



Preparation and Evaluation of Zafirlukast Compression Coated Tablets for Chronotherapeutic Drug Delivery

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The objective of the present study was to formulate and evaluate an oral, time-controlled drug delivery system of Zafirlukast. Zafirlukast belongs to BCS class II drugs as it has poor aqueous solubility and good permeability. Hence an attempt has been made to improve its aqueous solubility by solid dispersion technique so that its dissolution, bioavailability, and therapeutic effect can be optimized. The optimized solid dispersion was then formulated into a chronotherapeutic drug delivery system by compression coating technology. FT-IR study revealed that there was no chemical interaction between the drug and polymers used. Tablets were prepared by direct compression method using different super disintegrants and then followed by compression coating using natural polymers. Pre-compression and post-compression parameters complied with the Pharmacopoeia limit for the tablets. *In vitro* release studies were performed and the results indicated the formulation Z9F9 to be the optimized formulation.

Keywords: Zafirlukast; FTIR studies; solid dispersion; compression- coating technique; *In vitro* drug release studies.

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1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration [1]. The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this brought a new approach to development of drug delivery system [2].

Chronotherapy considers a person's biological rhythms in determining the timing and amount of medication to optimize a drug's desired effects and minimize the undesired ones [3]. Coordinating biological rhythms with medical treatment is known as chronotherapy, which allows for appropriate dosing of actives at the most suitable times of the day, thus improving efficacy and reducing undesirable side effects [4].

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases like hypertension, asthma, allergic rhinitis, peptic ulcer disease, rheumatoid arthritis and related disorders which follow body's circadian rhythm. Administration of the most appropriate drug in the form of pulsatile delivery system wherein the delivery device is capable of releasing the drug after predetermined lag time could offer a more effective therapy providing maximum drug concentration at maximum intensity of disease condition. [5,6]

Pulsatile drug delivery denotes the capability of a controlled release preparation to deliver the drug at varying rates from very low to high over a desirable time. Out of various timed release formulations available, compression-coated tablets gained wide attention. Compression-coated tablets (CCT's) are composed of an inner core that contains an active pharmaceutical ingredient surrounded by an outer layer that slowly dissolves or disintegrates to make a lag time of drug release. A timed-release formulation could allow drug release and a greater plasma drug concentration at the point in the circadian cycle when clinical signs develop or increase. [7]

Asthma is a chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during early morning hours [8].

The objective of the present study was to formulate and evaluate an oral, time-controlled drug delivery system of Zafirlukast (an oral leukotriene receptor antagonist that blocks the action of the cysteinyl leukotrienes on the CysLT1 receptors which is chemically designated as cyclopentyl N-[3-[[2-methoxy-4-[(2-methylphenyl) sulfonyl carbamoyl] phenyl] methyl]-1-methylindol-5-yl]carbamate) [9] based on chronopharmaceutical approach by the press (compression) coating technology using natural polymers for the treatment of nocturnal asthma. Zafirlukast, a BCS class II drug has poor aqueous solubility and good permeability. Hence, enhancement of its aqueous solubility has been attempted by means of solid dispersion technique [10].

2. MATERIALS AND METHODS

2.1 Materials

Zafirlukast was purchased from BMR Chemicals, Hyderabad. PEG 15000 was purchased from Himedia Laboratories Pvt. Ltd., Mumbai, microcrystalline cellulose, sodium starch glycolate, croscarmellose sodium, talc (purchased from S.D.Fine chemicals, Mumbai), magnesium stearate (from Central drug house (p) Ltd, Bombay), sodium lauryl sulphate (from Rankem Laboratories, Hyderabad), xanthan gum, locust bean gum, tamarind gum and dammar gum (from N.R.Chem., Mumbai) and all other ingredients used were of pharmaceutical grade.

2.2 Methods

2.2.1 Drug-excipient compatibility study (Fourier transform infra-red spectroscopy) [11]

FT-IR spectra ($400-4400\text{cm}^{-1}$) were obtained on a Perkin-Elmer FT-IR spectrophotometer with a resolution of 4 cm^{-1} . KBr pellets were prepared gently by mixing the 1 mg sample with 100 mg Potassium bromide.

2.2.2 Preparation of Solid Dispersions using PEG 15000 [12,13]

Solid dispersions of Zafirlukast via PEGylation with PEG 15000 in different weight ratios (1:0.5, 1:1, 1:1.5, 1:2, 1:2.5) were prepared by physical mixing, kneading, and solvent evaporation methods as shown in Table: 1.

- a) **Physical mixtures:** Accurately weighed quantities of drug and polymer were taken in a glass mortar and mixed thoroughly. The resultant mixture was passed through sieve number 100 and was stored in a desiccator for complete removal of moisture.
- b) **Kneading method:** The weighed quantities of drug and polymer at different ratios were taken in a mortar and triturated with a small volume of acetone. The obtained mass was kneaded for 45 min, dried in a desiccator for 48 hours. The dried product was pulverized, sifted through sieve number 100, and stored in a well-closed container, and kept in a desiccator.
- c) **Solvent evaporation method:** Drug and polymer were mixed in different ratios in a mortar. Acetone was added proportionately with constant and continuous stirring until the mixture was completely dissolved. Acetone was evaporated under constant stirring and

resultant solid dispersions were crushed, pulverized, and sifted through 100 mesh.

2.2.3 Formulation of Core Tablets of Zafirlukast by Direct Compression

The inner core/immediate-release tablets containing Zafirlukast were prepared by the direct compression method. As per the formulation variables shown in the Table: 2, the solid dispersions of Zafirlukast, microcrystalline cellulose and super disintegrant were dry blended for 15 min followed by the addition of talc and magnesium stearate. The mixtures were then further blended for 5 min. The resultant powder blends were then evaluated for flow properties like the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio and finally compressed using a single punch CADMACH machine at a compression pressure of around 5-6 kg/cm² to obtain tablets of 6.0mm diameter and weighing 100mg each. The tablets were packed in aluminum foil, wrapped with brown paper.

2.2.4 Preparation of Compression-Coated Tablets of Zafirlukast

The press coated tablets of Zafirlukast (Z9F1-Z9F9) were prepared by compression coating of the optimized core tablet formulation (ZF9) with outer barrier layers of 400mg each having different compositions of polymers like xanthan gum, tamarind gum, locust bean gum, and dammar gum, the formulae of which are mentioned in the Table:3.

Table 1. Preparation of solid dispersions using PEG 15000

METHOD	Drug: Polymer Ratio	Drug (mg)	Polymer PEG 15000 (mg)
Physical Mixing	1:0.5	100	50 (PF1)
	1:1	100	100 (PF2)
	1:1.5	100	150 (PF3)
	1:2	100	200 (PF4)
	1:2.5	100	250 (PF5)
Kneading Method	1:0.5	100	50 (PF6)
	1:1	100	100 (PF7)
	1:1.5	100	150 (PF8)
	1:2	100	200 (PF9)
	1:2.5	100	250 (PF10)
Solvent Evaporation Method	1:0.5	100	50 (PF11)
	1:1	100	100 (PF12)
	1:1.5	100	150 (PF13)
	1:2	100	200 (PF14)
	1:2.5	100	250 (PF15)

Table 2. Formulation table for core tablets of Zafirlukast

S.NO.	Ingredients	ZF1	ZF2	ZF3	ZF4	ZF5	ZF6	ZF7	ZF8	ZF9
1.	Zaf:PEG 15000 (1:2.5) solid dispersion equivalent to 10 mg Zafirlukast	38	38	38	38	38	38	38	38	38
2.	Microcrystalline cellulose	57	57	57	55	55	55	53	53	53
3.	Croscarmellose sodium	2	--	--	4	--	--	6	--	--
4.	Sodium starch glycolate	--	2	--	--	4	--	--	6	--
5.	Ludiflash	--	--	2	--	--	4	--	--	6
6.	Magnesium stearate	2	2	2	2	2	2	2	2	2
7.	Talc	1	1	1	1	1	1	1	1	1
8.	Erythrosin red	Qs	qs	qs	qs	qs	Qs	qs	qs	qs
Total (mg)		100	100	100	100	100	100	100	100	100

Table 3. Formulation table for compression-coated tablets of Zafirlukast

Ingredients	Z1F9	Z2F9	Z3F9	Z4F9	Z5F9	Z6F9	Z7F9	Z8F9	Z9F9
Core	100	100	100	100	100	100	100	100	100
Xanthan gum	200	250	175	-	-	-	200	250	175
Locust bean gum	200	150	225	-	-	-	-	-	-
Tamarind gum	-	-	-	200	250	175	-	-	-
Dammar gum	-	-	-	200	150	225	200	150	225

Before compression, the prepared polymer blends were evaluated for flow properties like the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The core tablets were press-coated with 400mg of prepared barrier blend as per the mentioned formulae from Z1F9 to Z9F9. 200mg of barrier layer material was weighed and transferred into a 10mm die and then the core tablet was placed manually at the center. The remaining 200mg of the barrier layer material was added into the die and compressed.

2.2.5 Evaluation of Solid Dispersions

a) Drug entrapment efficiency [13]

The drug content in the solid dispersion was determined spectrophotometrically. An accurately weighed sample of solid dispersion equivalent to 10 mg of Zafirlukast was dissolved in 10 ml of acetone. The solution was filtered, suitably diluted with distilled water with 0.5% SLS and the absorbance was measured at 230 nm. The drug content was calculated from the calibration curve and expressed as percent entrapment efficiency as explained in the equation below-

$$\text{Entrapment efficiency} = \frac{\text{Actual drug loading}}{\text{Theoretical drug loading}} \times 100$$

b) *In vitro* dissolution studies [14]:

Dissolution studies of pure drug and all the solid dispersions of Zafirlukast were carried out using USP type II dissolution apparatus (paddle type) by using 900ml of distilled water with 0.5% SLS as the dissolution medium at a speed of 50rpm and a temperature of 37±0.5°C. 5ml samples were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted, and assayed for Zafirlukast by measuring absorbance at 230 nm.

2.2.6 Evaluation of Core Tablets [14,15,16]

All the prepared core tablets were optimized by average weight, hardness, friability, thickness, drug content, disintegration time, wetting time, and *in vitro* dissolution for further conversion of selected core tablet in the form of compression-coated tablets of Zafirlukast.

2.2.6.1 Average weight

Average weight was carried out for 20 tablets selected at random from the batch containing 100 tablets. The results are given in Table: 7.

2.2.6.2 Hardness

Hardness was determined by Monsanto hardness tester.

2.2.6.3 Friability

The friability of 20 tablets was determined by Roche friabilator at 25 rpm for 4 min.

2.2.6.4 Thickness

Thickness was measured by vernier calipers.

2.2.6.5 Drug content

Drug content was determined by weighing and grinding 10 randomly selected tablets and dissolving powder equivalent to 10 mg of the drug in 100 ml of distilled water with 0.5% SLS. The solution was then sonicated for 5 min and then filtered through a 0.45 μ membrane filter. The absorbance of this solution was determined at 230 nm and drug content was calculated.

2.2.6.6 Disintegration time

The *in vitro* disintegration studies were carried out using a digital tablet disintegration test apparatus. One tablet was placed in each of the 6 tubes of the basket assembly and then a disk was added to each tube. This assembly was then suspended in a 1-liter beaker containing water with its temperature being maintained at 37 \pm 2 $^{\circ}$ C. The basket was then moved up and down through a distance of 5 to 6 cm, at the frequency of 28 to 32 cycles per minute. The time required for the complete disintegration of the tablet was recorded. It is expressed in seconds.

2.2.6.7 In vitro dissolution rate studies

In vitro release rate studies of the core tablets were performed using the USP type II apparatus (paddle type) by using 900ml of distilled water with 0.5% SLS as the dissolution medium at a speed of 50rpm and a temperature of 37 \pm 0.5 $^{\circ}$ C. 5ml samples were withdrawn through a filter of 0.45 μ m at different time intervals, suitably diluted, and assayed for Zafirlukast by measuring absorbance at 230 nm.

2.2.6.8 Wetting time

A tissue paper folded twice was placed in a Petri dish. 10ml of water is added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as wetting time.

2.2.7 Evaluation of compression-coated tablets

All the prepared compression-coated tablets were evaluated for average weight, hardness,

friability, thickness, swelling index, and *in vitro* dissolution.

2.2.7.1 % Swelling Index [16]

The tablets were weighed and placed in a Petri dish containing 10ml of dissolution medium. At specified time intervals, the tablets were removed, lightly blotted with tissue paper to remove excess liquid, and then weighed. The swelling index was calculated using the formula, Swelling index (%) = $[W_s - W_d / W_d] * 100$
Where W_s = weight of swollen tablet at a time'
 W_d = weight of the dry tablet

2.2.7.2 In vitro dissolution rate studies

In vitro release rate studies of the press coated tablets were performed using the USP type II apparatus (paddle type) by using 900ml of distilled water with 0.5% SLS as the dissolution medium at a speed of 50rpm and a temperature of 37 \pm 0.5 $^{\circ}$ C. 5ml samples were withdrawn through a filter of 0.45 μ m for every hour up to 10 hours and the lag time was observed for every batch of tablets. The withdrawn samples were analyzed spectroscopically by measuring the absorbance at 230nm.

3. RESULTS AND DISCUSSION

3.1 Drug-Excipient Interaction Studies

The FTIR spectrum of Zafirlukast sodium exhibited a peak at 3443.98 cm^{-1} due to N-H stretching and at 1616.51 cm^{-1} due to SO₂ stretching.

There was no interference of the functional group as the principal peaks of the Zafirlukast were found to be unaltered in the final optimized formulation, indicating they were compatible chemically.

3.2 Evaluation of Solid Dispersions

3.2.1 Drug entrapment efficiency

From the drug entrapment values it was observed that solid dispersions prepared with the solvent evaporation method were better entrapped compared to physical mixing and kneading methods.

3.2.2 In vitro drug release studies

All the solid dispersions of Zafirlukast were subjected to *in vitro* drug release studies to

select the optimized formulation possessing an increased in-vitro dissolution rate. The dissolution profiles of Zaf: PEG 15000 solid dispersions were shown in Fig. 3,4 and 5. The dissolution rate of Zafirlukast was found to be increased in all the solid dispersions prepared by physical mixing, kneading, and solvent evaporation methods in comparison to the dissolution rate of pure drug. The solid dispersions prepared by the solvent evaporation method exhibited better dissolution profiles than those prepared by physical mixing and kneading methods. Amongst all the solid dispersions of Zafirlukast, the formulation PF15 prepared by the solvent evaporation method in Zaf: polymer ratio of 1:2.5 was found to possess the highest dissolution rate of 95.69% in 60 min (Fig. 5). The increased dissolution rate may be due to the

higher solubility of PEG 15000 in the dissolution medium and the better wettability of Zafirlukast in the conjugate.

3.3 Evaluation of Immediate Release Core Tablets

3.3.1 Pre-compression parameters

Powder blends used for preparing immediate release core tablets (ZF's) were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index, The values for the angle of repose, Hausner's ratio, and compressibility index were found to be in good correlation, indicating that all the formulations possess passable flow property and compressibility.

Table 4. Drug Entrapment efficiency values

Formulation Code	Entrapment efficiency
PF1	52.5
PF2	52.6
PF3	52.8
PF4	53.14
PF5	54.68
PF6	76.33
PF7	83.84
PF8	85.02
PF9	89.76
PF10	91.35
PF11	63.69
PF12	71.22
PF13	78.01
PF14	88.16
PF15	93.45

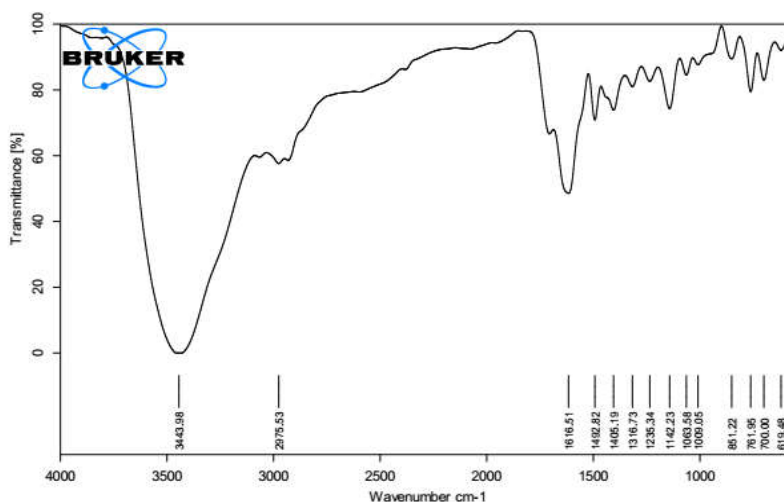


Fig. 1. FTIR of Zafirlukast (Pure Drug)

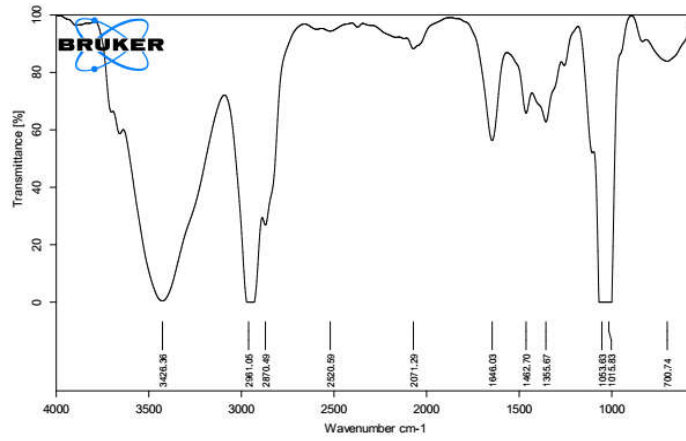


Fig. 2. FTIR of Optimized Formulation (Z9F9)

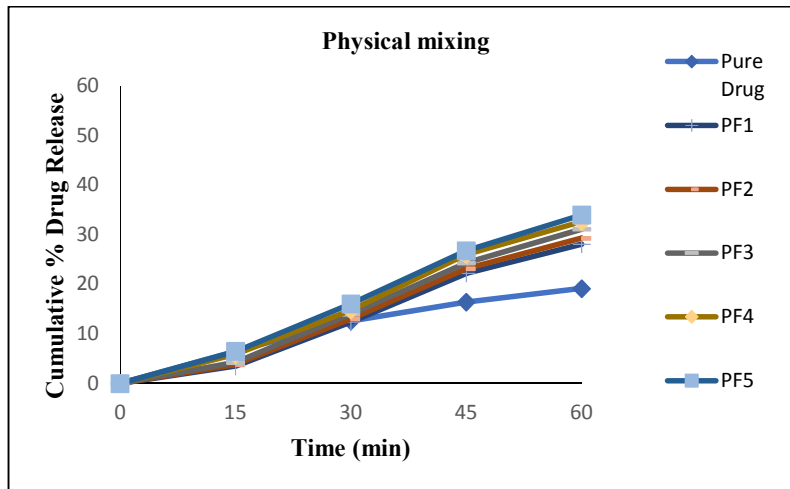


Fig. 3. Dissolution profiles of solid dispersions prepared by Physical mixing

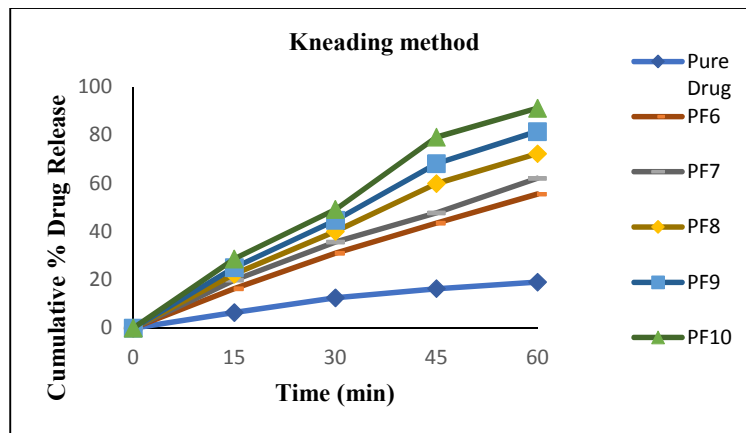


Fig. 4. Dissolution profiles of solid dispersions prepared by Kneading method

Table 5. Cumulative percentage drug release of solid dispersions prepared using PEG 15000

Time (min)	Pure Drug	Physical mixture														
		Kneading Method										Solvent Evaporation Method				
		PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9	PF10	PF11	PF12	PF13	PF14	PF15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	6.5	3.45	3.86	4.25	5.84	6.47	16.32	19.87	22.3	25.12	28.7	28.78	30.12	34.89	38.77	45.08
30	12.6	12.36	13.01	13.98	14.76	16.01	31.1	35.66	40.12	44.76	49.25	42.11	46.88	51.17	56.6	62.63
45	16.4	22.19	23.11	24.26	25.97	26.73	43.6	47.78	59.98	68.23	79.19	53.55	59.6	64.4	71.57	80.01
60	19.1	28.07	29.26	31.08	32.58	33.94	55.56	62.08	72.35	81.54	91.24	68.45	73.58	78.5	86.5	95.69

Table 6. Pre-compression evaluation parameters

F.No	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
ZF1	0.361	0.431	16.24	1.19	24.15
ZF2	0.345	0.410	15.85	1.19	23.69
ZF3	0.341	0.413	17.43	1.21	24.13
ZF4	0.369	0.436	15.36	1.18	25.65
ZF5	0.357	0.429	16.78	1.20	24.78
ZF6	0.361	0.411	12.17	1.14	28.01
ZF7	0.358	0.423	15.37	1.18	26.64
ZF8	0.360	0.435	17.24	1.21	25.45
ZF9	0.374	0.442	15.39	1.18	22.12

Table 7. Evaluation of post-compression parameters

Formulation	Weight variation (mg)	Hardness (kg/cm ²)	Thickness (mm)	Friability (%)	Disintegration time (sec)	Drug content (%)	Wetting time(sec)
ZF1	98.78	5.1	4.23	0.23	121	96.41	36
ZF2	99.15	5.2	4.30	0.13	116	95.46	35
ZF3	99.45	5.3	4.16	0.56	97	97.18	32
ZF4	98.86	5.4	4.10	0.47	109	96.50	31
ZF5	99.16	5.1	4.34	0.78	90	97.71	30
ZF6	98.79	5.3	4.42	0.69	72	98.78	34
ZF7	99.66	5.5	4.50	0.28	89	98.80	28
ZF8	99.47	5.2	4.13	0.09	74	99.15	28
ZF9	99.59	5.3	4.27	0.13	58	99.45	23

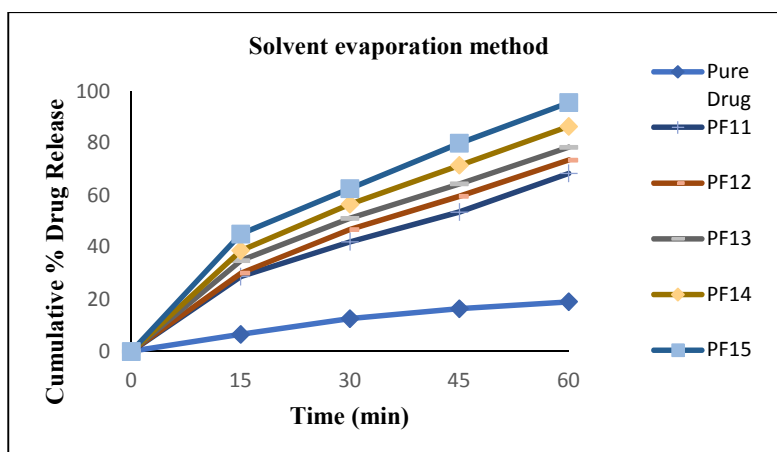


Fig. 5. Dissolution profiles of solid dispersions prepared by the solvent evaporation method

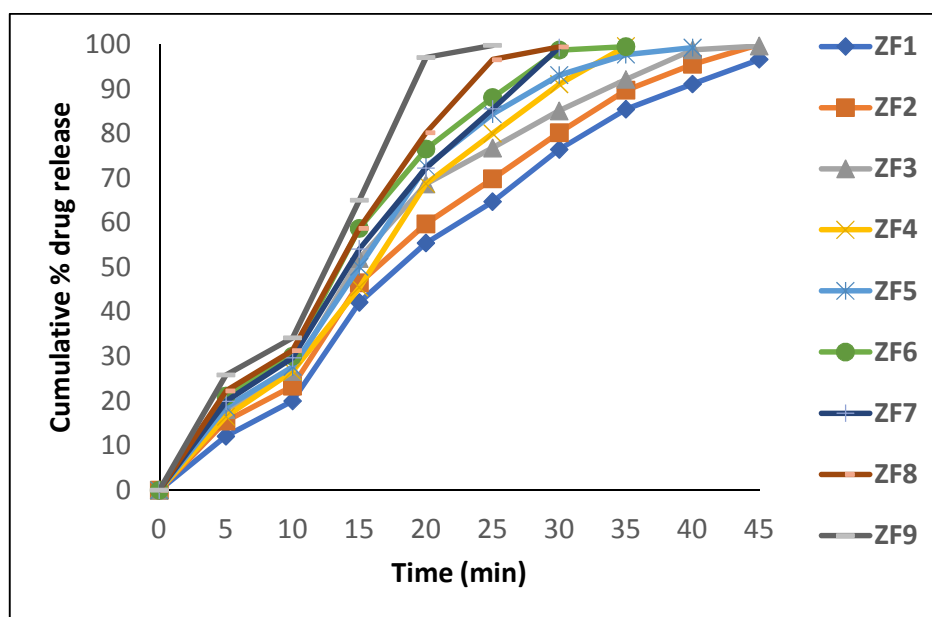


Fig. 6. Dissolution profiles of core tablet formulations (ZF1-ZF9)

3.3.2 Post-Compression Parameters

The prepared core tablets were evaluated, and were found to exhibit satisfactory tablet characteristics as shown in Table 7 and 8. The drug content of all the formulations was found to exist between 90 and 100% and formulation ZF9 was found to be within the USP limits as per the drug content. The *in vitro* disintegration time and wetting time were found to be very less for ZF9 formulation that is 58 seconds and 23 seconds respectively and this batch tablets have also shown better dissolution profile (99.85% drug release in 25 minutes) when compared to remaining formulations. Hence, it was optimized

as the best immediate release core tablet formulation for the burst release of the drug. The results of the dissolution profiles of all the formulations (ZF1-ZF9) were represented graphically in Fig. 6.

3.4 Evaluation of Compression-coated Tablets

3.4.1 Evaluation of polymer layer blends

The polymer layer blends of all the compression-coated tablet formulations (Z1F9-Z9F9) were evaluated for flow properties and it was found that the flow property of the prepared polymer

layer blend of Z4F9 and Z5F9 was good, that of Z1F9 and Z2F9 was fair, Z3F9, Z8F9, and Z9F9 have passable flow properties whereas the flowability of remaining blends was poor.

3.4.2 Evaluation of compression-coated tablets

The prepared compression-coated tablets were evaluated for all the post-compression parameters and were found to exhibit satisfactory tablet characteristics. The swelling index was found to be maximum at the 5th hour for the formulation Z9F9. The results were tabulated in table: 10 and 11.

From the results of *in vitro* drug release studies (Table: 12), it can be seen that all the press coated tablets showed distinct lag times (Fig. 7). The formulations Z1F9 to Z8F9 showed a lag time of 4 hrs with drug release extending up to 10 hours but are not consistent with the demands of chronotherapeutic drug delivery. The formulation Z9F9 with the barrier layer composition of xanthan gum and dammar gum showed the pre-expected lag time of 5 hours with a considerable drug release of 98.89% for 3 hours. Hence, this formulation was selected as the optimized formulation for further studies.

Table 8. *In vitro* Drug Release Studies

Time (min)	CUMULATIVE PERCENTAGE OF DRUG RELEASE (%)								
	ZF1	ZF2	ZF3	ZF4	ZF5	ZF6	ZF7	ZF8	ZF9
0	0	0	0	0	0	0	0	0	0
5	12.11	15.54	18.08	16.52	18.65	21.14	19.97	22.30	25.89
10	20.03	23.36	26.67	26.68	27.70	30.09	29.70	31.32	34.21
15	42.16	46.55	52.02	45.50	50.16	58.77	54.16	58.79	65.12
20	55.49	59.80	68.72	68.81	72.69	76.59	72.30	80.23	97.15
25	64.77	69.91	76.82	80.05	84.40	88.14	85.59	96.65	99.85
30	76.48	80.22	85.15	91.13	93.17	98.79	99.36	99.48	-
35	85.50	89.77	92.20	99.66	97.78	99.56	-	-	-
40	91.17	95.59	98.84	-	99.32	-	-	-	-
45	96.69	100.03	99.7	-	-	-	-	-	-

Table 9. Polymer layer blend evaluation parameters

F.No	Angle of repose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio
Z1F9	36.14	0.42	0.51	17.65	1.21
Z2F9	39.56	0.41	0.50	18	1.22
Z3F9	42.09	0.39	0.49	20.41	1.26
Z4F9	35.64	0.43	0.49	12.24	1.14
Z5F9	32.03	0.44	0.52	15.38	1.18
Z6F9	51.27	0.33	0.46	28.26	1.39
Z7F9	46.13	0.41	0.57	28.07	1.39
Z8F9	41.75	0.39	0.51	23.53	1.31
Z9F9	43.46	0.32	0.41	21.95	1.28

Table 10. Evaluation of Compression-coated tablet parameters

Form code	Hardness (kg/cm ²)	Thickness (mm)	Weight variation (mg)	Friability (%)
Z1F9	7.1	6.85	498.80	0.80
Z2F9	7.6	6.56	498.99	0.97
Z3F9	8.1	7.02	499.16	0.64
Z4F9	7.9	6.93	497.86	0.71
Z5F9	8.2	7.05	501.08	0.55
Z6F9	8.2	7.01	499.86	0.61
Z7F9	8.5	6.99	497.99	0.72
Z8F9	8.9	7.16	500.46	0.09
Z9F9	8.7	7.05	499.54	0.36

Table 11. % Swelling index values

Time(hrs)	Z1F9	Z2F9	Z3F9	Z4F9	Z5F9	Z6F9	Z7F9	Z8F9	Z9F9
0	0	0	0	0	0	0	0	0	0
1	142	118	149	96	108	146	154	125	144
2	146	156	164	118	114	168	176	154	178
3	164	164	202	124	126	196	208	174	224
4	189	178	228	132	148	214	225	206	262
5	216	184	242	148	172	232	246	229	296
6	184	172	216	126	158	184	215	198	174
7	168	146	194	114	122	162	184	158	155
8	141	128	188	92	105	139	159	132	116
9	115	106	146	76	98	114	122	102	98

Table 12. In vitro Drug release studies

Time (hrs)	Cumulative percentage of drug release (%)								
	Z1F9	Z2F9	Z3F9	Z4F9	Z5F9	Z6F9	Z7F9	Z8F9	Z9F9
0	0	0	0	0	0	0	0	0	0
1	0.54	0.41	0.18	0.89	0.51	0.55	0.28	0.41	0.22
2	0.63	0.97	0.94	1.36	0.77	1.23	0.56	0.77	0.64
3	2.03	1.75	1.22	4.47	3.69	5.60	2.81	3.69	0.84
4	4.12	2.98	5.07	9.98	8.79	10.23	9.24	8.79	1.97
5	19.65	13.69	25.18	26.6	26.65	21.36	26.65	26.65	13.36
6	32.30	38.79	79.02	47.48	48.87	34.45	48.87	48.87	74.46
7	44.47	52.65	99.97	69.14	66.30	66.54	66.30	66.30	85.97
8	74.12	68.78	-	87.19	87.90	80.21	87.90	87.90	98.89
9	84.20	79.96	-	95.24	99.02	96.54	99.86	92.64	-
10	98.46	92.64	-	100.01	-	98.26	-	96.22	-

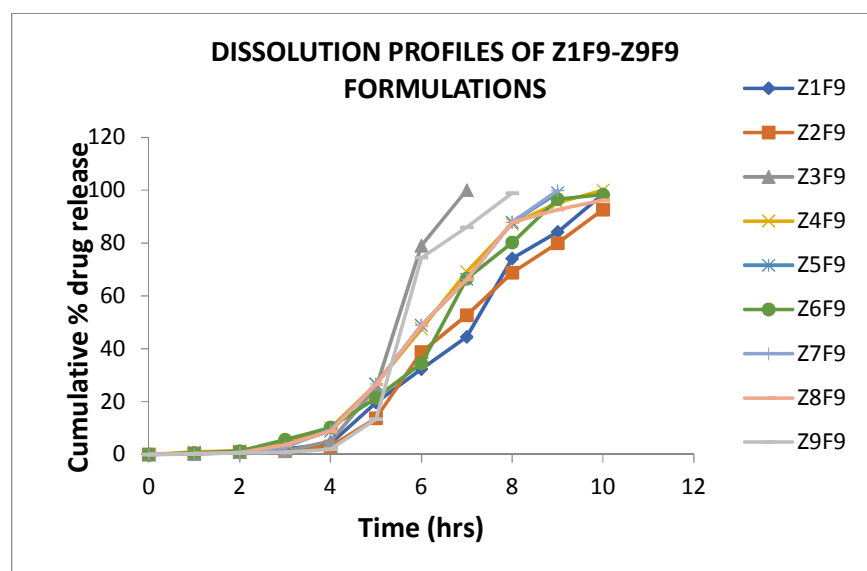


Fig. 7. Drug release profiles of compression-coated tablets (Z1F9-Z9F9)

4. CONCLUSION

Compression coated tablets of Zafirlukast for chronotherapeutic delivery were developed

successfully using natural polymers. FT-IR studies also revealed that there was no chemical interaction between the drug and polymers used in the optimized formulation (Z9F9). Various

parameters such as drug entrapment efficiency, flow properties, hardness, friability, weight variation, drug content, wetting time, swelling index, *in vitro* drug release rate were evaluated for all the formulations. The formulation Z9F9 containing xanthan gum and dammar gum as the barrier layer for retarding the release of the drug from the tablet was found to exhibit the results which are consistent with the demands of chronotherapeutic drug delivery. In conclusion, it can be suggested that the combination of xanthan gum and dammar gum in the optimized composition could be promising in achieving chronotherapeutic benefits in asthma patients.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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