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Research Article

Formulation and Evaluation of Pulsatile Drug Delivery System of Metoprolol Tatrate

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ABSTRACT

Background: Hypertension exhibits marked circadian variations, with an increased risk of cardiovascular events during the early morning hours. Conventional dosage forms fail to synchronize drug release with these biological rhythms, highlighting the need for chronotherapeutic drug delivery systems. Pulsatile drug delivery offers a promising strategy by providing a programmed lag phase followed by rapid drug release at the desired therapeutic time.

Objective: The present study aimed to develop and evaluate a compression-coated pulsatile drug delivery system of Metoprolol Tartrate for chronotherapeutic management of hypertension.

Materials and Methods: Metoprolol Tartrate core tablets were prepared by direct compression and enteric coated using Eudragit L100. The coated core tablets were subsequently compression coated with optimized immediate-release and sustained-release layers. The formulations were evaluated for pre- and post-compression parameters, FTIR drug–excipient compatibility, acid uptake, drug content, and *in vitro* dissolution studies.

Results: FTIR analysis confirmed the compatibility of Metoprolol Tartrate with the selected excipients. The optimized formulation exhibited satisfactory physicochemical properties and complied with pharmacopeial specifications. The enteric coating provided effective gastric protection, while the compression-coated system produced a distinct lag phase followed by controlled drug release, achieving 81.85% cumulative drug release within 8 hrs.

Conclusion: The developed compression-coated pulsatile tablet successfully achieved time-dependent release of Metoprolol Tartrate and demonstrated its potential as a chronotherapeutic drug delivery system for hypertension. The formulation may improve therapeutic efficacy by synchronizing drug release with the circadian pattern of cardiovascular events.

Keywords: Metoprolol Tartrate, Pulsatile Drug Delivery, Compression-Coated Tablets, Chronotherapy, Hypertension, Modified-Release System.

INTRODUCTION

Pulsatile drug delivery systems (PDDS) are advanced modified-release formulations designed to release the drug after a predetermined lag time, followed by rapid drug release to synchronize therapy with the body's circadian rhythms[1]. Unlike conventional sustained-release systems, PDDS improve therapeutic efficacy, reduce adverse effects, and enhance patient compliance by delivering the drug when it is most needed. Various approaches, including osmotic, time-dependent, capsule-based, multiparticulate, and compression-coated systems, have been developed to achieve pulsatile release[2-3]. The release mechanism is primarily governed by polymer swelling, erosion, dissolution, or rupture of the coating barrier. Both natural and synthetic polymers, such as HPMC, ethyl cellulose, and Eudragit®, play a crucial role in controlling the lag time and release profile. Among these approaches, compression-coated tablets have attracted considerable interest owing to their simple manufacturing process, reproducibility, and ability to provide site-specific and chronotherapeutic drug delivery, particularly for the management of diseases such as hypertension, asthma, rheumatoid arthritis, and diabetes mellitus[4-5]. Tablets remain the most preferred pharmaceutical dosage form owing to their ease of administration, accurate dosing, cost-effective manufacturing, and excellent stability[6]. Recent advances in formulation have led to the

development of modified-release systems, particularly compression-coated tablets, which provide controlled, delayed, and pulsatile drug release. Compression coating, also known as tablet-in-tablet technology, is a solvent-free approach in which a drug-loaded core tablet is surrounded by an outer polymeric layer to achieve a predetermined release profile[7]. Drug release is primarily governed by the composition and thickness of the coating layer, as well as the physicochemical properties of the polymers employed. Compared with conventional film coating, compression coating offers improved stability, separation of incompatible ingredients, and greater flexibility in designing chronotherapeutic formulations. Enteric polymers such as Eudragit® L100 and release-retarding polymers such as ethyl cellulose are widely used to regulate site-specific and time-dependent drug release. Owing to its simple manufacturing process and reproducible release characteristics, compression coating has emerged as a promising strategy for pulsatile drug delivery, particularly for cardiovascular disorders where synchronization of drug release with circadian rhythms is essential[8].

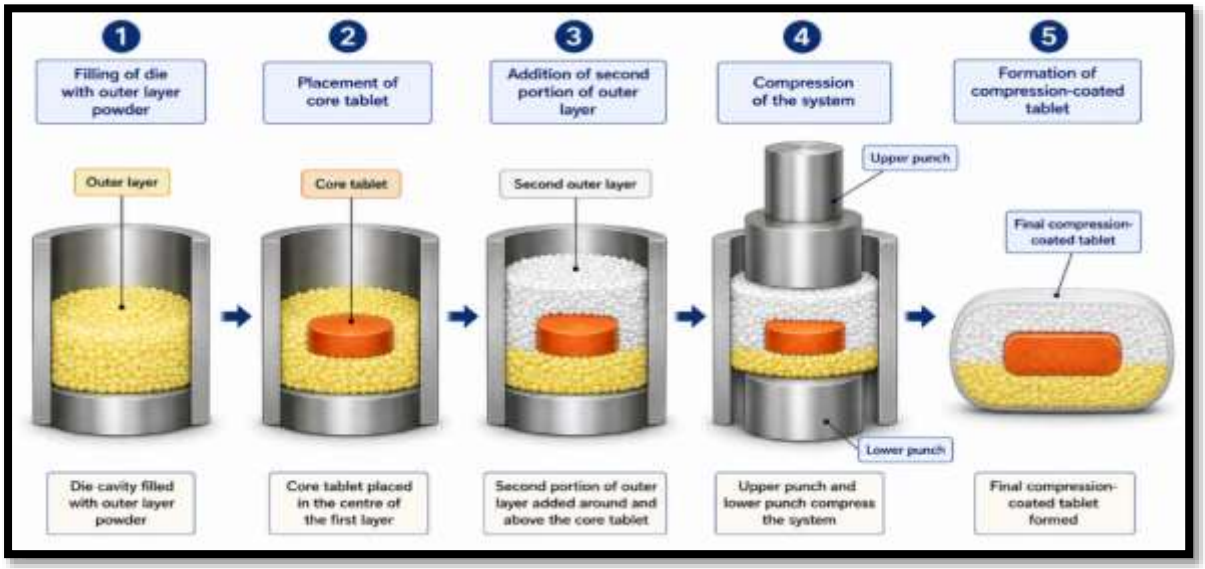

Figure 1: Manufacturing Steps of Compressed Coated Tablet

MATERIALS AND METHODS

Materials

The materials used in the present study included Metoprolol Tartrate and Eudragit® L100 (gift samples), microcrystalline cellulose (Research Lab Fine Chem Industry), lactose monohydrate, sodium starch glycolate, povidone K30, ethyl cellulose, polyethylene glycol 6000 (PEG 6000), and talc (Central Drug House Pvt. Ltd., India), magnesium stearate (Pallav Chemical and Solvents Pvt. Ltd., India), and ethanol (Variety Traders, India). All chemicals and excipients used were of analytical or pharmaceutical grade and were utilized without further purification.

Formulation of Core Tablet

Metoprolol Tartrate core tablets were prepared by the direct compression method. All ingredients were accurately weighed, sieved, blended uniformly, lubricated with magnesium stearate, and compressed into 160 mg tablets using a rotary tablet compression machine[9]. The prepared tablets were subsequently evaluated and used for the development of compression-coated pulsatile tablets[10].

The lubricated granules were compressed into core tablets using a Rotary Press tablet Compression Machine (Karnavati Engineering Pvt. Ltd., Mini Press II DL) fitted with 7.14 mm punch. The prepared tablets were evaluated for physical integrity and stored in airtight containers for further studies.

The prepared core tablets were evaluated for appearance, thickness, hardness, friability, weight variation, disintegration time, and drug content using standard pharmacopeial methods. Thickness, hardness, and friability were determined using a Vernier calliper, Monsanto hardness tester, and Roche friabilator, respectively, while drug content was estimated by UV–Visible spectrophotometry using the established calibration curve[11].

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The optimized core tablets were enteric coated by the dip coating method using a Eudragit® L100 coating solution. The tablets were repeatedly dipped and air-dried until the desired coating thickness was achieved. The coated tablets were then stored in airtight containers for subsequent evaluation[12].

The acid uptake study was performed to evaluate the integrity and acid resistance of the enteric-coated tablets. The tablets were weighed before and after exposure to 0.1 N HCl under specified conditions, and the percentage acid uptake was calculated from the change in weight to assess the efficiency of the enteric coating during the lag phase[13].

Table 1: Composition of Core Tablet

Sr. No.	Ingredients	Quantity (%)
1.	Metoprolol Tartrate	7.81
2.	Microcrystalline Cellulose	46.88
3.	Lactose Monohydrate	36.25
4.	Sodium Starch Glycolate	6.25
5.	PVP K 30	1.88
6.	Magnesium Stearate	0.94
	Total	**100.00**

Preparation of Sustained Release Layer

The sustained release outer layer was prepared using wet granulation method. The composition for sustained release layer is as shown in the table no. 2. The prepared sustained release granules were evaluated for pre-compression parameters including bulk density, tapped density, Carr's Index, and Hausner's Ratio to assess flowability, packing properties, and suitability for compression[16]. The sustained release trial formulations with varying polymer concentrations were developed and evaluated for physicochemical properties and in vitro drug release. The optimized formulation was selected for the preparation of the compression-coated pulsatile tablets[14-15].

Table 2: Composition of Sustained Release Layer

Sr No.	Ingredients	F1	F2
1.	Metoprolol Tartrate	3.13	6.25
2.	Ethyl Cellulose	27.50	10.00
3.	Microcrystalline Cellulose	35.00	42.00
4.	Lactose Monohydrate	27.50	35.75
5.	PVP K 30	3.00	5.00
6.	Mg. Stearate	1.37	1.00
	Total	**100.00**	**100.00**

The Weight Sustained Release Layer is 400 mg

Preparation of Immediate Release Granules

The immediate release layer was formulated using wet granulation method using the ingredients such as MCC, lactose monohydrate, sodium starch glycolate, PVP K30, and magnesium stearate as shown in the table no. 3. The prepared immediate release granules were evaluated for pre-compression parameters including bulk density, tapped density, Carr's Compressibility Index, and Hausner's Ratio to determine flowability, packing properties, and suitability for tablet compression[18]. To achieve rapid drug release following the lag phase. Trial formulations with varying excipient concentrations were prepared and evaluated for granule characteristics and drug release. The optimized formulation was selected for the development of the compression-coated pulsatile tablet system[17].

Table 3: Formulation of Immediate Release Tablet

Sr No.	Ingredients	F1 (%)	F2(%)
1.	Metoprolol Tartrate	3.13	3.13
2.	Microcrystalline Cellulose	37.50	52.50
3.	Lactose Monohydrate	50.00	35.00
4.	Sodium Starch Glycolate	7.00	7.00
5.	PVP K 30	1.50	1.50
6.	Magnesium Stearate	0.88	0.88
	Total	**100.00**	**100.00**

The Weight of Immediate Release Layer is 400 mg

Formulation of Compression-Coated Pulsatile Tablet

Compression-coated pulsatile tablets were prepared using the optimized sustained release layer, enteric-coated core tablets, and immediate release layer. The tablets were compressed using a rotary tablet compression machine (Karnavati Engineering Pvt. Ltd., Mini Press II DL) using 19×11 mm, oval shaped punch under optimized compression conditions to obtain uniform tablets with adequate mechanical strength.

Procedure for Compression-Coated Tablet Preparation

The sustained release granules were filled into the die cavity and lightly compressed to form a uniform base layer. The dip-coated core tablet was accurately placed at the centre, followed by addition of immediate release granules. The complete assembly was compressed to obtain the final compression-coated pulsatile tablets. The prepared tablets were visually inspected and stored in suitable containers for further evaluation[19].

Evaluation of Compression-Coated Tablets

The prepared compression-coated pulsatile tablets were evaluated for post-compression parameters, including appearance, thickness, hardness, drug content, and in vitro drug release. Tablet appearance was assessed by visual inspection, while thickness and hardness were determined using a Vernier calliper and Monsanto hardness tester, respectively. Drug content was estimated by UV–Visible spectrophotometry after suitable extraction and dilution of powdered tablets[20].

The *in vitro* dissolution study was performed using a USP Type I dissolution apparatus (Lab India) under simulated gastrointestinal conditions. The tablets were exposed to 0.1 N HCl for the initial 2 h, followed by phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C with a basket rotation speed of 50 rpm. Samples were withdrawn at predetermined intervals, filtered, and analyzed at 274 nm using a UV–Visible spectrophotometer. The cumulative percentage drug release was calculated to evaluate the pulsatile release behaviour of the formulation[21].

RESULTS AND DISCUSSION

Granulometric Evaluations

The results of granulometric evaluations of optimized batches of core tablet, sustained release layer granules and the immediate release layer are shown in the table 4. The granulometric evaluations include angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.

Table 4: Pre-compression Evaluations Parameters of Granules

Sr No.	Parameters	Core Tablet Granules	Sustained Release layer	Immediate Release Layer
1.	Angle of Repose (°)	27.84 ± 0.22	27.45 ± 0.31	26.95 ± 0.18
2.	Bulk Density	0.548 ± 0.01	0.556 ± 0.02	0.561 ± 0.02
3.	Tapped Density	0.586 ± 0.02	0.592 ± 0.01	0.595 ± 0.01
4.	Carr's Index	6.48 ± 0.15	6.08 ± 0.21	5.71 ± 0.19
5.	Hausner's Ratio	1.06 ± 0.01	1.06 ± 0.01	1.05 ± 0.02

Table 5: % Acid Uptake of Core Tablet

Tablet	Initial Weight (mg)	Final weight (mg)	Weight Gain (mg)	% Acid uptake
1	213	231	18	8.45%

2	210	221	11	5.24%

% Acid Uptake of core tablet

The acid uptake study of dip-coated core tablets indicated percentage uptake values of 8.45% and 5.24% for tablet 1 and tablet 2 respectively. Both the values were within the acceptable limit of not more than 10%, confirming the integrity and effectiveness of the Eudragit L 100 coating in preventing excessive penetration of the acidic medium into the core tablets during the gastric phase. Also provided that coating was successfully done for the enteric purpose.

Post-compression Evaluations of Compressed Coated Pulsatile Release Tablet

Figure 2: Compressed Coated Tablet

Table 6: Post-compression Evaluations of Compressed Coated Pulsatile Release Tablet

Sr No.	Evaluation Parameters	Results
1.	Thickness	6.66 ± 0.05 mm
2.	Hardness	7.5 – 8.2 Kg/cm^2
3.	%Weight Variation	0.03-1.67%
4.	% Drug Content	97.22%

The prepared compression-coated pulsatile tablets exhibited a smooth oval appearance without visible defects and showed satisfactory post-compression characteristics. The tablets had a thickness of **6.66 ± 0.05 mm**, hardness of **7.5–8.2 kg/cm²**, an average weight of **972.75 mg**, and **0.03–1.67%** weight variation, all within acceptable pharmacopeial limits. The optimized formulation also exhibited a drug content of **97.22%**, as determined by UV–Visible spectrophotometry (Lab India) using the established calibration curve, confirming uniform drug distribution and content uniformity.

In-vitro Drug Release

The optimized compression-coated pulsatile tablet exhibited a distinct lag phase followed by controlled drug release, in contrast to the marketed and conventional tablets, which showed immediate drug release in the acidic medium. The developed formulation achieved 90.74% cumulative drug release within 480 mins, demonstrating the desired biphasic release profile and its suitability for chronotherapeutic delivery of Metoprolol Tartrate.

Comparative Study between Compressed Coated Tablet, Conventional Tablet and Marketed Tablet

The comparative in vitro dissolution profiles of the marketed tablet, conventional tablet, and the developed compressed coated tablet are presented in Figure 3. A distinct difference in the drug release behaviour was observed among the three formulations. The marketed and conventional tablets exhibited rapid and continuous drug release, achieving 99.80% and 98.70% cumulative drug release within 300 min, respectively. In contrast, the compressed coated tablet exhibited a significantly slower and controlled release profile, with 76.06% drug release at 300 min, which gradually increased to 90.74% at 480 min. The modified dissolution behaviour of the compressed coated tablet can be attributed to the presence of the compression-coated polymeric barrier, which effectively delayed the penetration of the dissolution medium into the tablet core, thereby retarding the onset of drug release. Following

hydration of the coating layer, gradual swelling and erosion of the polymer matrix facilitated a controlled diffusion of the drug, resulting in a sustained release profile over the dissolution period. This behaviour confirms the successful functionality of the compression coating in regulating drug release while maintaining the integrity of the core tablet during the initial phase of dissolution.

The observed release pattern is highly desirable for pulsatile drug delivery systems, where an initial lag phase followed by rapid or controlled drug release is required to synchronize drug availability with the circadian rhythm of disease symptoms. The prolonged lag phase provided by the compression coat minimizes premature drug release and enables site- and time-specific drug delivery, thereby enhancing therapeutic efficacy while potentially reducing dose-related adverse effects. Such a release profile is particularly advantageous in the chronotherapeutic management of diseases such as hypertension, and migraine where symptoms exhibit predictable circadian variation.

Overall, the dissolution results demonstrate that the developed compressed coated tablet successfully modulated the drug release profile compared with the marketed and conventional formulations. The controlled and extended release behaviour confirms the suitability of the developed formulation as a promising pulsatile drug delivery system**.**

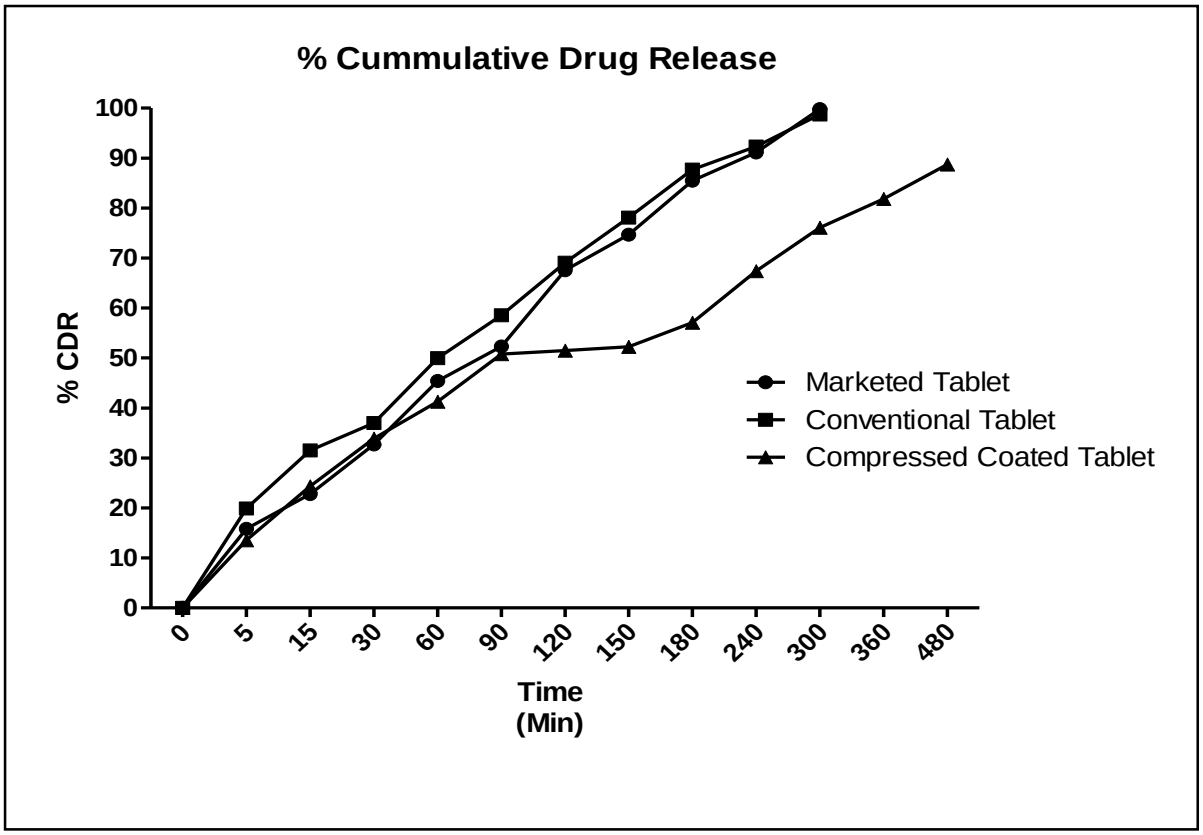

Figure 3: Comparative Study between Marketed Tablet, Conventional Tablet and Compressed Coated Tablet

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