisted of 900 mL phosphate buffer (pH 7.4) maintained at 37 ± 0.5°C with a rotation speed of 50 rpm. At predetermined time intervals, 5 mL samples were withdrawn and filtered through Whatman filter paper. The volume withdrawn was replaced with equal volume of fresh pre-warmed dissolution medium to maintain sink conditions. Samples were suitably diluted and analyzed spectrophotometrically at 296 nm. The cumulative percentage drug release was calculated and plotted against time to evaluate release kinetics and lag time.

**Stability Studies**

Accelerated stability studies of the optimized formulation (F2) were conducted according to ICH guidelines by storing the tablets

at 40°C ± 2°C and 75% ± 5% relative humidity for three months in aluminum foil packaging. Samples were evaluated initially and after 3 months for physical appearance, hardness, drug content, and in-vitro drug release profile to assess formulation stability.

## RESULTS AND DISCUSSION

### Pre-Compression Studies

The micromeritic properties of powder blends (C1–C4) were evaluated to ensure suitability for direct compression. Bulk density ranged from 0.509 to 0.574 g/cc and tapped density from 0.633 to 0.733 g/cc. The compressibility index values (18.3–24.9%) and Hausner's ratio (1.22–1.34) indicated fair to good flow properties. The angle of repose (28°–31°) confirmed acceptable flow behavior. These findings suggest that the powder blends possessed adequate flowability and compressibility, ensuring uniform die filling and minimal weight variation during compression. The micromeritic parameters complied with pharmacopoeial specifications, confirming suitability for tablet formulation by direct compression.

**Table 3:** Pre-Compression Parameters

| Batch | Bulk Density (g/cc) | Tapped Density (g/cc) | Compressibility Index (%) | Hausner's Ratio | Angle of Repose |
|---|---|---|---|---|---|
| C1 | 0.554 | 0.752 | 24.3 | 1.30 | 31°33′ |
| C2 | 0.535 | 0.719 | 24.9 | 1.34 | 31°33′ |
| C3 | 0.526 | 0.644 | 18.3 | 1.22 | 30°01′ |
| C4 | 0.509 | 0.633 | 19.4 | 1.24 | 28°36′ |

### Post-Compression Evaluation of Core Tablets

All core tablet formulations (C1–C4) were evaluated for weight variation, hardness, thickness, friability, and drug content. The weight variation results were within pharmacopoeial limits, indicating uniform die filling and consistent tablet mass. Hardness values ranged from 3.0 to 3.5 kg/cm², which was sufficient to withstand mechanical handling without compromising disintegration. Friability values were below 1%, confirming adequate mechanical strength. Thickness ranged from 3.1 to 3.3 mm, demonstrating uniform compression. Drug content ranged from 94.3% to 96.65%, indicating acceptable content uniformity. Among the batches, C2 demonstrated optimal mechanical properties and drug content and was therefore selected for press coating.

**Table 4:** Post-Compression Parameters

| Parameter | C1 | C2 | C3 | C4 |
|---|---|---|---|---|
| Weight variation (mg) | 151 ±1.2 | 150 ±1.4 | 150 ±1.4 | 151 ±1.2 |
| Thickness (mm) | 3.2 ±0.30 | 3.3 ±0.40 | 3.1 ±0.30 | 3.2 ±0.50 |
| Hardness (kg/cm²) | 3 ±0.42 | 3.5 ±0.23 | 3.2 ±0.34 | 3.2 ±0.34 |
| Friability (%) | 0.92 ±0.2 | 0.95 ±0.1 | 0.96 ±0.1 | 0.92 ±0.1 |
| Drug content (%) | 95.75 ±0.6 | 96.65 ±0.7 | 94.3 ±0.4 | 94.3 ±0.4 |

### Evaluation of Press-Coated Pulsatile Tablets

Press-coated tablets (F1–F4) were prepared using varying ratios of hydrophilic polymer HPMC K4M and hydrophobic polymer Ethyl Cellulose to modulate lag time and release behavior. All formulations complied with pharmacopoeial requirements for weight variation, friability (<1%), thickness, and drug content (96.30–98.42%). The hardness of coated tablets ranged from 2.6 to 4.6 kg/cm², indicating adequate mechanical strength despite the presence of a polymeric barrier layer. The variation in hardness among formulations may be attributed to differences in polymer concentration and compression characteristics of hydrophilic and hydrophobic polymers.

**Table 5:** Evaluation of Press-Coated Tablets

| Parameter | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| Weight variation (mg) | 350.20 ±0.85 | 350.70 ±0.36 | 350.10 ±0.95 | 350.35 ±0.55 |
| Thickness (mm) | 4.1 ±0.3 | 4.3 ±0.5 | 4.4 ±0.2 | 4.0 ±0.2 |
| Hardness (kg/cm²) | 2.6 ±0.10 | 4.4 ±0.35 | 4.6 ±0.46 | 2.8 ±0.25 |
| Friability (%) | 0.81 | 0.98 | 0.97 | 0.86 |
| Drug content (%) | 97.61 ±0.23 | 98.12 ±0.67 | 98.42 ±0.19 | 97.36 ±0.26 |

**In-Vitro Drug Release Studies**

In-vitro dissolution studies were performed in phosphate buffer pH 7.4 to simulate intestinal conditions and to evaluate the effect of polymer composition on lag time and drug release behavior. The release profiles clearly indicated that polymer ratio played a critical role in modulating pulsatile release characteristics. Formulation F1, containing HPMC K4M alone, exhibited no significant lag time and released 88% of the drug within 7 hours, which may be attributed to rapid swelling and hydration of the hydrophilic polymer leading to early rupture of the coating layer. In contrast, formulation F2 containing a combination of HPMC and Ethyl Cellulose in the ratio of 125:75 mg demonstrated an optimal lag phase followed by rapid drug release, achieving 96.3% cumulative release at the end of 8 hours. The presence of both hydrophilic and hydrophobic polymers created a balanced barrier system, where HPMC contributed to swelling while Ethyl Cellulose controlled water penetration and delayed drug release. Formulation F3 (105:95 mg) exhibited a comparatively prolonged release profile with 91.6% drug release, indicating increased retardation due to higher hydrophobic polymer content. Similarly, formulation F4 containing Ethyl Cellulose alone produced a more sustained release pattern with 90.82% drug release, primarily due to the dominant hydrophobic barrier restricting medium ingress. Overall, the results demonstrate that increasing the concentration of Ethyl Cellulose enhanced lag time by reducing water penetration, whereas HPMC facilitated swelling and eventual rupture of the coating layer. The synergistic combination of hydrophilic and hydrophobic polymers in formulation F2 successfully achieved the desired pulsatile release pattern, making it suitable for chronotherapeutic management of hypertension.

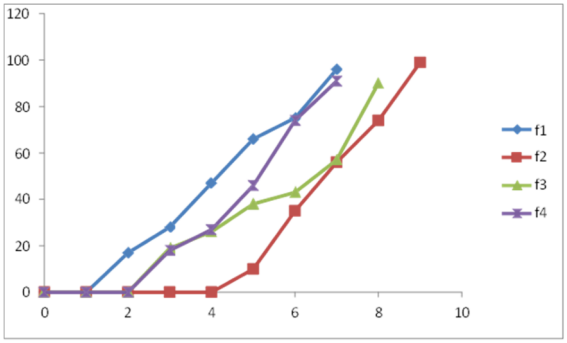



**Fig 1:** *In-vitro* comparative TEL release profile of all the formulations

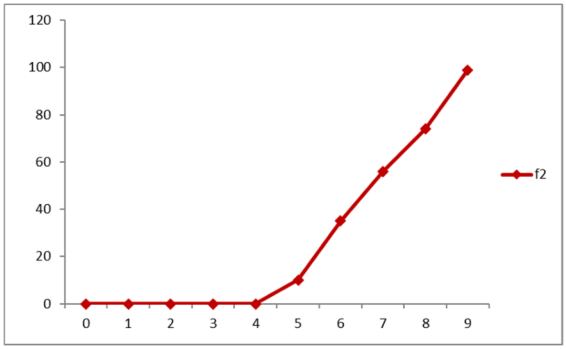



**Fig 2:** I*n-vitro* drug release profile for optimized batch formulation 'C 2'

**Stability Studies**

Accelerated stability studies of optimized formulation F2 were conducted at 40°C ± 2°C and 75% ± 5% RH for 3 months as per ICH guidelines. No significant changes were observed in physical appearance, hardness (6 to 5.8 kg/cm²), drug content, or in-vitro drug release profile. The stability results confirmed that the optimized press-coated pulsatile tablet maintained its integrity and release characteristics under accelerated storage conditions, indicating good formulation stability.

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## CONCLUSION

The present study successfully formulated and evaluated a press-coated pulsatile drug delivery system of Telmisartan using HPMC K4M and Ethyl Cellulose. The powder blends exhibited acceptable micromeritic properties, ensuring suitability for direct compression. Core tablets complied with pharmacopoeial specifications for post-compression parameters. Among the press-coated formulations, batch F2 demonstrated an optimal lag time followed by rapid and complete drug release (96.3% at 8 hours), fulfilling the requirements of a pulsatile drug delivery system for chronotherapy in hypertension. Stability studies confirmed the robustness and stability of the optimized formulation under accelerated conditions. Thus, the developed pulsatile drug delivery system of Telmisartan shows promising potential for chronotherapeutic management of hypertension by synchronizing drug release with the early morning surge in blood pressure, thereby improving therapeutic efficacy and patient compliance.

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