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Original Article

Preparation and Characterization of Eudragit L100/S100 Coated Zafirlukast Pellets for Chronotherapy

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ABSTRACT

Background: The initial goal of the current research investigation was to design, develop oral formulation of Pulsatile Drug Delivery Systems (PDDS) for Zafirlukast with aim of treatment for asthma. Delivery system was designed as Pellets type of system with Immediate and extended release of drug occurs at after the lag time period. In chronic asthma condition patients suffered during the early morning hours (04.00 AM to 06.00 AM) so immediate release dosage forms are not suitable but the modified release formulation that is given at bed time and releases the drug as pulsed manner despite to wake up the patient. **Materials and Methods:** In this present investigation, Zafirlukast pellets were prepared using Extrusion-Spheronization method, seal coating with HPMC E5 and enteric coating with Eudragit L100 and Eudragit S100 polymers by Fluid Bed Processor (FBP) for extending lag period prior the drug release. The formulations were designed as pellets of Immediate (IR) and Extended (ER) release of drug following lag time. IR pellets were designed as drug release immediate after the lag time and ER tablets designed as extend the release of drug from the pellets after the lag time. **Results:** The optimised formulations of FZ9 showed release of drug 99% at 6 hr with 04 hr lag time and FZX12 showed 99% of drug release at 11.5 hr with 4.5 hr lag time. The drug-excipient compatibility for the formulation was assessed using FTIR and DSC; the results obtained shown that no chemical interactions among the drug and incorporated excipients. SEM Studies showed porous nature of extrudes and covered with coatings of seal, enteric polymers. As per ICH standards for optimized formulations, stability experiments were also conducted for 6 months at 40ºC at 75% RH and it was concluded to be stable. **Conclusion:** The designed pellets of both IR and ER release with enteric coating beneficial to patients with night time dosing that can prevent the asthma episodes at early morning and development of exacerbations.

Keywords: Enteric coating, Extrusion, Lag time, Pulsatile, Spheronization.

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INTRODUCTION

A Pulsatile release profile is one which the drugs release rapidly at once following a predetermined lag time; this is beneficial when implementing many therapies to address therapeutic demands related to circadian rhythms of disease or body functions.[1] Hyper responsiveness to a variety of stimuli is characteristic for asthma which is a long-term inflammatory disorder of the airways. Chronotherapy of Asthma aims to maximize the benefits of bronchodilator drugs in early morning hours due to the importance of circadian rhythms in aetiology and management for the condition. The pulsatile systems were designed as time release pattern of drug and it is helpful for the preventing asthmatic attacks at early morning and to enhance the patient compliance nature and dosing frequency is reduced.[2,3]

Now a days Multiparticulate dosage forms due to their potential advantages including gastric emptying, convenient release patterns, reduction in risk of dose dumping, and enhanced bioavailability with less inter, intra subject variability are having great importance versus single-unit dosage forms. Despite of their unique clinical and technical advantages pellets have attracted more attention on behalf of several kinds of multiple unit dosage forms. Fine powders of agglomeration accompanied with a binding solution formulate pellets. Pellets have been described as spherical, granules of free-flowing have narrow size distribution, for pharmaceutical applications usually varying between the size of 500 and 1500 µM. When comparison to single-unit regimen, pellets formulated as drug delivery system offers many therapeutic properties namely negligible irritation of the gastrointestinal tract and a side effect decrease due to dose dumping.[4]

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Moreover, pellets as delivery system provides favours like better flow properties, narrow particle size distribution, reduced friable dosage form, ease of coating and packed uniformly. It has been said that multi-unit dosage formulations have considerable importance in contrast to controlled release pattern as single units of conventional dosage form. This familiarity is because of fast dispersion of formulated pellets in the GI tract with absorption is maximum, reduction of fluctuations in plasma peak and minimize side effects by maintaining drug bioavailability.[5] Microcrystalline Cellulose (MCC) is commonly employed excipient in preparation of pellets owing the plasticity and also cohesiveness associated with its wet masses.[6]

One of the ingredients on slow acting Substance that cause Anaphylaxis (SRSA) is Zafirlukast, is a selective and competitive Leukotriene D4 and E4 (LTD4 and LTE4) receptor antagonist. The pathophysiology of asthma involves altered cellular activity smooth muscle contraction, airway edema and the inflammatory process has been connected to cysteine leukotriene and receptor occupation.[7]

MATERIALS AND METHODS

Materials

Zafirlukast has been provided by the Aurobindo Pharma limited as a gift sample. Microcrystalline cellulose 102, Sodium starch glycolate, HPMC E5, Triethyl citrate, Polysorabate 80, Eudragit L100, Eudragit S100, Eudragit NE 30D and HPMC K 4M, Talc and mannitol were obtained from Therallen Pharma Pvt. Ltd., Hyderabad as a gift sample respectively. Remaining chemicals used were also analytical grade.

Methods

Preparation of Extrudes from wet mass

Zafirlukast pellets of immediate release (FZ1 to FZ5) and Extended release (FZX1 to FZX8) were prepared using Extrusion-Spheronization method. In this method, initially wet damp mass of Zafirlukast was formulated by wet granulation technique. Water was used as granulating fluid.

For IR extrudes the drug Zafirlukast, Microcrystalline cellulose, Sodium starch glycolate and HPMC E5 was passed into Sieve no# 40 and thoroughly mixed to get above dry mix unit, water was incorporated to get the damp mass. For ER extrudes the drug Zafirlukast, Microcrystalline cellulose, Eudragit NE 30D and HPMC E5 was passed into Sieve no# 40 and thoroughly mixed to get above dry mix, water was incorporated to get damp mass.

For the IR and ER extrudes, wet mass kept into the extruder of 1 mm screen size (Umang pharma tech) at 30 rpm. Collected extrudes were then introduced to the spheronizer equipped with chequered plate of 1 mm at 1500 rpm. Obtained spheroids were collected simultaneously dried at 50°C until the moisture is evaporated. The pellets were collected and kept until further usage in an airtight container. The formulated pellets composition of various batches is shown in Tables 1 and 2.

Coatings on prepared Zafirlukast IR, ER Pellets

Seal Coating

The Selected IR and ER spheroids from the dissolution study. The spheroids of Zafirlukast were loaded on Fluid Bed Processor (FBP). The inlet temperature was kept at 50°C and bed temperature was constantly maintained at 45°C. The HPMC E5 solution was sprayed onto the pellets at a spray rate of 5 g/min. The airflow was maintained at 1500-2500 cfm. The seal coated pellets were dried for complete evaporation of moisture. The formulations were summarized in Table 3.

Enteric Coating

The enteric coating on seal coated pellets was given in two layers. Layer I was given with Eudragit L100 and layer II was given with Eudragit S100.The seal coated pellets were loaded in the FBP. The pellets were pre warmed at 50°C. The bed temperature was maintained at 45°C. Initially layer I was given at a spray rate of 5-6 g/min. The cfm was maintained at 1500-2500 and adjusted as per the bed weight. The pellets were dried and then the coating of layer-II was continued. The formulations were summarized in Table 4.

Evaluation of formulations

UV analytical method

To obtain 100 µg/mL (Stock solution) a precise amount 10 mg of weighed drug was placed in a 100 mL ethanol present in volumetric flask. To get different concentrations of 5, 10, 15, 20, 30, and 40 µg/mL with HCl buffer pH 1.2 and to get concentration of 5, 10, 15, 20, and 25 µg/mL prepared by phosphate buffer pH 6.8, aliquots regarding prepared solution were separated into 10 mL volumetric flask. At λ_{max}, absorbance maximum was measured against corresponding blank buffer solution. The λ_{max} was observed at 238 nm in 6.8 phosphate buffer. The shift in λ_{max} to 232 nm was observed in acidic media 0.1N HCl.[8]

Drug excipient compatibility study

Differential Scanning Calorimetry (DSC) as well as Fourier-Transformed Infrared spectroscopy (FTIR) was used to assess drug with selected excipients compatibility.

Using a BRUKER FTIR IFS 68 Spectrophotometer, FTIR was done across a wavelength between 4000-400 cm^{-1}. Sample is incorporated with KBr and pressed into discs using hydraulic press for 5 min under 5 tons of pressure, the pellet was analysed to obtain the spectrum.[7-9]

A DSC-60 calorimeter of Shimadzu, Tokyo, Japan was used to perform DSC. The samples were kept in a 40 µL aluminium pan with thickness of 0.1 mm. The pan is then sealed by aluminium

perforated cover and heated up to 250°C using nitrogen flow at a rate of 5°C min.[8-10]

Characterization of Zafirlukast pellets

Bulk density

Weighed required amount of pellets were placed into 100 mL measuring cylinder and measure the occupied volume. Bulk density is determined using following calculation:[11]

Bulk density = Mass of Pellets/Bulk Volume

Drug Content

Pellets were grounded by placing in a mortar and pestle and 20 mg kept into volumetric flask of 50 mL, dissolved in 5 mL of methanol/ethanol and sonicate for 5 min. Finally, makeup the solution with phosphate buffer pH 6.8, shaken thoroughly and undissolved material was separated using Whattman's filter paper grade No.41. Finally, the serial dilutions were made and absorbance was measured at 238 nm for diluted solutions.[12,13]

Scanning Electron Microscopy (SEM)

The Extrudes having surface morphology has been determined by scanning electron microscope (JEOL 5400, Japan) for visualization of surface.[14]

In vitro Dissolution studies

USP Type I dissolution of Paddle type was used (Labindia DS 8000, India) and the study was performed at 37±0.5°C at 50 rpm. The dissolution studies of pellets have been performed at *in vitro* in 0.1N HCl for 2 hr (stated as average gastric emptying time) and in pH 6.8 phosphate buffer for next hours (stated as average transit time of small intestine). The pellets placed in capsule, for IR pellets dissolution studies done by using Phosphate buffer pH 6.8. For Enteric coated pellets in capsule of IR, ER dissolution study performed by first 2 hr with 500 mL of 0.1 N HCl and followed by using phosphate buffer of pH 6.8. The aliquots were taken at specified time intervals and each 5 mL of sample was replaced by freshly prepared medium. The samples prepared were determined by UV-visible spectrophotometer of λ_{max} 238 nm with phosphate buffer 6.8 pH and also 232 nm in acidic media 0.1N HCl.[8,15]

Table 1: Zafirlukast IR Pellets formulations by Extrusion-Spheronization Method.

Ingredients	Functional category	FZ1	FZ2	FZ3	FZ4	FZ5
Zafirlukast	Drug	20	20	20	20	20
MCC 102	Plasticity, cohesiveness to wet masses	160	155	145	140	135
Sodium starch glycolate	Disintegrant	15	20	25	30	35
HPMC E5	Binder	5	5	10	10	10
Purified water	Vehicle	Q. S	Q. S	Q. S	Q. S	Q. S
Total weight in mg		200	200	200	200	200

Table 2: Zafirlukast ER Pellets formulations by Extrusion-Spheronization Method.

Ingredients	Functional category	FZX 1	FZX 2	FZX 3	FZX 4	FZX 5	FZX 6	FZX 7	FZX 8
Zafirlukast	Drug	20	20	20	20	20	20	20	20
MCC 102	Plasticity, cohesiveness to wet masses.	125	115	105	95	85	83	81	79
Eudragit NE 30 D	Extended-release polymer.	20	30	40	50	60	60	60	60
HPMC K 4M	Binder	30	30	30	30	30	30	30	30
Mannitol	Pore forming agent.	0	0	0	0	0	2	4	6
Talc	Anti tacking agent.	5	5	5	5	5	5	5	5
Purified Water	Solvent	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Total Weight in mg		200	200	200	200	200	200	200	200

Stability Studies

The optimized formulations of Enteric coated IR, ER Pellets were selected, filled, sealed in 100 CC HDPE container. Three sets of each formulation were prepared and stored at stability chamber for six months at 40°C±2°C/70%RH±5%RH. The samples were evaluated at 1, 3 and 6 months for colour change, drug content and drug release.[16]

Microscopic Analysis

Photographs were collected at 40X optical magnification and a microscopic analysis of Zafirlukast IR and ER Extrudes was conducted. The QUASMO ANISO 9001-2000 microscope type, which has a digital camera DCE2.17, is the one used to examine the morphological features.[17]

RESULTS

Evaluation of Zafirlukast pellets

Evaluation test investigations were performed on prepared formulations and the outcomes were deemed satisfactory.

Bulk density results within the limits of 0.498-0.655 g/cm^3 respectively. The drug content percentages for formulations were observed to be between 98.24%-100.12%.

In vitro Dissolution studies

From the *in vitro* studies of IR pellets FZ1-FZ5, 99% of drug release of FZ5 with in 45min, so selected for seal coating and Enteric coating of IR pellet FZ7-FZ9 formulations, the FZ9 showed 99% of drug release in 6 hr with 4 hr lag time. ER pellets of FZX1-FZX8, the FZX8 showed 99% of drug release was extended type upto 6 h, so selected for seal coating and Enteric coating of FZX10-FZX12, the FZX12 showed 99% of extended release of drug in 11.5 hr with 4.5 hr lag time. The results illustrated in Figure 1.

Drug-Excipient Compatibility

It was assessed for the formulations using FTIR and DSC so the results obtained shown that no chemical interactions among the drug and incorporated excipients. The Spectra of FTIR and DSC thermograms were illustrated in Figures 2 and 3.

Stability studies

Stability Studies were performed for optimised formulations, FZ9 and FZX12 in a stability chamber for six months period at 40°C±2°C/70%RH±5%RH. The aliquots were withdrawn at 1, 3 and 6 months. The optimized formulation was stable as evidenced by the absence of deviations in drug content (99.78% and 99.23%),

Table 3: Seal coating of Zafirlukast Pellets formulations by Fluid bed processor Method.

Seal coating	Functional category	FZ6	FZX9
Selected pellet formulation		200	200
HPMC E5	Binder	16	16
Talc	Anti-tacking agent	2	2
Total Weight in mg		218	218

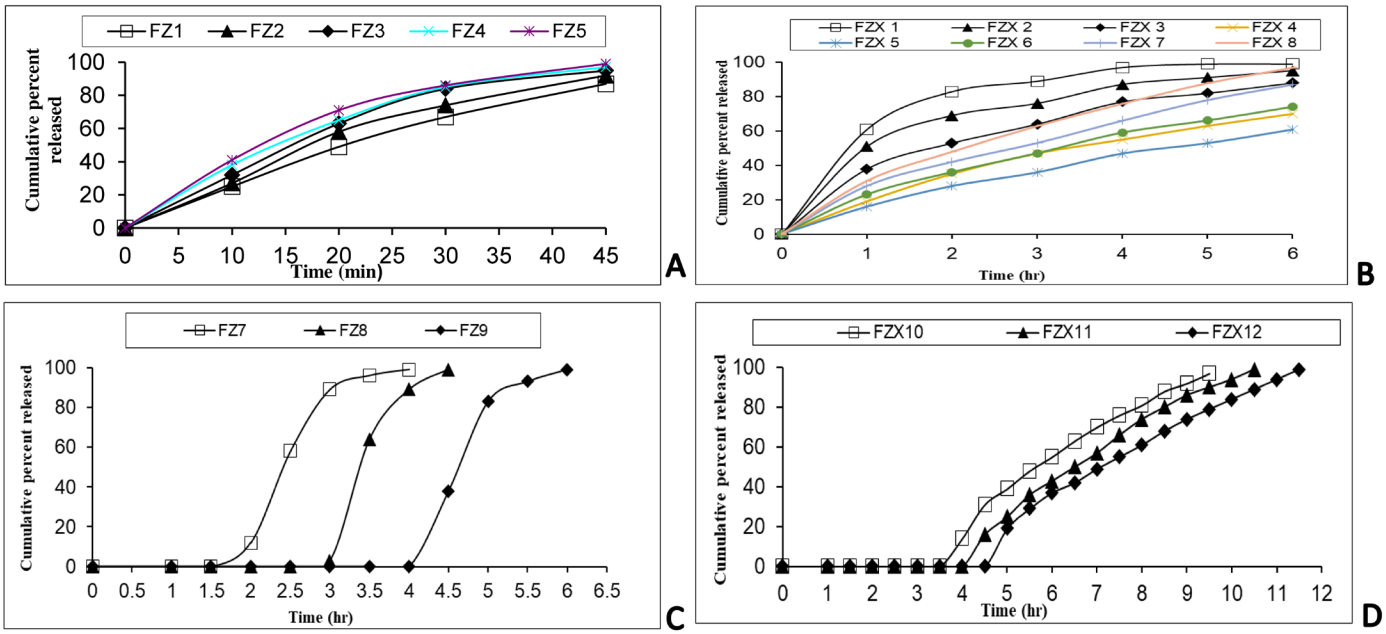

Figure 1: Dissolution curve of Zafirlukast Pellets; A) IR; B) ER; C) Enteric coated IR; D) Enteric coated ER.

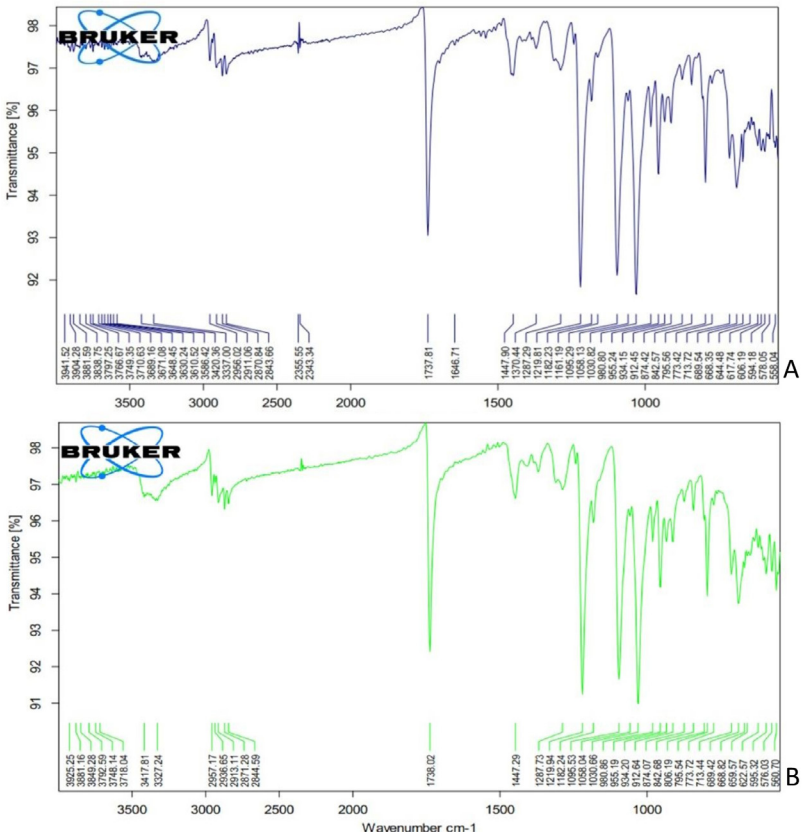

Figure 2: FTIR Spectrum of A) Zafirlukast; B) Zafirlukast+ HPMC K4 M+ Eudragit NE 30 D+ Eudragit L100+Eudragit S100.

Table 4: Enteric coating on seal coated Zafirlukast Pellet formulations by Fluid Bed Processor Method.

		IR Pellets			ER Pellets		
Ingredients	**Functional category**	**FZ7**	**FZ8**	**FZ9**	**FZX10**	**FZX11**	**FZX12**
Enteric Layer I							
Seal Coated Pellets		218	218	218	218	218	218
Eudragit L 100	Enteric coated Polymer	55.00	75	95	55.00	75	95
Triethyl citrate	Solubilizer, Emulsifier	5.50	7.50	9.50	5.50	7.50	9.50
Polysorbate 80	Plasticizer	1.00	1.50	2.00	1.00	1.50	2.00
Talc	Anti-tacking agent	3.50	4.00	4.50	3.50	4.00	4.50
Ethanol	Solvent	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Purified water	Solvent	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Total weight in mg		283.00	306.00	329.00	283.00	306.00	329.00
Enteric Layer II							
Eudragit S 100	Enteric coated Polymer	14.00	15.5	16.5	14.00	15.5	16.5
Triethyl citrate	Solubilizer, Emulsifier	1.00	1.00	1.00	1.00	1.00	1.00
Talc	Anti-tacking agent	3.00	3.5	4.5	3.00	3.5	4.5
Purified water	Solvent	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Ethyl alcohol	Solvent	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Total Weight in mg		301.00	326.00	351.00	301.00	326.00	351.00

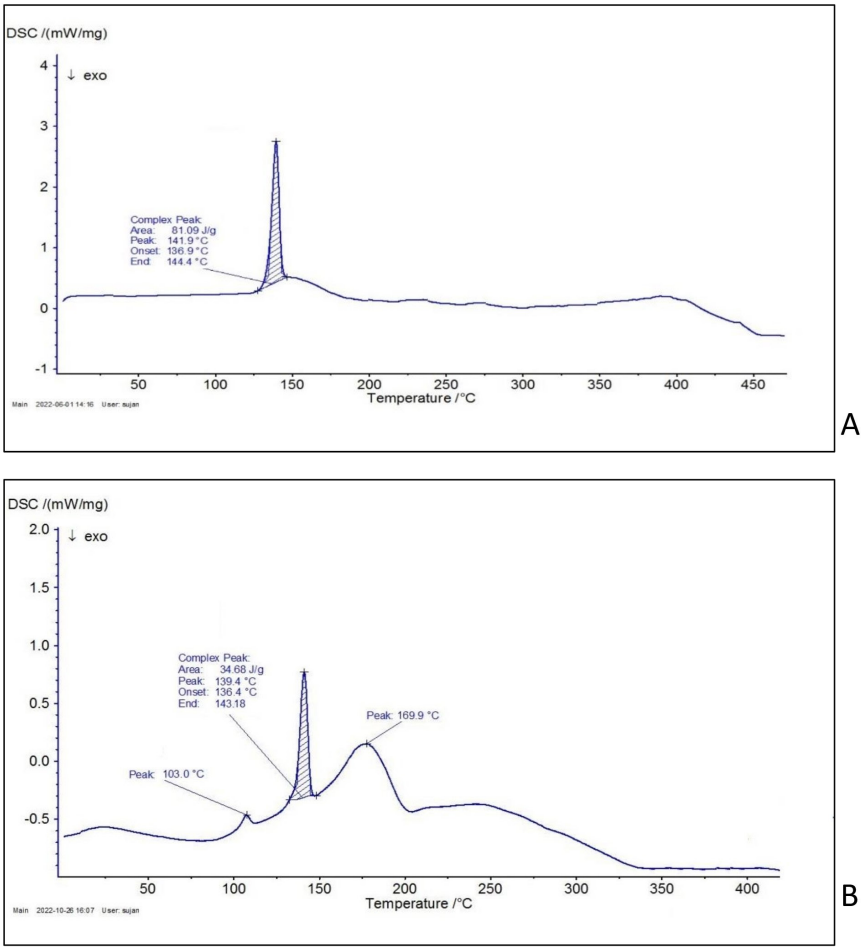

Figure 3: DSC thermogram of A) Zafirlukast; B) Zafirlukast +HPMC K4 M+ Eudragit NE 30 D+ Eudragit L100+Eudragit S100.

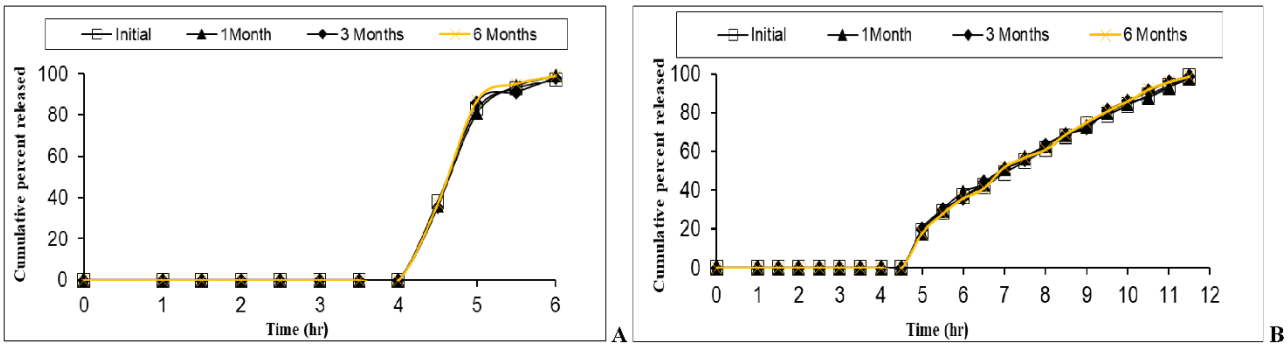

Figure 4: Stability study of optimised formulations; A) FZ9; B) FZX12.

colour change and drug release. The graphs of dissolution studies illustrated in Figure 4.

Microscopic Analysis

Zafirlukast IR, ER extrudes were examined under a microscope. The photomicrographs of prepared Extrudes were illustrated in Figure 5.

Scanning Electron Microscopy (SEM) of Extrudes

The size and shape related to the dosage form could have an impact on physicochemical and also biopharmaceutical behaviour of final dosage forms. It is critical in formulation development by the influence of shape on flow, stability, mixing efficiency, dissolution and also on homogeneity in formulation. Hence, the surface morphology was identified by SEM and some

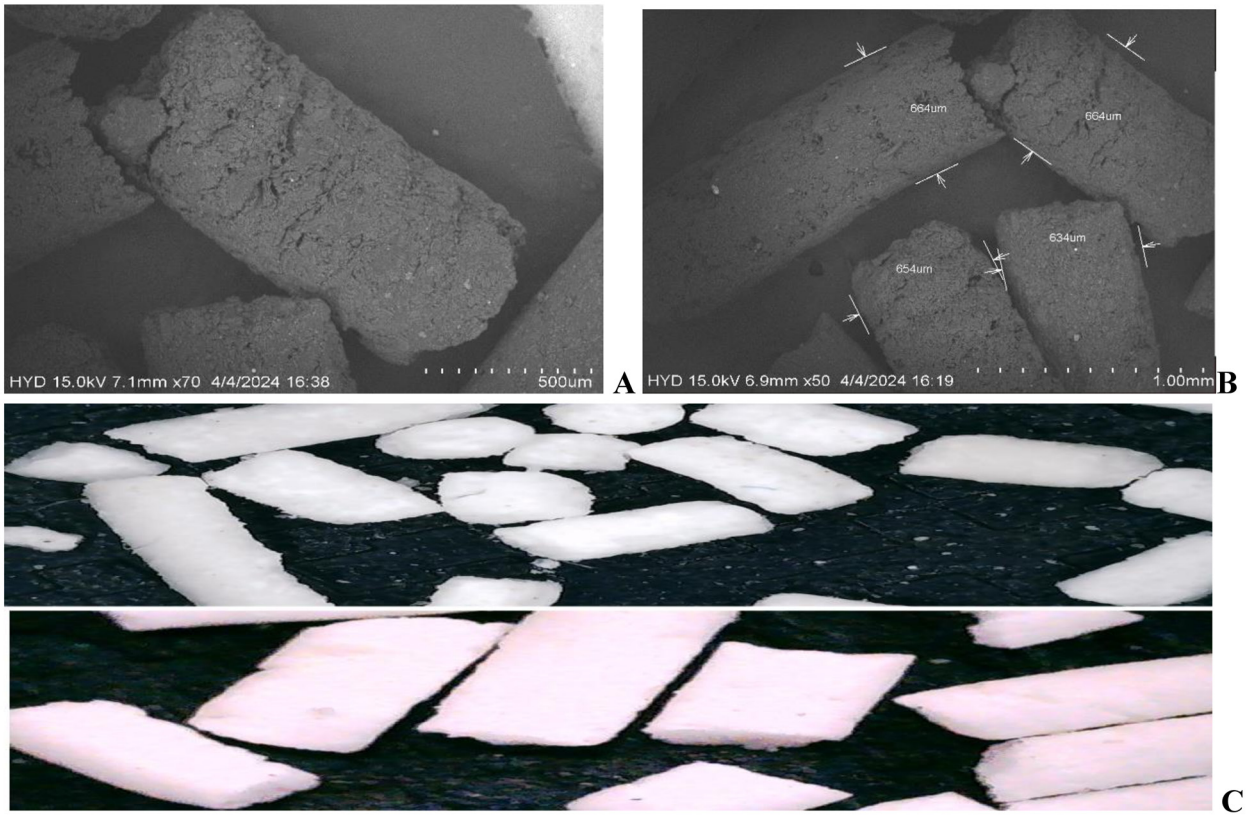

Figure 5: SEM images of Zafirlukast; A)IR Extrudes; B) ER Extrudes; C) Photomicrographs of IR, ER Extrudes of Zafirlukast.

extrudes were porous in nature and observed rough surface was minimal and SEM images illustrated in Figure 5 but it will not affect overall performance to the formulation because again coated with seal and enteric coatings.

DISCUSSION

The characterization studies of bulk density and drug content results showed satisfactory. The FTIR spectra and DSC thermograms results states that no chemical interactions of drug and incorporated excipients. Based on the dissolution studies of both IR, ER pellets type of systems showed immediate drug release after the lag time and extended-release pattern of drug after the lag time due to enteric coating of polymers. The optimized formulation was stable as evidenced by the absence of deviations in drug content %, colour change and drug release in stability studies. SEM studies showed extrudes were porous in nature and observed rough surface was minimal and However, Pore extrudes will covered with seal and enteric coating.

CONCLUSION

Utilising an already available active component (zafirlukast), a good trial was constructed efficient pulsatile drug delivery systems. Dosage forms of pellets prepared by Extrusion and spheronization with enteric coating designed as Immediate Release (IR) and Extended Release (ER). The IR pellets were designed in such a way to release the drug immediately after the lag time. The ER pellets were designed to release the drug at an extended rate after a lag time. So, the enteric coating on Zafirlukast IR, ER pellets given by the selected polymers Eudragit L100 and Eudragit S100 showed release of drug after the lag time period. The optimised formulations of FZ9 showed release of drug 99% at 6 hr with 04 hr lag time and FZX12 showed 99% of drug release at 11.5 hr with 4.5 hr lag time. The characterization and compatibility study of the designed system reveals the in prepared formulations drug stability. Thus, it can be concluded from the above results that the polymers listed above can be used to formulate a pulsatile drug delivery system for enteric coated of Zafirlukast pellets and this type of drug release which is modified may be used for the therapy of the asthma attacks and also exacerbations observed in early hours at morning.

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ABBREVIATIONS

IR: Immediate Release; **ER:** Extended Release; **FBP:** Fluid bed Processor; **SEM:** Scanning Electron Microscopy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Zafirlukast pellets type of Pulsatile drug delivery system were formulated by extrusion and spheronization method with enteric coatings of selected polymers such as Eudragit L100 and Eudragit S100 with an aimed to release of drug effectively after lag time. From the prepared formulations the optimised formulations showed improved lag time and drug release due to enteric coatings of selected polymers.The stability of the formulation was confirmed by characterization and compatibility studies.

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