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Formulation And Characterization of a Pulsatile Zafirlukast Delivery System For Enhanced Asthma Therapy

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ABSTRACT

The objective of this study was to develop and optimize a pH-sensitive, sustained-release formulation of Zafirlukast using core and coated tablet designs for targeted, controlled drug release. Initial formulation involved preparing core tablets with various super disintegrants, where croscarmellose sodium (F3) was identified as the optimal agent based on disintegration and dissolution profiles. The core was then coated with Eudragit-RS100 and Eudragit-L30 polymers at varying concentrations. Among these, formulation F9, coated with 9.75% Eudragit-L30, exhibited an effective enteric coating with a lag time of 4.6 hours, followed by rapid drug release. FTIR studies confirmed no interactions between drug and excipients, while scanning electron microscopy verified the coating thickness. In vitro release studies indicated that F9 followed a zero-order kinetic release, demonstrating controlled and sustained drug delivery. This formulation approach for Zafirlukast offers potential for enhanced therapeutic outcomes and patient adherence.

Keywords: Zafirlukast, sustained-release, enteric coating, Eudragit, controlled release

I. INTRODUCTION

Pulsatile drug delivery systems (PDDS) are designed to release drugs in a controlled, time-dependent manner to align with the body's circadian rhythms and site-specific therapeutic needs. Unlike traditional sustained drug delivery, which offers a steady release of medication over time, PDDS release drugs in response to a programmed schedule. This allows for optimal release at specific times or targeted sites, improving therapeutic efficacy and reducing side effects. With chronic diseases and disorders often displaying time-dependent symptoms or worsening at certain times, PDDS offer a promising approach for enhanced patient outcomes.

PDDS release drugs in two or more distinct phases following an initial lag period, allowing release to be controlled by time, site, or both factors. Time-based systems delay drug release until specific

periods, catering to conditions that require night-time or early-morning dosing, such as asthma or hypertension. Alternatively, site-specific PDDS target particular gastrointestinal regions, such as the colon, which is beneficial for treating localized diseases like inflammatory bowel disease and can improve bioavailability for drugs sensitive to the upper digestive tract environment.

In PDDS, drug release is governed by formulation and the patient's gastrointestinal environment. Time-controlled systems use polymer barriers that degrade or dissolve to trigger release after a set period, while site-specific systems are influenced by GI factors. Through such mechanisms, PDDS enable delivery tailored to disease states and minimize continuous drug presence in the bloodstream, which can lead to tolerance and reduced therapeutic effect. Conditions benefitting from PDDS include those with circadian rhythms, where symptoms fluctuate, as in asthma, cardiovascular disease, and arthritis.

The circadian rhythm, an intrinsic biological clock, affects physiological processes over a 24-hour cycle. Many diseases exhibit symptoms linked to these rhythms, such as bronchial asthma and myocardial infarction, which often peak at night or early morning. PDDS are therefore ideal for delivering drugs in sync with these fluctuations, allowing for a more natural and effective treatment approach. Current PDDS research aims to develop systems that match these rhythms, which can lead to improved patient compliance, reduced side effects, and enhanced therapeutic effectiveness.

Chronopharmaceutics, a field focused on creating delivery systems that align with the body's natural rhythms, is crucial to PDDS. By leveraging circadian rhythms, chronopharmaceutic systems allow the release of medications at the most opportune times, based on the biological needs of specific diseases. The goal is to maximize efficacy while minimizing adverse effects, especially for drugs that interact with sensitive body systems, such as those that cause gastric irritation or nausea.

With advancements in PDDS technology, a more dynamic approach to medication is emerging, shifting from continuous, zero-order release to adaptive, time-based strategies. This evolution in drug delivery is essential for managing diseases where conventional methods fall short.

II. LITERATURE REVIEW

Sachin et al. (2019) demonstrated the effectiveness of multiparticulate drug delivery systems for achieving sustained or delayed oral release with low risk of dose dumping and short gastric residence

time. Their study highlights the flexibility of multiparticulates to adapt to different release profiles and emphasizes their benefits over single-unit dosage forms. Specifically, they explored the use of floating multiparticulates formulated via solvent evaporation techniques to increase gastric retention time, showcasing this approach as a significant advancement in pulsatile drug delivery.

Ahmed et al. (2020) developed a multifunctional system incorporating a “tablets-in-capsule” design for the programmable release of ketorolac and famotidine. Their formulation involved mini-tablets providing rapid and delayed release of famotidine to ensure maximum gastric protection, while ketorolac was designed for timed release. This dual drug delivery approach ensured a pulse of famotidine after a lag time of 6 hours, demonstrating the versatility of this capsule-in-capsule technique for treating conditions requiring staggered release to improve therapeutic efficacy.

MD. Sarfaraz, Prasad Y, et al. (2021) formulated press-coated time-release tablets of nifedipine aimed at managing hypertension chronotherapeutically. Using a compression coating technique, nifedipine was embedded within a polymer matrix of PEG 6000 and HPMC K 100M. The lag time achieved ranged between 2 and 6 hours, showing the system's adaptability to patient-specific circadian requirements in hypertension management, further substantiating the utility of polymeric coatings for achieving desired release patterns.

Efentakis et al. (2022) examined an innovative oral pulsatile drug delivery system using a core-in-cup tablet design, where the active ingredient was encapsulated within a cellulose acetate propionate outer shell. A soluble polymer top layer, composed of hydrophilic materials like polyethylene oxide and sodium alginate, controlled the drug release of caffeine or theophylline. This three-part configuration allowed for timed and efficient drug release, suggesting that such designs could be highly effective in regulating drug exposure to synchronize with circadian rhythms.

Kausalya et al. (2023) developed a multiparticulate chronotherapeutic delivery system for flurbiprofen using cellulose acetate cores within Eudragit S-100 microspheres. The system was formulated through emulsion solvent evaporation at different drug-to-polymer ratios and demonstrated a pH-dependent release profile. The release was influenced by the cellulose acetate content, achieving a 12-hour lag time in pH 7.4, indicating the potential of this formulation in achieving targeted, delayed release tailored for specific GI conditions.

Jalap R. Patel et al. (2023) formulated and evaluated an oral controlled drug delivery system for metformin, a drug with inherently poor water solubility and bioavailability constraints. By incorporating polymers like HPMC, PVP, ethylcellulose, and carbopol-934, they enhanced the solubility and sustained the release of metformin, with direct compression used as the preparation technique. Their results underscore the effectiveness of HPMC and ethylcellulose in enhancing metformin's bioavailability, presenting promising polymers for controlled release systems designed to improve therapeutic outcomes in diabetes management.

III. RESEARCH METHODOLOGY

This study outlines a detailed procedure for the formulation and evaluation of Zafirlukast tablets designed for controlled drug release. The methodology encompasses the preparation of standard solutions, construction of a calibration curve, drug-excipient compatibility studies, tablet formulation through direct compression, coating with specific polymers, and in-vitro release studies. Core tablets containing Zafirlukast were formulated using superdisintegrants such as sodium starch glycolate, croscarmellose sodium, and crospovidone. Additional excipients included polyvinyl pyrrolidone-K30 as a binder, microcrystalline cellulose (MCC) as a diluent, and magnesium stearate and talc as lubricants. The ingredients were precisely weighed and mixed, sieved through a 60-mesh screen, and compressed into tablets using a rotary compression tablet machine (Rimek mini press I) with an 8-mm concave punch. The compressed Zafirlukast tablets were coated using Eudragit-L 30 and Eudragit-RS 100 polymers to control drug release. The coating solution was prepared using a solvent mixture of isopropyl alcohol (IPA), acetone, and water. Triethyl citrate was incorporated as a plasticizer, titanium dioxide as an opacifier, and talc as an anti-tacking agent. Eudragit powder was initially dissolved in 50% of the solvent mixture, followed by the addition of talc and triethyl citrate in the remaining diluent. The complete suspension was sieved through a 0.5 mm mesh to remove any undissolved particles, ensuring a smooth and uniform coating.The release of Zafirlukast from the coated tablets was tested in-vitro using a modified USP XXIII dissolution apparatus (Lab India, DS-800). The test conditions included a dissolution medium of 900 ml phosphate buffer at pH 6.8, with a rotational speed of 50 rpm at 37°C, replicating human physiological conditions. At fixed intervals, 5 ml samples were withdrawn, measured for absorbance at 240 nm, and replaced with fresh buffer to maintain the volume constant. These values provided a release profile for Zafirlukast, helping evaluate the effectiveness of the controlled release formulation in achieving the intended lag and release times.

IV. RESULT AND DISCUSSIONS

In the present study, a standard calibration curve for Zafirlukast was established in 0.1 N HCl media. Concentrations of 5, 10, 15, 20, and 25 µg/ml were prepared through serial dilutions, and the absorbance at 242 nm was measured for each. A linear relationship between concentration and absorbance was observed, yielding a straight line on the calibration graph with a coefficient of determination R2R^2R2 of 0.9987. The calibration constants obtained were K1=0.0392K_1 = 0.0392K1=0.0392 and K0=0.012K_0 = 0.012K0=0.012, indicating a high degree of accuracy and reliability for concentration determination in subsequent dissolution studies. Fourier Transform Infrared (FTIR) analysis confirmed that the Zafirlukast pure drug and the optimized formulation exhibited absorption peaks within the expected wavenumber range, corresponding to the nature of chemical bonds present. No significant differences in absorption peaks between the pure drug and the formulation indicated the absence of any interaction between Zafirlukast and the excipients used in the tablet formulation. This compatibility is crucial for maintaining the stability and efficacy of the drug within the formulated product. Physical properties of the powder blends used to formulate the rapid-release core tablets were evaluated as part of preformulation studies. Parameters such as angle of repose, bulk density, tapped density, Carr's consolidation index, and Hausner's ratio were assessed, showing that the powders had good flow properties as well as favorable volume and density characteristics. These properties are essential for ensuring uniformity and consistency during tablet compression. In-vitro drug release studies demonstrated the efficacy of the sustained-release mechanism for all tested formulations over a 5-hour period. The enteric coating applied to the formulations remained intact for the first 2 hours in a gastric pH of 1.2, successfully resisting the acidic environment, and then gradually dissolved in the intestinal pH. Among the formulations, F7 and F8 released the drug within 262 minutes due to a lower percentage of coating, while F9 and F10, with a slightly higher coating percentage, extended the release up to 320 minutes. Specifically, formulation F9 achieved an optimal balance, releasing 96.6% of the drug within 16 minutes following a lag time of 4.6 hours. Formulation F9, coated with 9.35% Eudragit L30, exhibited the most favorable release profile among the tested formulations. This coating composition provided both adequate gastric resistance and a controlled release in the intestinal environment, aligning with the objectives of sustained and delayed release. Overall, F9 was identified as the most promising formulation, providing an efficient release mechanism while protecting the drug from premature dissolution in gastric conditions. This controlled-release characteristic could significantly enhance the therapeutic effectiveness of Zafirlukast.

Table 1 Dissolution profile of formulations

T (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	36.62	38.06	44.15	30.42	37.26	44.41
4	54.02	55.49	53.26	49.44	49.66	52.44
6	62.37	69.61	72.16	61.55	60.16	70.62
8	77.23	74.69	82.11	73.23	72.98	79.83
10	80.55	85.56	88.01	79.06	79.77	86.11
12	83.41	89.54	91.77	84.60	85.62	88.62
14	88.39	91.69	98.48	92.15	88.49	93.13
16	92.46	93.80	98.74	94.76	94.01	96.34
18	94.27	95.16	98.06	94.95	95.22	96.66
20	95.25	96.93	98.40	94.23	95.32	96.85

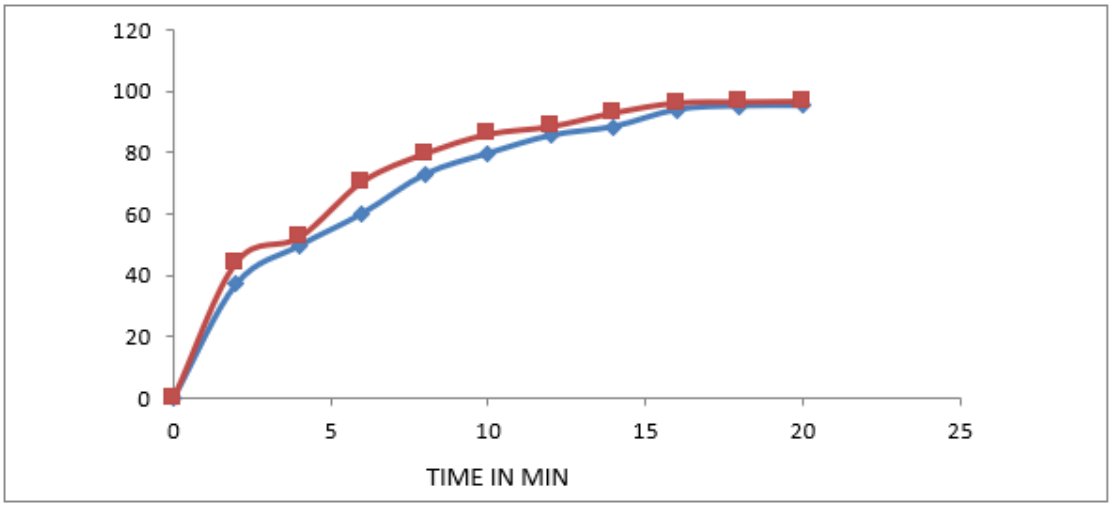

Figure 1 : Dissolution of optimized formulation

V. CONCLUSION

This study successfully developed and optimized a Zafirlukast sustained-release tablet formulation with enteric coating for controlled drug release. FTIR analysis confirmed compatibility between the drug and excipients, ensuring formulation stability. Among the core formulations, F3, containing croscarmellose sodium, was optimized based on favorable disintegration and dissolution times. This core was then coated with pH-sensitive polymers, specifically Eudragit-RS100 and Eudragit-L30, to achieve delayed release.The final optimized formulation, F9, coated with 9.75% Eudragit-L30, demonstrated a desirable release profile with an initial lag time of 4.6 hours, followed by rapid drug release. Scanning electron microscopy confirmed an average coating thickness of 33.28 µm, indicative of effective enteric protection. In vitro release studies showed that F9 followed a zero-order release mechanism, providing sustained drug delivery aligned with therapeutic objectives. This formulation strategy offers a promising approach for the controlled delivery of Zafirlukast, enhancing its therapeutic efficacy and patient compliance.

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