World Journal of Pharmacy and Biotechnology

Journal Home Page: www.pharmaresearchlibrary.com/wjpbt

R E S E A R C H A R T I C L E

Formulation and Evaluation of Osmotic Tablets of Zafirlukast

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A B S T R A C T

In osmotic technology system a tablet containing a core of drug surrounded by a Semi permeable membrane drilled with a delivery orifice. Once this system comes in contact with the gastrointestinal fluids, the osmotically driven water enters the system through the semi permeable membrane, dissolves the soluble agents and exits through the delivery orifice. The main aim of the present work is formulate and evaluate of osmotic tablets of Zafirlukast and the objective is to release the drug in a controlled manner. Zafirlukast is an orally administered leukotriene receptor antagonist used for the chronic treatment of asthma. While zafirlukast is generally well-tolerated, headache and stomach upset often occur. It is usually administered orally. Cellulose acetate was used semi permeable membrane. Sodium chloride act as osmogent. FTIR results revealed that there was no interaction between dug and polymers used in the formulation. The prepared osmotic tablets showed good in vitro dissolution profile showing the release of constant drug for 12 hours. The stability study revealed that the formulations were found to be stable. From this, study it can be concluded that, osmotic tablets could be prepared to improve the bioavailability of Zafirlukast.

Keywords: Zafirlukast, osmotic pressure, semi permeable membrane, delivery orifice.

A R T I C L E I N F O

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PAPER-QRCODE

A R T I C L E H I S T O R Y: Received 22 April 2018, **Accepted** 22 May 2018, **Available Online** 29 June 2018

Citation: Tanguturi Jaya Harika. *Formulation and Evaluation of Osmotic Tablets of Zafirlukast. W. J. Pharm. Biotech..*, 2018, 5(1): 23-29.

C O N T E N T S

1. Introduction

Osmotically controlled drug delivery system, deliver the drug in a large extent and the delivery nature is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as

targeted delivery of drugs [1]. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents. Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure [2]. The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeiffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature [3]. In 1886, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature. To develop the controlled release system over a period of time [4].The main objective involved to increased patient compliance by reducing the dose frequency, Treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies by using osmotic approaches.Screening and selection of suitable polymers. Study of pre-compressive parameters for the tablet granules [5].Formulate and evaluate Zafirlukast osmotic tablets by wet granulation method. Cellulose acetate polymer used as a semipermiable membrane.

2. Materials and methods

The pure drug of Zafirlikast was obtained from Zeta formulation private Limited and excipiens like Sodium lauryl sulphate, Poly vinyl pyrrolidone k 30 was obtained from Alkem Laboratories Ltd.

Methodology:

FTIR Studies: Drug taken for the present study of formulation is Zarfirlukast. It has got tertiary hydroxyl groups which have exhibited a broad peak around 3300 cm-1 and a carboxylic acid peak which is in the form of a salt has exhibited a strong peak near 1700 cm-1. Numbers of aromatic C-H peaks are also observed between 2900 cm-1 to 3000 cm-1. These are the characteristic absorption peak of Zarfirlukast [6].

Evaluation for pre-compression parameters

Angle of repose: The accurately weight 15gm granules was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the blend. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [7].

$$\tan \theta = h/r$$

Where, h –height of the powder cone

r - radius of the powder cone

Bulk density and tapped density: Both loose bulk density (LBD) and Tapped bulk density (TBD) were determined [8]. A quantity of 15gm of granules from each formula, previously shaken to break any agglomerates formed, was introduced in to 50ml measuring cylinder. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations.

LBD = Weight of the Granules/bulk volume

TBD = Weight of the Granules/true volume

Hausner's Ratio: It is an indirect index of ease of powder flow. It is calculated by the following formula

Hausner's factor = Tapped density/Bulk density

Carr's compressibility index: The compressibility index of the granules was determined by Carr‟s compressibility index. (%) Carr‟s Index can be calculated by using the following formula

Compressibility % = [(TD - BD)/ TD] ×10

Formulation of osmotic tablet: Osmotic tablets of Zarfirlukast were prepared by wet granulation method [9]. Drug was uniformly mixed with sodium chloride and microcrystalline cellulose by using polyvinyl pyrrolidone (5%) as a binding agent. The wet granules subjected to dry at 60 ^{o}C and then mixed with lubricants like talc, magnesium stearate. Various formulations of ODDS were made as given in table 01.

Method of Preparation of Polymeric Coating Solution: Cellulose acetate was selected as semi permeable, pH independent polymer. Coating polymer used in different ratios 1.5, 2, 2.5 was hydrated in acetone by overnight storage. The solution was stirred for 15 min [10]. Plasticizer castor oil (10 %) was added into the polymeric solution. The solution of color (Sudan red III) in acetone was gradually mixed with the resultant polymeric solution for 80-100 RPM using Remi magnetic stirrer bath. After coating dry tablets were weighed for percentage weigh gain up to 5% by following equation.

% weigh gain = (Wt-Wo/ Wo) *100

Where,

Wt = weight of tablet after coating

Wo = weight of tablet before coating

Evaluation of core tablet

Hardness:

This is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauge in the barrel at which the tablet fractures [11].

Weight variation:

Ten tablets were selected at random and average weight was determined. Then individual tablets were weighted and the individual weight was compared with an average weight [12]. Not more than two of the individual weights deviate from the official standard (limit ± 5%).

Tablet size and Thickness:

The size and thickness of the tablets were measured by using Vernier Calipers scale [13].

Drug content analysis:

Five tablets weighted and crushed in a mortar then weighed powder contained equivalent to 10 mg of drug transferred in 100ml of 0.5% of SLS solution to give a concentration [14] of 100µg/ml. Take 15ml of this solution and diluted it up to 100ml with 0.5% of SLS solution to give a concentration of 15µg/ml. Absorbance measured at 342nm using UV-visible spectrophotometer.

***In vitro* dissolution studies:**

Dissolution rate of Zarfirlukast osmotic tablets from all formulations were performed using LAB INDIA dissolution

apparatus (USP II) with paddle. The dissolution fluid was 900 ml water with 0.5% w/v SLS at a speed of 50 rpm and a temperature of 37º C were used in each test. The dissolution experiments were conducted in triplicate. For all tests 5ml samples of the test medium were collected at set intervals (1, 2, 4, 6, 8, 10, 12hrs) and were replaced with equal volume of 0.5% SLS in distilled water [15]. The samples were analyzed at 342nm using a UV spectrophotometer.

Treatment of dissolution data with different kinetic equations:

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order [16], First order, Higuchi matrix, and Peppas. Based on the r-value, the best-fit model was selected.

Stability studies:

The formulation was subjected to accelerated stability studies as per ICH guidelines.

Formulation was sealed in an aluminum foil and stored at 4 0 ± 2 ºC, 75 ± 5% RH for 6 months. The ICH guidelines for evaluation of stability data describe when and how extrapolation should be considered while proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by available data from the stability under the log-term storage condition [17]. The data of multiple batches were analyzed using linear regression, poolability tests and ANCOVA statistical modeling these were amenable to analysis for quantitative attributes with upper acceptance criteria of 110% and lower acceptance criteria of 90% of label claim.

3. Results and discussion

The FTIRcharacteristic of montelukast sodium with polymers resembles almost with the Spectra of authentic sample of Zafirlukast.

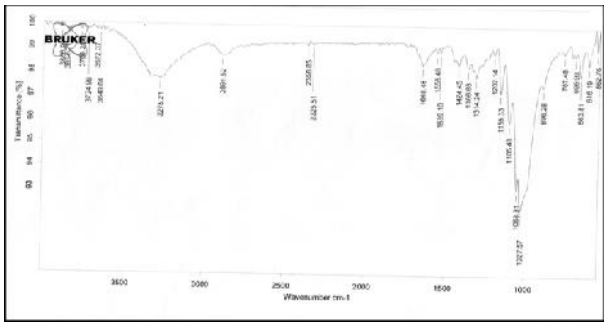

Fig 1: FTIR Spectra of Zafirlukast

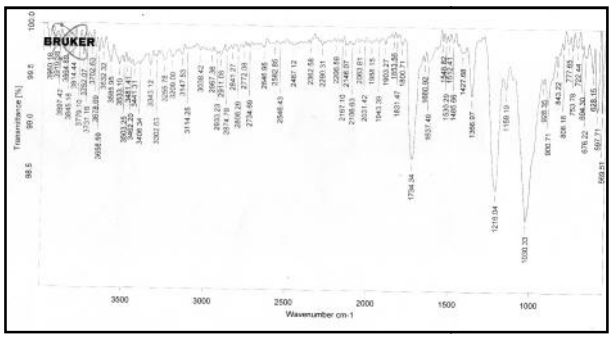

Fig 2:FTIR Spectra Of cellulose acetate

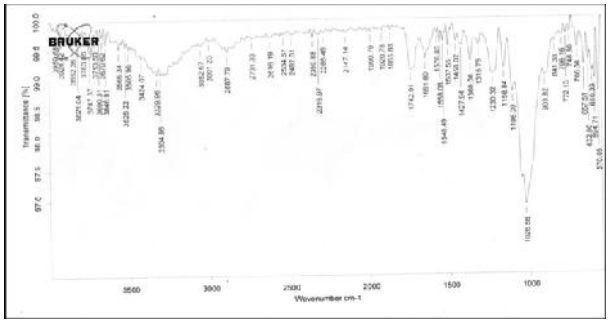

Fig 3: FTIR Spectra of Zafirlukast +cellulose acetate

Pre formulation parameters:

The results of pre formulation parameters for formulated physical mixtures of all batches are shown in table 07. The evaluation studies on granules of all the formulations were proved to be within limits and were shown good derived and flow properties. Angle of repose ranges from 24.22 to29.34°, bulk density ranges from 0.47 to 0.57 g/c3, tapped density ranges from 0.49 to 0.57, % Carr's index ranges from 5.47 to 10.90%.

Physicochemical properties:

The values of hardness, friability, thickness, weight and dru g content of prepared core tablets. The thickness, diameter, hardness, weight of the coated tablets is recorded in the tabl e 08.

Weight variation test: It was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit.

Content uniformity: It was also carried out as per official method and it was found that all batches shows good content uniformity. The values for all the formulations were in the ranges from 90.22 to 98.44%.

Hardness test states that all the formulations were found in the range 6 to 7 kg/cm^2.

Friability test: Another measure of tablet hardness was thefriability. Compressed all formulations are within limits (<1%)**.**

***In vitro* release studies:**

From dissolution profile of different batches Z1 to Z9 with increasing in % wt gain, t90was increased. From batches Z1 to Z9 with increasing in concentration of osmogent, increasing osmotic pressure which increased release rate. The results of dissolution test of Batch Z6 was clearly suggests constant order release of drug for period of 12 hours as shown in table 10. So Batch Z6 was considered as optimized batch showing the results as per our need.

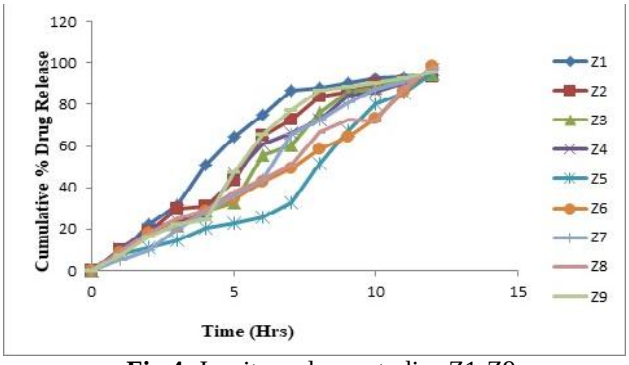

Fig 4: In-vitro release studies Z1-Z9

Stability studies: Optimized formulations of Zafirlukast were packed, maintained at 40 ˚C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for drug content,hardness, and release studies. The results of the accelerated stability studies are given inthe following tables. It shows that a slight reduction in %drug content at the end of 2months. The data of multiple batches were analyzed using linear regression, poolability tests and ANCOVA statistical modeling these were amenable to analysis for quantitative attributes with upper acceptance criteria of 110% and lower acceptance criteria of 90% of label claim. There was a significant difference in intercepts (Y= 101.27, 102.08, 100.56) but no significant difference in slope -0.609 among the batches. The predicted shelf life was found to be 14.68 months. It was observed that there was no substantial change in dissolution profile after six months. The stability study revealed that the best formulation may be stable for the period of 14.68 months.

Table 1: Formulation table for osmotic tablets of Zarfirlukast

Ingredients	**Z1**	**Z2**	**Z3**	**Z4**	**Z5**	**Z6**	**Z7**	**Z8**	**Z9**
Zafirlukast (mg)	10	10	10	10	10	10	10	10	10
Sodium chloride (mg)	100	150	200	100	150	200	100	150	200
sodium lauryl sulphate (mg)	20	20	20	20	20	20	20	20	20
PVP K-30 (mg)	5	5	5	5	5	5	5	5	5
MCC (mg)	161	111	61	161	111	61	161	111	61
Talc (mg)	3	3	3	3	3	3	3	3	3
MagnesiumStearate (mg)	6	6	6	6	6	6	6	6	6
total wt (mg)	300	300	300	300	300	300	300	300	300

Table 2: Coating solution polymer and solvent ratios profile

Ingredients	OC1	OC2	OC3	OC4	OC5	OC6	OC7	OC8	OC9
Cellulose acetate	1.5w/v	1.5	1.5	2.0	2.0	2.0	2.5	2.5	2.5
Castor oil	10v/v	10	10	10	10	10	10	10	10
Acetone	Qs	qs	qs	Qs	Qs	qs	Qs	qs	Qs

Table 3:IR Interpretation of Drug & Mixtures

Interpretation of Zafirlukast	
Group	**Wavenumber**
N-H str	3325.28-3251.48
C-H str	2943.84-2855.47
C=O str	1686.83
C=N str	1651.47
N-F df	1443.98
Ar H	605.98
Interpretation of cellulose acetate	
O-H str	3169.82
C-H str	2556.81
C=O str	1714.11
C-H df	1172.11
C=O str	1455.56
Zafirlukast + Cellulose acetate	
O-H str	3542.29
C-H str	2920.63
C=O str	1647.94
C-H df	1102.35

Table 4: Values of pre-formulation parameters of drug granules

Form.	**Angle of Repose**	**Bulk density (g/ml)**	**Tapped Density**	**Hausner Factor**	**Carr's Index (%)**
Z1	25.71±0.04	0.47±0.03	0.49±0.02	0.90±0.02	9.25±0.03
Z2	24.22±0.02	0.49±0.01	0.49±0.05	0.89±0.04	10.90±0.02
Z3	26.94±0.05	0.53±0.02	0.50±0.02	0.90±0.06	9.09±0.04
Z4	29.12±0.02	0.57±0.05	0.50±0.03	0.90±0.03	7.40±0.02

Z5	27.62±0.01	0.50±0.02	0.50±0.04	0.94±0.04	5.66±0.03
Z6	25.99±0.03	0.48±0.03	0.53±0.06	0.90±0.01	9.43±0.05
Z7	24.60±0.03	0.52±0.02	0.55±0.02	0.94±0.02	5.45±0.02
Z8	26.78±0.05	0.52±0.05	0.56±0.03	0.92±0.05	7.14±0.01
Z9	29.34±0.04	0.53±0.04	0.57±0.04	0.94±0.04	7.01±0.03

Table 5: Physical characteristics of prepared core tablets

Formulation Code	Thickness ± S.D.(mm) (n= 5)	Hardness ($Kg/cm^{2)}$	Weight variation (mg)	Friability (%)	Drug contet (%)
Z1	3.72 ± 0.043	6.4±0.1	310.23	0.89	96.68
Z2	3.35 ± 0.055	6.3±0.3	300.5	0.80	97.44
Z3	3.75 ± 0.025	6.3±0.2	310.12	0.75	95.98
Z4	3.76 ± 0.067	6.3±0.1	305.5	0.66	90.96
Z5	3.51± 0.052	6.2±0.4	308.2	0.75	97.48
Z6	3.76 ± 0.038	6.1±0.2	304.6	0.52	98.44
Z7	3.31 ± 0.042	6.3±0.3	307.5	0.32	94.32
Z8	3.52 ± 0.039	6.3±0.1	312.4	0.90	94.64
Z9	3.28 ± 0.027	6.3±0.2	310.5	0.85	92.22

Table 6: Physicochemical parameters of coated osmotic tablets

Formulation Code	Thickness ± S.D. (mm) (n= 5)	Hardness ($Kg/cm^{2)}$	Weight variation (mg)	Drug content (%)
Z1	4.60 ± 0.043	6.8±0.1	320.23	97.68
Z2	4.54 ± 0.055	6.5±0.4	315.5	98.44
Z3	4.72 ± 0.085	6.9±0.3	310.12	92.98
Z4	4.70 ± 0.067	6.8±0.2	323.5	93.96
Z5	4.64 ± 0.054	6.6±0.3	318.2	97.48
Z6	4.76 ± 0.048	6.5±0.4	312.6	98.44
Z7	4.78 ± 0.028	6.3±0.2	315.8	94.32
Z8	4.83 ± 0.039	6.7±0.1	320.4	95.64
Z9	3.58 ± 0.026	6.3±0.3	312.5	93.22

Table 7: In vitro dissolution profile of batch Z1 to Z9

Time hour	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9
1	8.0	10.0	7.89	10.67	8.23	9.00	5.22	9.040	7.83
2	22.42	18.91	18.62	19.61	10.93	18.07	9.70	18.38	16.56
3	31.33	29.93	21.49	23.86	14.47	21.21	20.05	25.41	22.11
4	50.97	30.86	28.76	26.47	20.01	28.40	28.10	29.10	24.41
5	64.32	43.06	32.49	46.85	22.92	34.65	36.45	38.06	47.41
6	74.76	64.95	55.39	61.02	25.88	42.96	43.68	44.10	65.78
7	86.99	72.38	60.17	66.11	32.79	49.34	65.44	51.00	77.54
8	88.04	83.99	75.91	72.50	51.43	58.81	72.78	66.82	86.82
9	90.28	86.00	86.14	84.44	67.66	64.35	80.83	72.76	88.35
10	92.33	89.43	88.18	86.05	80.45	72.97	87.09	72.33	90.31
11	93.18	90.88	91.42	90.27	85.74	86.42	90.92	87.67	92.41
12	95.22	92.9	94.46	96.50	94.69	98.61	96.52	97.62	95.42

Table 8: Characteristic of best osmotic tablets (Z6)

Initial			6 month		
Hardness (Kg/Cm^2)	Weight variation (mg)	Uniformity of content (%)	Hardness (Kg/Cm^2)	Weight variation (mg)	Uniformity of content (%)
6.5	312.25	98.44	6.4	310.3	97.48

Table 9: Comparison of dissolution data of best formulation (Z6) subjected to stability study with standard release

Time (hour)	Cumulative % drug release of best formulation(Z_6)			
	Initial	2 month	4 month	6 month
0	0	0	0	0
1	9.52	9.42	9.21	9.00
2	18.07	17.83	17.52	17.02
3	21.21	21.30	20.43	20.22
4	28.40	27.34	26.45	25.40
5	34.65	34.10	33.58	32.53
6	42.96	42.85	42.85	42.96
7	49.34	49.20	49.02	48.24
8	58.81	58.10	57.83	56.62
9	64.35	64.35	63.10	63.24
10	72.97	72.97	72.43	71.82
11	86.42	86.32	85.30	85.31
12	95.61	95.32	95.01	94.88

Table 10: Comparison of observed with calculated assay of best Formulation subjected to stability study

Time in months	Observed Assay (%) Mean ± SD	Calculated Assay (%) Mean ± SD
0	101.37±0.94	101.30±0.76
1	100.81±0.66	100.65±0.71
2	99.99±0.49	100.00±0.64
3	99.01±0.48	99.35±0.59
4	98.66±0.56	98.70±0.53
5	98.03±0.66	98.05±0.48
6	97.59±0.41	97.40±0.44

*****Each value represents the mean ± standard deviation (n=3)

4. Conclusion

Summary: Osmotic devices are most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device. Osmosis is an aristocratic biophenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. Osmotic system utilize the principles of osmotic pressure for delivery of drug. Osmotic drug delivery system utilizes the osmotic pressure for release of drug. Release of drug from osmotically controlled system is found to be independent of pH of the body fluid, presence of food in GIT, hydrodynamic conditions, and otherbody's physiological factors. Osmotic system has a high degree IVIVC, becauserelease is found to be independent of the above mentioned factors, which are responsible for causing differences in release profile *in vivo* and *in vitro.* The aim of the present study was to formulate and evaluate of osmotic tablets of Zafirlukast to give control release of drug by utilizing the osmotic pressure. Suitable analytical method based on UV-Visible spectrophotometer was developed for zafirlukast. ƛmax of 342 nm was identified for Zafirlukast 0.5% SLS solution. By performing compatibility studies with FT-IR no interaction was confirmed. Prior to compression, drug and granules were evaluated for flow properties such as angle of repose, loose bulk density, tapped bulk density, % compressibility, and hausner ratio. Core tablets of Zafirlukast (Z1- Z9) were successfully prepared by wet granulation method. Core and coated formulation for Zafirlukast was developed and evaluated for pharmacopoeial and non pharmacopoeial (industry specified) tests and found within the limits. Formulation was found to be reproducible and short term accelerated stability study of optimized formulation of Zafirlukast was carried out at 40 ± 2°C and at 75 ± 5 RH for one month. At the end of study tablets were analyzed for physical appearance, percentage drug content, hardness, and *in vitro* drug release studies. No significant change or variation was observed in any parameters throughout the study.

Conclusion: In the present work, efforts have been made to prepare and evaluate osmotic tablets of Zafirlukast were formulated with good release profile for a time period up to 12 hours. The rate of the drug release from these tablets increased with increased concentrations of the osmogen. It could decrease the frequency of dose administration, prevent nocturnal attack and improve patient compliance.

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