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FORMULATION DEVELOPMENT AND IN-VITRO CHARACTERIZATION OF PULSATILE DRUG DELIVERY SYSTEM FOR SPIRONOLACTONE

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ABSTRACT

spironolactone is a steroid-based aldosterone antagonist belonging to the spirolactone class and is widely prescribed as an adjunct therapy in Chronic Heart Failure (CHF) and hypertension, particularly in patients with aldosterone-mediated resistant hypertension.[1] The present investigation aimed to formulate and evaluate press-coated tablets of spironolactone using polymers such as ethyl cellulose and hydroxypropyl methylcellulose (HPMC) for achieving pulsatile drug release. Based on consistent and reproducible experimental outcomes obtained from both core and press-coated tablets, formulation F6 of the core tablet and E2f6 of the press-coated tablet demonstrated a lag time of approximately 6 hours followed by a rapid burst release during the 7th hour and maximum drug release by the end of the 8th hour. Hence, these formulations were identified as optimized systems suitable for pulsatile drug delivery design. The findings confirm that press-coated spironolactone tablets can be effectively used as a time-controlled chronopharmaceutical dosage form.[2-5]

KEYWORDS: *Spironolactone, sodium starch glycolate, ethyl cellulose, hpmc.*

INTRODUCTION

Chronotherapeutics refers to a therapeutic strategy that aligns drug administration with the body's biological rhythms, particularly circadian cycles associated with disease manifestation, in order to enhance therapeutic efficacy and minimize adverse effects.[6,7] Pulsatile drug delivery systems administered at bedtime with a predetermined lag phase can ensure drug release during early morning hours, when several cardiovascular disorders show peak symptoms.[8]

Appropriate timing of drug delivery allows achievement of plasma drug concentrations at optimal periods, reduces dosing frequency, and helps avoid issues such as tolerance development and saturable first-pass metabolism[9,10] Colon-targeted delivery systems are especially beneficial when delayed absorption is therapeutically advantageous, such as in diseases including nocturnal asthma, angina pectoris, rheumatoid arthritis, and hypertension.[11–13]

A primary goal of chronotherapy in various pathological conditions is to deliver higher drug concentrations at times when disease severity is maximal, corresponding to circadian disease onset.[14] Objectives of Chronotherapeuticals can be achieved through suitably designed conventional dosage forms such as press-coated tablets and capsules.[15] Pulsatile drug delivery systems have gained considerable attention because continuous release formulations are often unsuitable for diseases exhibiting rhythmic patterns.[16]

Press-coated pulsatile systems offer multiple advantages, including protection of drugs that are hygroscopic, photosensitive, or acid-labile, while also being simple, economical, and scalable in manufacturing.[17]

The present study focuses on the development of press-coated spironolactone tablets using a direct compression approach for the management of CHF. The formulation consists of a rapidly disintegrating core tablet surrounded by a polymeric barrier layer composed of HPMC and ethyl cellulose to regulate the lag time and subsequent drug release.[18,19,20]

MATERIALS AND METHODS

Drug–Excipient Compatibility Study

Compatibility between spironolactone and formulation excipients was assessed using Fourier Transform Infrared (FTIR) spectroscopy (Shimadzu 8400S). Samples containing 2% w/w drug were thoroughly blended with potassium bromide (KBr) and compressed into transparent discs under a pressure of 10,000 psi. The discs were scanned over a resolution of 2 cm^{-1} using Happ-Genzel apodization, and characteristic absorption peaks were analyzed to detect potential interactions.[21]

Formulation of Spironolactone Tablets

Preparation of Core Tablets

Core tablets were manufactured by the direct compression method based on the formulation composition listed in Table 1. Precisely weighed quantities of spironolactone, microcrystalline cellulose (MCC), sodium starch glycolate (SSG), croscarmellose sodium (CCS), and talc were blended uniformly for 15 minutes. Magnesium stearate was then added and mixed for an additional 10 minutes. The final blend was compressed using a tablet punching machine to obtain uniform core tablets.[22]

Table 1: Formulation Table of Spironolactone Core Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Spironolactone	25	25	25	25	25	25
CCS	3	6	9	-	-	-
SSG	-	-	-	3	6	9
MCC	118	115	112	118	115	112
Mg. sterate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total	150	150	150	150	150	150

Preparation of Press-Coated Tablets

Optimized core tablets were press-coated using barrier layer materials comprising HPMC K4M and ethyl cellulose. A measured quantity of coating material was placed into a 12-mm die, followed by manual positioning of the core tablet at the center. The remaining coating blend was added and compressed using a rotary tablet press fitted with flat oval punches. All the prepared tablets were evaluated for physical and release characteristics, as detailed in Table 2.[23]

Table 2: Composition of press coated tablets of Spironolactone.

Excipients	E1F6	E2F6	E3F6	E4F6	E5F6
Core (mg)	150	150	150	150	150
HPMC K4M (mg)	150	100	200	75	225
Ethyl cellulose (mg)	150	200	100	225	75
Total weight (mg)	450	450	450	450	450

EVALUATION OF TABLETS

Both core and press-coated tablets were evaluated for weight variation, hardness, friability, thickness, drug content uniformity, disintegration time, and in-vitro drug release.[24]

- **Weight variation:** Twenty tablets were weighed individually and compared with the mean weight in accordance with USP specifications.
- **Hardness:** Tablet crushing strength was determined using a Monsanto hardness tester and expressed in kg/cm².
- **Friability:** Twenty tablets were subjected to 100 revolutions in a Roche friabilator at 25 rpm, and percentage weight loss was calculated.
- **Thickness:** Tablet thickness was measured using Vernier calipers.
- **Content uniformity:** Powder equivalent to 20 mg drug was dissolved, filtered, and analyzed spectrophotometrically at 244 nm.
- **Disintegration time:** Disintegration testing was performed using USP apparatus at 37 ± 1°C temperature.

IN-VITRO DISSOLUTION STUDY

Dissolution testing was carried out using the USP paddle method at 75 rpm and 37 ± 0.5°C. Tablets were initially tested in 0.1 N HCl for 2 hours, followed by phosphate buffer pH 6.8 for the remaining duration to simulate gastrointestinal transit conditions. Samples were withdrawn at predetermined intervals and analyzed using a UV spectrophotometer. All studies were conducted in triplicate.[25]

RESULTS AND DISCUSSION

Evaluation of Core Tablets

FTIR analysis confirmed the absence of chemical interactions between spironolactone and formulation excipients, indicating formulation compatibility. Pre-compression and post-compression parameters were within acceptable

pharmacopoeial limits. All formulations (F1–F6) complied with weight variation requirements. Tablet hardness ranged from 3.09 ± 0.06 to 3.98 ± 0.82 kg/cm², ensuring mechanical stability. Tablet thickness and diameter showed minimal variation, and friability values remained below 1%, confirming adequate tablet strength. Drug content uniformity ranged from 97.98 ± 0.87% to 101.64 ± 0.45%

Dissolution of Core Tablets

Among the six core tablet formulations prepared using SSG and CCS as superdisintegrants, formulation F6 containing 6% CCS exhibited rapid and maximum drug release within 45 minutes. Consequently, F6 was selected as the optimized core tablet for press-coating.

Evaluation of Press-Coated Tablets

Post-compression evaluation of press-coated tablets demonstrated acceptable physical parameters. In-vitro dissolution studies revealed that formulation E2F6 containing HPMC K15M and ethyl cellulose in a 1:2 ratio provided a lag phase of 6 hours followed by complete drug release by the end of 8 hours. Therefore, E2F6 was identified as the optimized pulsatile formulation, and release kinetics were further analyzed and tabulated in table 3.

Table 3: Evaluation of press coated tablets of Spironolactone.

Formula code	Weight variation	Hardness (Kg/cm²)	Friability (%)	Thickness (mm)	Diameter (mm)	Drug content (%)
E1F6	1.09 ± 0.06	6.76 ± 0.65	0.24 ± 0.006	4.64 ± 0.012	12.02 ± 0.01	96.56 ± 0.10
E2F6	2.23 + 0.04	6.38 + 0.09	0.14 ± 0.004	4.82 ± 0.019	12.09 ± 0.01	98.09 ± 0.26
E3F6	2.98 ± 0.09	6.98 ± 0.23	0.09 ± 0.026	4.87 ± 0.005	12.12 ± 0.01	96.56 ± 0.14
E4F6	3.09 ± 0.02	6.97 ± 0.62	0.34 ± 0.091	4.58 ± 0.092	12.20 ± 0.09	99.57 ± 0.43
E5F6	2.89 ± 0.19	7.09 ± 0.91	0.18 ± 0.078	4.79 ± 0.014	12.09 ± 0.01	98.09 ± 0.09

CONCLUSION

The present study successfully demonstrated the feasibility of developing a time-dependent pulsatile drug delivery system of spironolactone for hypertension management. Both pre-compression and post-compression parameters of core and press-coated tablets were found to be satisfactory. Based on drug content uniformity, dissolution behavior, and kinetic analysis, formulation F6 (core tablet) and E2F6 (press-coated tablet) were selected as optimized formulations. The findings confirm that spironolactone can be effectively formulated as a chronopharmaceutical dosage form using ethyl cellulose and HPMC polymers. Overall, the developed pulsatile system offers a promising approach for chronotherapy of cardiovascular disorders.[25]

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