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Research Article

Formulation And Evaluation of Pulsatile Drug Delivery System

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ABSTRACT

Pulsatile drug delivery systems (PDDS) are designed to release drugs in a transient manner, following a predetermined lag time, to synchronize with the body's circadian rhythms or specific biological events. This study aimed to develop and evaluate a press-coated pulsatile tablet of Telmisartan, a drug commonly used to treat hypertension, where blood pressure typically peaks in the morning. Preformulation studies confirmed the drug's purity and solubility profile, with UV spectroscopy determining the maximum wavelength at 295 nm. Standard calibration curves were linear (2-18 µg/ml) in a phosphate buffer (pH 6.8) at 295 nm. FT-IR spectroscopy showed no interaction between Telmisartan and the polymers used. Core tablets were evaluated for micromeritic properties, with bulk density ranging from 0.50 to 0.52 g/cc, tapped density from 0.57 to 0.59 g/cc, compressibility index from 10.34% to 13.79%, and a Hausner's ratio between 1.11 and 1.16, indicating good flowability. Post-compression parameters for core tablets were within acceptable limits: weight variation (100-101 mg), hardness (3.4-3.6 Kg/cm²), friability (0.86-0.90%), thickness (3.0-3.2 mm), drug content (96.72-99.16%), and disintegration time (28-38 sec). In vitro dissolution studies showed that formulations with 4% Croscarmellose Sodium exhibited the fastest drug release. Pulsatile tablets were successfully developed and evaluated, demonstrating the potential for chronotherapeutic drug delivery, aligning drug release with circadian rhythms.

INTRODUCTION

Pulsatile drug delivery systems (PDDS) are designed to release drugs in a pulsating manner, offering a distinct approach from continuous release systems. These systems are valuable when a drug needs to be released at a specific time or synchronized with the body's natural rhythms. Key characteristics of PDDS include a lag time before drug release and a subsequent rapid release of the

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drug. These systems often consist of a core tablet containing the drug, coated with a polymeric barrier that controls the lag time. Chronobiology, the study of biological rhythms, is closely related to PDDS. Circadian rhythms, approximately 24-hour cycles, influence various physiological processes. Chronopharmacology explores how drug actions vary with these rhythms, and chronotherapy aims to align treatments accordingly. Pulsatile drug delivery is particularly relevant for conditions where symptoms vary with circadian rhythms, such as asthma, cardiovascular diseases, and hypertension. In the development of pulsatile drug delivery systems, various parameters and formulations are evaluated. Preformulation studies, including melting point determination and solubility tests, are conducted to characterize the drug. Standard calibration curves are prepared to quantify the drug. Compatibility studies, often using FT-IR spectroscopy, assess interactions between the drug and other formulation components. The evaluation of core tablets involves assessing pre-compression parameters like bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose, which are important for tablet formation. Post-compression parameters such as weight variation, hardness, friability, thickness, drug content, and disintegration time are also evaluated to ensure tablet quality. In-vitro dissolution studies are conducted to assess drug release profiles.

2. MATERIALS AND METHODS

This research investigated the formulation and evaluation of press-coated pulsatile tablets of Telmisartan for controlled drug delivery. The following materials and methods were employed:

2.1 MATERIALS

- **Active Pharmaceutical Ingredient:** Telmisartan (Glenmark Pharmaceuticals, Goa).
- **Polymers:** Hydroxypropyl methylcellulose (HPMC) K100M and HPMC E5 (S. D. Fine Chemicals).
- **Disintegrants:** Croscarmellose Sodium and Sodium Starch Glycolate (S. D. Fine Chemicals).
- **Diluent:** Microcrystalline cellulose (S. D. Fine Chemicals).
- **Lubricants:** Talc and Magnesium Stearate (S. D. Fine Chemicals).
- **Solvent:** Phosphate buffer pH 6.8 (prepared in-house using analytical grade chemicals).

2.2 Equipment:

The following equipment was used throughout the study: Electronic Balance (Citizen), Hardness Tester (Pfizer), Friability test apparatus (Roche Friabilator), Tablet Punching Machine (Shakti Press, India), Dissolution Test Apparatus (USP) and Tablet Disintegration test apparatus (Electro Lab, India), Tap Density Tester (Labline, India), UV Spectrophotometer (Shimadzu, Japan UV 1601), IR Spectrophotometer (Schimadzu, Japan), Hot Air Oven and Stability Chamber (both from Labline, India), Melting point apparatus (local manufacture), Vernier caliper (local manufacture).

2.3 Preformulation Studies:

Prior to formulation, Telmisartan underwent preformulation studies including:

- **Melting Point Determination:** Using the capillary method.
- **Solubility Assessment:** In various aqueous and non-aqueous solvents.

- **UV Spectroscopy:** To determine the λmax in phosphate buffer pH 6.8.

2.4 Preparation of Standard Curve of Telmisartan:

A standard calibration curve was prepared by dissolving Telmisartan in phosphate buffer pH 6.8 to obtain a stock solution, followed by serial dilutions. Absorbance of these solutions was measured at 295 nm using a UV-Vis spectrophotometer, and a calibration curve of absorbance versus concentration was plotted.

2.5 Drug-Excipients Compatibility Studies:

Drug-excipient compatibility was assessed using IR Spectroscopy. Physical mixtures of Telmisartan with each excipient (1:100 ratio with KBr) were compressed into pellets, and their IR spectra were compared with that of pure Telmisartan to detect any potential interactions.

2.6 Preparation of Core Tablets of Telmisartan:

Core tablets containing 40 mg of Telmisartan were prepared by direct compression. Four different formulations (C1-C4) were prepared, varying the type and concentration of disintegrants (Croscarmellose Sodium and Sodium Starch Glycolate), while keeping the total weight at 100 mg using microcrystalline cellulose as a diluent and magnesium stearate and talc as lubricants (Table 6.3). The powder blends were prepared by mixing the accurately weighed ingredients, passing them through sieve no. 30, and compressing them using an 8 mm flat face punch on a multi-station tablet punching machine.

2.7 Formulation of Press Coated Pulsatile Tablet of Telmisartan:

Press-coated pulsatile tablets were prepared using the optimized core tablet formulation (C2) and a coating layer composed of HPMC K100M and HPMC E5 in different weight ratios (Table 6.4). The press-coating process involved placing the core tablet within a powder bed of the coating polymers in a 12 mm die and compressing the outer layer using a 12 mm flat punch to achieve a total tablet weight of 300 mg. Magnesium stearate and talc (1% w/w) were used as lubricants in the coating layer.

2.8 Evaluation of Powder Blend (Precompression Parameters):

The powder blend for the core tablets was evaluated for:

- **Bulk Density (Db):** Measured by dividing the mass of the powder by its bulk volume.
- **Tapped Density (Dt):** Determined by tapping the powder until a constant volume was achieved and dividing the mass by the tapped volume.
- **Angle of Repose (θ):** Measured using the funnel method and calculated using the formula $\tan(\theta)=h/r$.
- **Carr's Index (% Compressibility):** Calculated using the formula $I=DtDt-Db \times 100$.
- **Hausner Ratio:** Calculated as the ratio of tapped density to bulk density ($HausnerRatio=DbDt$).

2.9 Evaluation of Pulsatile Tablets:

The prepared press-coated tablets were evaluated for various quality control parameters:

- **Weight Variation:** Twenty randomly selected tablets were individually weighed, and the percentage deviation from the average weight was calculated.

- **Hardness:** Measured using a Monsanto tablet hardness tester.
- **Thickness:** Measured using a Vernier caliper.
- **Friability:** Determined using a Roche friabilator by subjecting a pre-weighed sample of tablets to 100 revolutions and calculating the percentage weight loss.
- **Content Uniformity:** The drug content of ten randomly selected tablets was determined spectrophotometrically at 295 nm after dissolving the powdered tablets in phosphate buffer pH 6.8.
- **Disintegration Test:** The disintegration time of the core tablets was determined using a USP disintegration test apparatus in phosphate buffer pH 6.8 at 37 ± 1 °C.
- **In-Vitro Dissolution Study:** Drug release from the press-coated tablets was studied using USP dissolution test apparatus type II (paddle) in 900 ml of phosphate buffer pH 6.8 at 50 rpm and 37 ± 0.5 °C. Samples were withdrawn at predetermined time intervals, filtered, and analyzed spectrophotometrically at 295 nm.

2.10 Drug Release Kinetics:

The in-vitro drug release data were fitted to various kinetic models: Zero-order, First-order, Higuchi, and Korsmeyer-Peppas to determine the drug release mechanism. The Korsmeyer-Peppas model was further used to determine the release exponent (n) to characterize the drug release mechanism.

2.11 Stability Study:

Accelerated stability studies were conducted on the optimized formulation by storing the tablets in aluminum foil strips in a stability chamber maintained at 40 °C and 75% RH for 3 months, according to ICH guidelines. The tablets were evaluated for changes in appearance, hardness, disintegration time, drug content, and in-vitro drug release at initial time points and after 3 months.

3. RESULTS AND DISCUSSION

3.1 Preformulation Study

- **3.1.1 Determination of Melting Point:** The melting point of Telmisartan was found to be between 269 and 270°C, confirming the drug's purity.
- **3.1.2 Solubility:** Telmisartan was insoluble in water but soluble in ethanol, methanol, acetonitrile, and dichloromethane.
- **3.1.3 UV-Spectroscopy:** The maximum wavelength (λmax) of Telmisartan in a phosphate buffer solution (pH 6.8) was observed at 295 nm.

3.2 Standard Calibration Curve of Telmisartan

- A standard calibration curve was prepared using Telmisartan solutions (2 to 18 µg/ml) in a 6.8 pH phosphate buffer, and absorbance was measured at 295 nm.
- The calibration curve was linear, and absorbance increased with concentration, following Beer-Lambert's Law.

Table 3.1: Standard Calibration Curve of Telmisartan in Phosphate Buffer Solution pH 6.8

Sr. No	Concentration (µg/ml)	Absorbance
0	0	0
1	2	0.114
2	4	0.215
3	6	0.324

4	8	0.421
5	10	0.534
6	12	0.645
7	14	0.75
8	16	0.844
9	18	0.967

3.3 Compatibility Studies (FT-IR)

- FT-IR spectroscopy showed no chemical interaction between Telmisartan and the polymers used in the study.
- The principal peaks in the infrared spectra of the drug and polymer mixture remained unchanged.

3.4 Evaluation of Core Tablets of Telmisartan

- **3.4.1 Pre-compression Parameters:** The micromeritic properties of the powder blend for core tablets were evaluated.

Table 3.2: Micromeritics Properties of Powder Blend of Core Tablets of Telmisartan Formulation (C1 to C4)

Batch	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (Θ)
C1	0.52 ± 0.05	0.59 ± 0.06	11.86 ± 0.07	1.13 ± 0.02	25.32
C2	0.51 ± 0.06	0.59 ± 0.05	13.55 ± 0.09	1.15 ± 0.02	25.62
C3	0.50 ± 0.04	0.58 ± 0.08	13.79 ± 0.05	1.16 ± 0.04	27.50
C4	0.52 ± 0.05	0.57 ± 0.04	10.34 ± 0.07	1.11 ± 0.05	26.30

- The powder blends showed acceptable micromeritic properties for tablet compression.

3.5 Post-Compression Parameters

- The post-compression parameters of the core tablets were evaluated.

Table 3.3: Post Compression Parameters of Core Tablets Formulation (C1 to C3)

Batch	Weight Variation (mg)	Hardness (Kg/cm²)	Friability (%)	Thickness (mm)	Drug Content (%)	Disintegration Time (sec)
C1	100 ± 1.4	3.5 ± 0.48	0.90 ± 0.16	3 ± 0.06	97.56 ± 0.81	34 ± 1.12
C2	101 ± 1.2	3.5 ± 0.61	0.86 ± 0.20	3.1 ± 0.04	99.16 ± 0.74	28 ± 1.51
C3	100 ± 1.6	3.4 ± 0.52	0.88 ± 0.18	3.2 ± 0.03	96.72 ± 0.66	38 ± 0.74
C4	101 ± 1.4	3.6 ± 0.56	0.87 ± 0.23	3 ± 0.04	98.45 ± 0.60	32 ± 0.64

- All batches met the requirements for weight variation, hardness, friability, thickness, drug content, and disintegration time.

- **3.5.7 In-Vitro Dissolution Study**

Table 3.4: In Vitro Drug Release of Core Tablets of Telmisartan

Time (min)	C1	C2	C3	C4
5	41.15 ± 1.16	52.26 ± 0.87	44.72 ± 1.66	48.66 ± 1.20
10	58.33 ± 1.32	76.24 ± 2.06	54.75 ± 2.10	70.21 ± 1.05
15	72.21 ± 1.51	98.84 ± 1.40	70.02 ± 1.75	90.12 ± 1.36
20	86.20 ± 1.55	-	87.62 ± 1.45	98.69 ± 2.25
30	97.56 ± 2.25	-	98.61 ± 1.92	-

- The type and concentration of superdisintegrants significantly influenced drug release.

3.6 Evaluation of Press-Coated Pulsatile Tablet of Telmisartan

- Pulsatile tablets were prepared, and evaluated.

Table 3.5: Evaluation of Telmisartan Press Coated Pulsatile Tablets (F1 to F6)

Batch	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)	Lag Time (Hr)
F1	301 ± 0.23	5.4 ± 0.42	0.62 ± 0.34	4.50 ± 0.52	97.61 ± 0.23	5
F2	300 ± 0.41	5.5 ± 0.32	0.51 ± 0.30	4.53 ± 0.33	98.02 ± 0.67	0
F3	302 ± 0.57	5.6 ± 0.57	0.50 ± 0.27	4.50 ± 0.35	96.42 ± 0.19	0
F4	300 ± 0.22	5.5 ± 0.21	0.58 ± 0.25	4.52 ± 0.47	99.36 ± 0.26	5
F5	302 ± 0.25	5.3 ± 0.36	0.54 ± 0.38	4.51 ± 0.64	96.30 ± 0.30	5
F6	301 ± 0.38	5.4 ± 0.30	0.58 ± 0.36	4.52 ± 0.31	97.41 ± 0.53	5

- The results showed that formulations F1, F4, F5, and F6 exhibited the desired lag time for pulsatile drug release.

- **3.6.1 In Vitro Drug Release of Press Coated Pulsatile Tablets**

Table 3.6: In Vitro Drug Release of Telmisartan Pulsatile Tablets

Time (Hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	0.56 ± 0.12	30.36 ± 1.88	10.14 ± 0.32	0.82 ± 0.12	0.64 ± 0.10	0 ± 0.00
2	1.14 ± 0.45	59.16 ± 1.67	15.47 ± 0.56	1.31 ± 0.43	1.12 ± 0.94	1.06 ± 0.56
3	2.16 ± 1.24	78.36 ± 2.30	26.84 ± 0.67	2.12 ± 1.12	1.78 ± 1.15	1.81 ± 1.20
4	3.24 ± 0.88	99.3 ± 2.10	38.25 ± 1.56	2.28 ± 1.46	3.67 ± 1.20	3.12 ± 1.44
5	3.88 ± 1.36	-	44.65 ± 1.27	3.26 ± 1.89	3.18 ± 0.78	2.92 ± 1.70
6	5.12 ± 1.55	-	56.2 ± 2.05	23.41 ± 1.92	20.34 ± 1.05	17.45 ± 2.30
7	12.25 ± 2.12	-	74.41 ± 1.66	56.24 ± 1.67	44.27 ± 1.48	36.73 ± 2.34
8	21.32 ± 1.63	-	92.26 ± 2.16	98.61 ± 2.34	88.27 ± 1.77	80.34 ± 1.90

- The dissolution profiles varied based on the polymer composition.

3.7 Drug Release Kinetics

- The drug release data were evaluated using various kinetic models.
- The Korsmeyer-Peppas model provided the best fit for all formulations.

Table 3.7: Model Fitting Release Profile Of Formulations F1 To F6

Formulation	Zero Order	First Order	Higuchi	Korsmeyer-Peppas		Best Fitting Model
	R^2	R^2	R^2	R^2	('n' Value)	
F1	0.725	0.701	0.526	0.916	1.61	Peppas
F2	0.989	0.774	0.957	0.995	0.85	Peppas
F3	0.975	0.773	0.84	0.978	1.07	Peppas
F4	**0.642**	**0.427**	**0.429**	**0.74**	**2.23**	**Peppas**
F5	0.632	0.488	0.423	0.801	2.28	Peppas
F6	0.62	0.5	0.413	0.735	2.06	Peppas

4. CONCLUSION

This study successfully developed and evaluated a pulsatile drug delivery system for Telmisartan using a press-coated tablet strategy. The core tablets formulated with 4% Croscarmellose Sodium (Batch C2) displayed superior disintegration and dissolution profiles, qualifying it as the optimal core. The press-coating layer composed of varying concentrations of HPMC K100M and E5 significantly influenced the lag time and drug release kinetics. The formulation F4 (HPMC K100M:E5 in a 150:50 mg ratio) emerged as the most effective pulsatile system, offering controlled lag time of 5 hours, near-complete drug release (98.61% at 8 hours), consistent physical characteristics, and adequate drug content uniformity. The study underscores the critical role of polymer viscosity and ratio in designing chronotherapeutic drug delivery systems. By aligning drug release with the circadian rhythm of hypertension, the pulsatile formulation enhances therapeutic outcomes, reduces side effects, and improves patient compliance. Overall, the optimized pulsatile formulation of telmisartan holds significant potential for targeted and time-specific hypertension therapy. Further in vivo studies would be beneficial to confirm its clinical effectiveness and establish its superiority over conventional dosage forms.

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