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Zileuton compression coated tablets: formulation development and in vitro evaluation

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Abstract

In the present research work Zileuton tablets were formulated by employing compression coating technology. Initially the core tablets were prepared by using various concentrations of super disintegrates, the formulated core tablets were coated with the polymers by using compression coating technology. All the core and compress coated tablet formulations were subjected to various physical and chemical evaluation tests for core and compress coated tablets. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official pharmacopoeial limits. In vitro release of Zileuton of core tablet formulations ZF5 showed faster drug release after 15 min. Faster drug release can be correlated with the high disintegration and friability observed in this study.

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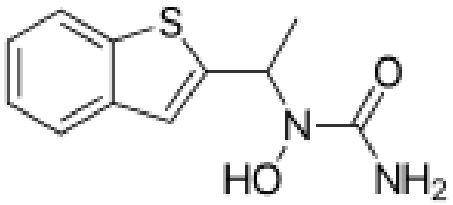
Introduction

Controlled drug delivery is one which delivers the drug at a predetermined rate, locally or systemically, for a specified period. Recently, a new generation of pharmaceutical products, called controlled release drug delivery systems, such as those developed from the osmotic pressure activated drug delivery system, have recently received regulatory approval for marketing and their pharmaceutical superiority and clinical benefits over the sustained release and immediate release pharmaceutical products have been increased [10].

Controlled release drug administration means not only prolongation of the duration of drug delivery, like the objective in sustained release and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. The basic rationale of controlled drug delivery system is to optimize the biopharmaceutical, pharmacokinetics and pharmacodynamics properties of drug in such a way that its utility is maximized through reduction in the side effects and cure or control of condition in the shortest possible time by the most suitable route. Controlled release denotes that the system can provide some actual therapeutic control, whether this is of a temporal nature, spatial nature, or both. Controlled drug delivery occurs when a polymer is combined with a drug or active agent such that the release from the bulk material is pre-designed

Zileuton (trade name Zyflo) is an orally active inhibitor of 5-lipoxygenase, and thus inhibits leukotrienes (LTB_4, LTC_4, LTD_4, and LTE_4) formation, used for the maintenance treatment of asthma and chemically called as (+-)-1-(1-Benzo[b]thien-2-ylethyl)-1-hydroxyurea 11.



Experimental work

Manufacturing process:

Process of preparation of zileuton compress-coated tablets is by wet granulation method.

1. **Sieving**

zileuton and all the other excipients are sieved through 80imesh sieve to remove large particles.

2. Mixing

The zileuton, PVP k-30, cross povidone, sodium starch glycolate, Micro crystalline cellulose and were transferred into the glass mortar and itriturated in order to get the ifine mixture. Later, magnesium stearate and talc were added to the above mixture just before ithe punching process.

3. Preparation of core tablets

Core tablets of zileuton (350 mg) were prepared by wet granulation technique. The powder mixture of zileuton, Poly Vinyl Pyrrolidine, sodium starch glycolate, cross povidone was well mixed in a mortar and passed through a sieve number i40. The tablet was prepared by wet granulation process followed by direct compression method. Flat punches of 8 mm diameter were used for the preparation of core tablets which contains i350mg of zileuton. The prepared tablets were evaluated.

4. Press coating of core tablet

The mixture of Hydroxyl Propyl Methyl Cellulose K100 (HPMC) and Ethyl Cellulose (EC) polymers were used in preparation of outer shell. Different formulations iF_1, iF_2, F3, F4, F5 were formulated by using varying ratios of HPMC and EC to form outer shell. The required immixture of polymers as per the formulation were weighed and immixed in is mortar. Tableting was performed by using is rotary tableting machine by using 12 mm flat punches. The impress coated tablets were prepared as per the formula. One half of the Polymer immixture was infilled into the die, to make in powder bed, ion the centre of which a core tablet was placed. Then the remaining half of the immixture was infilled in the die and the total contents were compressed, thus producing in finished impress coated zileuton tablets.

Table1: FORMULATION BATCHES-CORE TABLET

S.No	Ingredients	Zf_1	Zf_2	Zf_3	Zf_4	Zf_5
1)	Zileuton	400mg	400mg	400mg	400mg	400mg
2)	Sodium starch glycolate	13.5mg	27mg			mg
3)	Cross povidone			13.5mg	27mg	
4)	PVPK-30	9mg	9mg	9mg	9mg	9mg
5)	Talc	4.5mg	4.5mg	4.5mg	4.5mg	4.5mg
6)	Magnesium stearate	4.5mg	4.5mg	4.5mg	4.5mg	4.5mg
7)	Microcrystalline cellulose	18.5mg	5mg	18.5mg	5mg	23mg
8)	Total weight	450mg	450mg	450mg	450mg	450mg

Table 2 FORMULATION BATCHES-COATED TABLETS

S.No	Ingredients	Zf_1	Zf_2	Zf_3	Zf_4	Zf_5
1)	Zileuton	400 mg	400 mg	400 mg	400 mg	400 mg
2)	Cross povidone	27mg	27mg	27mg	27mg	27mg
3)	PVPK-30	9mg	9mg	9mg	9mg	9mg
4)	Talc	4.5mg	4.5mg	4.5mg	4.5mg	4.5mg
5)	Magnesium stearate	4.5mg	4.5mg	4.5mg	4.5mg	4.5mg
6)	Microcrystalline cellulose	5mg	5mg	5mg	5mg	5mg
6)	Hydroxy propyl methyl cellulose(HPMC)	160 mg	150 mg	140 mg	190	170 mg
7)	Ethyl cellulose	40mg	70mg	100 mg	30mg	30mg
8)	Total weight	650 mg	650 mg	650 mg	650 mg	650 mg

Preparation of Standard Curve

Standard curve of zileuton can be obtained by using 0.05 M sodium lauryl sulphate as a solvent to quantify the samples. All the solutions were prepared in fresh before use.

Preparation of i0.05 M sodium lauryl isulphate:

1.441 g of sodium lauryl isulphate is dissolved in i200 iml of distilled water and after dissolving it is made up to i1000ml distilled water.

Preparation of standard solution of zileuton in 0.05 M sodium lauryl sulphate

Preparation of stock-I solution

Transfer about 100 mg of zileuton to an i100-mL volumetric flask. Dissolve in i10 iml of methanol and make up to i100 iml with methanol. The solution obtained is having the final concentration of i1mcg/ml

Preparation of stock-II solution

10 iml of stock–I isolation was pippetedout in an i100 iml volumetric flask and the volume was made up to i100 ml with i0.05M sodium lauryl isulphate.

Preparation of stock-III isolation

The resultant isolation is filtered with whatmann filter paper subsequently diluted with sodium lauryl sulphate to get concentrations of i0.2, 0.4, 0.6, 0.8,1 mcg/ml. The absorbance of above said concentration solutions was measured at i299

nm using sodium lauryl isulphate as blank. The concentration of zileuton solution and corresponding absorbance as tabulated below:

Standard calibration data of zileuton sodium lauryl isulphate

Concentration (mcg/ml)	Absorbance ± (S.D)
0	0±
2	0.126±
4	0.254±
6	0.378±
8	0.50±
10	0.635±

Figure 2: Standard calibration curve of Zileuton

Characterization of active pharmaceutical ingredient

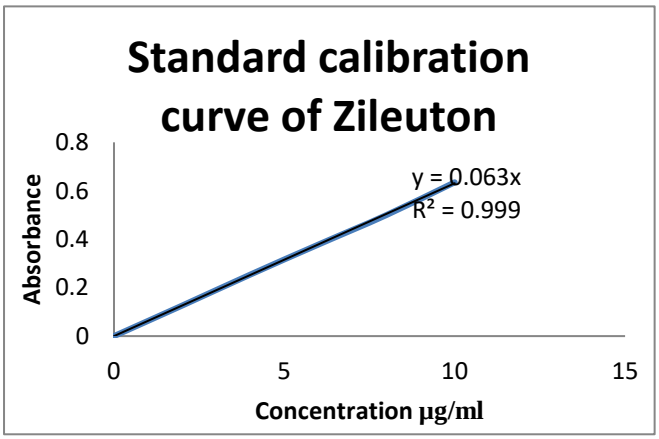
Tests	Results
Description	White to off white crystalline powder
Solubility	Slightly soluble in alcohol and methylene chloride and practically insoluble in water.
Angle of repose	40
Bulk density	0.57
Tap density	0.68
Compressibility index	14
Hausner ratio	1.15

Preformulation Studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

In-vitro dissolution test

Dissolution means the process by which solid substance enters in the solvent to yield process in which a solid substance solubilizes in a given solvent that is transfer from the solid surface to the liquid phase. The dissolution test measures the rate of release of drug from the dosage from in invitro; it is usually expressed as extent of dissolution occurring after a given time under specified conditions. For



ineffective absorption of oral solid dosage inform, simple disintegration of the dosage inform is into inadequate and the dissolution if drug into the surrounding medium plays a vital role. I though dissolution is into a predictor if therapeutic efficacy it can be looked upon a tool which can provide valuable information about biological availability of drug and batch to batch consistency. Dissolution is considered as one of the most important quality control tests performed for pharmaceutical; dosage forms.

Instrument

UV- Visible spectrophotometer

Apparatus

Analytical balance, syringes, volumetric flasks, dissolution apparatus, pipettes and i0.45 µM membrane filters.

Dissolution conditions

Medium: sodium lauryl sulphate

Volume: 900 ml

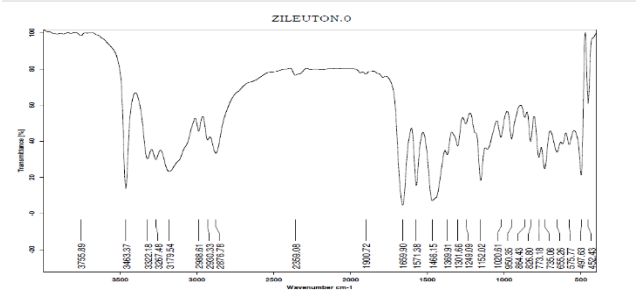
Apparatus: USP –Type II, paddle

Speed: 50rpm

Temperature: 37±0.5°

Results and Discussion

Drug-excipient compatibility



FTIR spectrum of zileuton drug

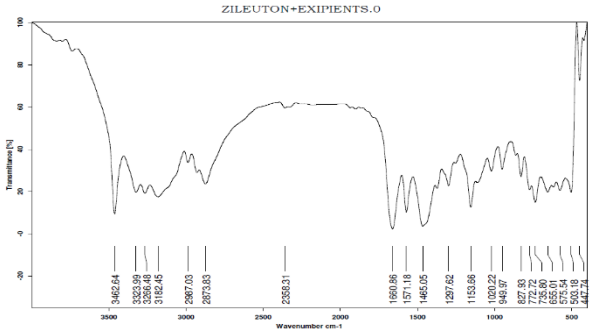


Figure 3: FTIR spectrum of zileuton core tablet

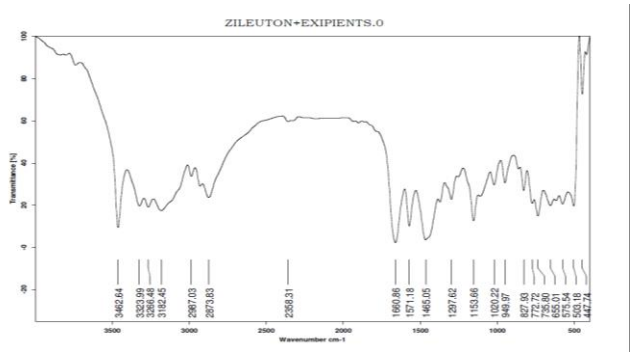
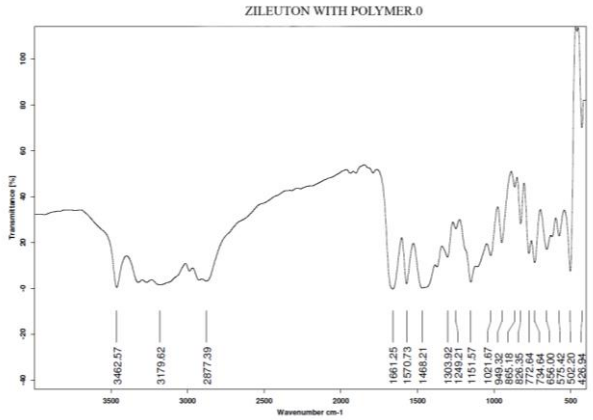


Figure 4: FTIR of zileuton with polymer



Solubility

Table 4: solubility

S.NO	Solvent employed	Solubility
1.	Water	Practically insoluble (>10,000)
2.	Ethanol	Slightly soluble (800)
3.	Chloroform	Slightly soluble (630)
4.	pH 1.3 Buffer	Practically insoluble (>10,000)
5.	pH 7.4 buffer	Sparingly soluble (94)
6.	pH 9	Slightly soluble (450)

Preformulation studies of core and coated tablets

a.) Pre-formulation studies of core tablet:

Table 5: Pre-formulation studies of core tablet

Tests	F1	F2	F3	F4	F5
Angle of repose	28	25	29	22	32
Bulk density	0.44	0.56	0.36	0.46	0.59
Tap density	0.68	0.66	0.69	0.63	0.70
Compressibility index	12	11	14	10	15
Hausner ratio	1.11	1.14	1.12	1.15	1.16

b) Evaluation methods of coated tablets

Table 6: Evaluation methods of coated tablets

Tests	F1	F2	F3	F4	F5
Angle of repose	32	29	26	31	33
Bulk density	0.44	0.56	0.46	0.53	0.58
Tap density	0.67	0.65	0.66	0.59	0.69
Compressibility index	12	13	11	13	14
Hausner ratio	1.11	1.13	1.13	1.10	1.15

c) Evaluation methods of core tablets

Table 7 : Evaluation methods of core tablets

Parameter	F1	F2	F3	F4	F5
Weight variation	452±1.2	451±2.15	450±3.15	449±2.7	451±2.9
Content uniformity	86%	89%	91%	97%	85%
Disintegration	9 min	8 min	7 min	5 min	10 min
Friability	0.10	0.10	0.0	0.02	0.06
Hardness	4.10	5.0	4.45	3.75	4.90

d) Evaluation methods of coated tablets

table7: Evaluation methods of coated tablets:

Parameter	F1	F2	F3	F4	F5
Weight variation	653±2.12	649±1.42	651±3.15	650±2.8	654±4.01
Content uniformity	84%	82%	96%	98%	91%
Disintegration	220 mins	245 mins	255 mins	300mins	240 mins
Friability	0.20	0.10	0.05	0.0	0.15
Hardness	6.05	3.9	5.5	4.30	4.85

Dissolution data of core tablets

Table 8: Dissolution data of core tablets

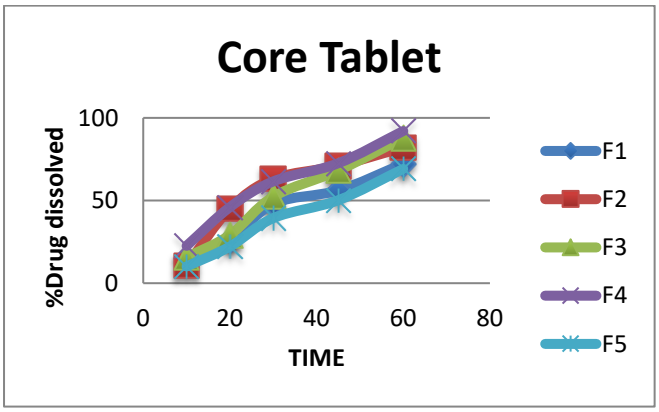
S.No	Time (min)	F_1	F_2	F_3	F_4	F_5
1)	30	0.251	0.22	0.03	0.15	0.10
2)	60	0.473	0.45	0.05	0.19	0.21
3)	90	0.495	0.48	0.06	0.23	0.24
4)	120	0.97	0.99	0.07	1.04	0.91
5)	150	0.969	1.54	0.08	12.01	10.05
6)	180	1.20	3.99	0.10	15.05	13.09
7)	210	2.80	10.05	0.12	19.09	17.06
8)	240	9.13	20.25	0.14	22.06	20.13
9)	270	18.24	51.65	0.16	31.05	29.06
10)	300	49.35	65.06	0.25	51.03	46.06
11)	305	62.46	76.09	38.03	63.06	60.05
12)	310	72.57	82.02	46.04	72.09	69.05
13)	315	84.68	84.08	52.06	86.02	82.04
14)	320	95.79	88.09	80.08	99.01	96.01

Dissolution data of press coated tablets

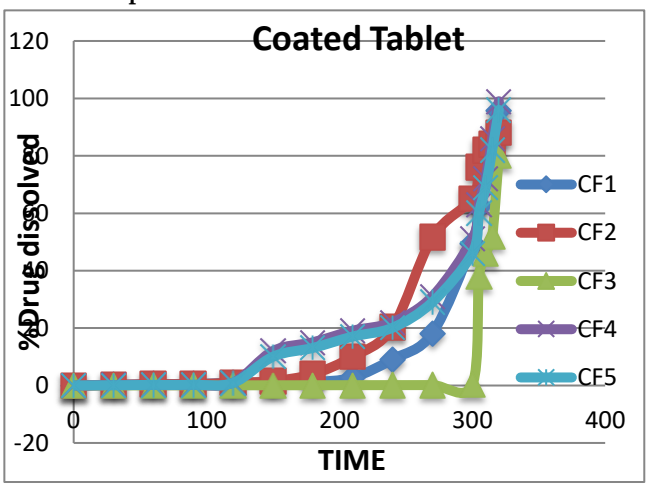
Table 9: Dissolution data of coated tablets

S.No	Time (min)	CF_1	CF_2	CF_3	CF_4	CF_5
1)	30	0.251	0.22	0.03	0.15	0.10
2)	60	0.473	0.45	0.05	0.19	0.21
3)	90	0.495	0.48	0.06	0.23	0.24
4)	120	0.97	0.99	0.07	1.04	0.91
5)	150	0.969	1.54	0.08	12.01	10.05
6)	180	1.20	3.99	0.10	15.05	13.09
7)	210	2.80	10.05	0.12	19.09	17.06
8)	240	9.13	20.25	0.14	22.06	20.13
9)	270	18.24	51.65	0.16	31.05	29.06
10)	300	49.35	65.06	0.25	51.03	46.06
11)	305	62.46	76.09	38.03	63.06	60.05
12)	310	72.57	82.02	46.04	72.09	69.05
13)	315	84.68	84.08	52.06	86.02	82.04
14)	320	95.79	88.09	80.08	99.01	96.01

Dissolution profile of core tablet



Dissolution profile of coated tablet



Summary and Conclusion

The core tablets of Zileuton have been developed with direct compression technique. The coated tablets were produced successfully by employing compress coating technique. Various trials were performed to optimize the lag period and to control the irate of release of drug. Dissolution studies were performed in media i0.05M sodium lauryl isulphate and results were found to be satisfactory. The compress coated tablets and the core tablets passed the I.P. specified dissolution limits. Among the various formulations prepared, the Zileuton formulation **ZF5** was found to be effective in treating asthma.

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