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FORMULATION DEVELOPMENT AND EVALUATION OF EXTENDED RELEASE BI-LAYER TABLETS OF ANTI ASTHMATIC DRUG-ZILEUTON

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ABSTRACT

The objectives of present investigation were to Formulation and development extended release of Zileuton Bilayer tablets were prepared by wet granulation technology and some critical process parameters were studied like in granulation time and extent of granulation, LOD of granules, compression. Developing extended release formulation of Zileuton by using of different extended release polymers like HPMC K4M, HPMC K15M. The prepared tablets were evaluated for official evaluation parameter pH of dissolution media were studied Zileuton bilayer tablets showed the same dissolution profile of the innovator at Water + 0.1M Sodium dodecyl sulphate (Sodium lauryl sulphate). Two month accelerated stability study of the Zileuton bilayer tablets (40°C /75%RH) showed as extended release than the initial.

KEY WORDS

Polymers HPMC K4M, HPMC K15M, wet granulation, Zileuton

INTRODUCTION:

Oral drug delivery is the most widely used route of administration remaining all the routes that have been explored for systemic delivery of drugs from pharmaceutical products of different dosage forms. Oral route is considered as most natural, uncomplicated, convenient and safe due to ease of administration, patient acceptability and cost-effective manufacturing process. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produce systemic effects are marketed as oral dosage forms.[1] Tablets are unit solid pharmaceutical dosage forms. They are containing the active pharmaceutical ingredients with or without suitable excipients and prepared either by compression or molding methods. Tablets are mostly in discoid in shape and round, oval, oblong, cylindrical or triangular.

Extended Release Dosage Form:

It is gives the prolonged therapeutic action and continuously releasing drug an extremely long period of time after administration of drug is called as extended release.

- **Advantages of extended release dosage form:**
  - This decreases the need for multiple dosing and hence improves patient compliance and chances of toxicity.
  - The sustained release drug levels provided by extended release drug products often eliminate the need for night dosing which is beneficial for the patient and the care giver.
  - Reduction in overall health care costs. Although the initial cost may be greater than that for conventional the overall cost of treatment may be less due to enhanced therapeutic benefit.
- **Disadvantages of extended release dosage form:**
  - Loss of flexibility in adjusting the drug dose

- Due to failure in drug technology, there may be a chance of release of entire drug at a time.

BI-LAYER TABLET TECHNOLOGY:

Bi-layer tablet is new era in solid dosage forms. Bi-layer tablet is suitable for sequential for release of two drugs in combination. Bi-layer tablet is improved beneficial new processing technique to overcome the shortcoming of the single layered tablet. Bi-layered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous).

- **Advantages of Bi-layer tablet dosage forms:**
  - Bi-layer tablets can be designed into two different layers can be kept as extended and the other as immediate release.
  - Separation of incompatible components.
  - Prospective use of single entity feed granules.
  - Patient compliance is improved leading to improve drug regimen efficiency.
  - Patient compliance is improved fewer daily dose are required compared to traditional delivery system.
- **Disadvantages of Bi-layer tablet dosage forms:**
  - Difficult to swallow in case of children and unconscious patients.
  - Adds complexity and bi-layer rotary presses are expensive.
  - Cross contamination between the layers.
  - Imprecise individual layer weight control.
  - Insufficient hardness, layer separation, reduced yield.

Polymers are major components in development of extended release formulation. They are in natural and synthetic form. Natural polymers like gelatin, Guar gum, Starch, Collagen. Synthetic polymers like Hydroxy propyl methyl cellulose, Polyvinyl chloride, Polyethylene's etc. Zileuton is anti-asthmatic drug and it is inhibition of 5-lipoxygenase, the enzyme that catalyzes the formation of leukotrienes from arachidonic acid. Specifically, it inhibits leukotriene LTB4, LTC4, LTD4, and LTE4 formation.

METHODOLOGY:

CHEMICALS:

Microcrystalline Cellulose, Mannitol, Crosspovidone, Sodium Starch Glycolate, Pre-gelatinized Starch, Hydroxy propyl Cellulose, HPMCK15M HPMC K 4M, Colloidal silicon Di oxide, Magnesium Stearate, Ferric Oxide.

INSTRUMENTS:

Electronic balance, Rapid mix granulator, Rapid dryer, Tab density tester, Compression Machine, Dissolution test apparatus, Disintegration tester, Friabilator, Hardness tester, Sieves, Sonic shifter, Moisture analyzer, stability chamber, HPLC, Verniar caliper.

PREFORMULATION STUDIES:

- Physical Characterization of API
- Solubility studies of API
- Flow properties of API
- Drug and Excipient compatibility studies

METHOD:

- **ASSAY:** 600 mg of Zileuton in 500 ml volumetric flask and added 350 ml of diluent sonicate for 20 min, make up with diluent and mix well. Take the 4 ml of solution from above stock solution and transferred it 100 ml volumetric flask, volume was made-up with diluent. Finally, sample was taken and filtered through 0.45micron filter paper.
- **DISSOLUTION:** Drug release studies were carried out by using USP type II (paddle) apparatus. 900 ml of 0.1M Sodium Dodecyl Sulphate was used as dissolution medium and the basket was rotated at 75 rpm at temperature (37ºC ± 0.5ºC). Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analyzed using HPLC.

FORMULATION DEVELOPMENT:

- **Physical Characterization of tablets:**
- Weight variation
- Hardness
- Friability
- Thickness

Table No: 01 Formulation

INGRIDIENT	F01 mg/ unit	F02 mg/ unit	F03 mg/ unit	F04 mg/ unit	F05 mg/ unit	F06 mg/ unit	F07 mg/ unit	F08 mg/ unit	F09 mg/ unit
INTRA-GRANULAR PART									
DRUG	600.00	600.00	600.00	600.00	600.00	600.00	600.00	600.00	600.00
MICRO CRYSTALLINE CELLULOSE	181.20	176.30	171.80	166.20	176.80	142.60	140.20	136.10	132.45
MANNITOL	81.00	84.70	72.80	72.20	80.75	74.60	73.95	75.00	75.00
CROSS POVIDONE	3.50	4.50	NA	NA	5.50	6.50	7.50	8.50	10.00
SODIUM STARCH GLYCOLATE	NA	NA	2.40	2.80	NA	3.20	3.60	4.00	4.50
PRE GELATINISED-STARCH	NA	NA	29.20	35.00	NA	35.50	35.50	35.50	35.50
HYDROXY PROPYL CELLULOSE	10.00	12.00	NA	NA	13.50	14.50	16.50	18.50	20.50
PURIFIED WATER	r.q	r.q	r.q	r.q	r.q	r.q	r.q	r.q	r.q
INTRA GRANULAR PART WT	875.70	877.50	876.20	876.20	876.55	876.90	877.25	877.60	877.95
EXTRA GRANULAR PART									
IR GRANULES 25%	218.93	219.38	219.05	219.05	219.14	219.23	219.31	219.40	219.49
FERRIC OXIDE	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
SODIUM STARCH GLYCOLATE	15.00	13.00	13.00	12.25	11.50	10.75	10.00	9.25	8.50
COLLOIDAL SILICON DI OXIDE	1.80	2.00	2.00	2.35	2.55	2.75	2.95	3.15	3.35
MAGNESIUM STEARATE	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
IR LAYER WT	240.73	239.38	239.05	238.65	238.19	237.73	237.26	236.80	236.34
ER GRANULES75%	656.78	658.13	657.15	657.15	657.41	657.68	657.94	658.20	658.46
HPMCK15M CR	40.00	40.00	50.00	55.00	60.00	65.00	70.00	75.00	77.00
HPMC K4M	60.00	60.00	50.00	45.00	40.00	35.00	30.00	25.00	23.00
COLLOIDAL SILICON DI OXIDE	4.50	4.50	5.80	6.20	6.40	6.60	6.80	7.00	7.20
MAGNESIUM STEARATE	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
ER LAYER WT	769.28	770.63	770.95	771.35	771.81	772.28	772.74	773.20	773.66
TOTAL BILAYER TABLET WT	1010.00	1010.00	1010.00	1010.00	1010.00	1010.00	1010.00	1010.00	1010.00

❖ **The following steps involved in formulation:**

- **Dispensing**
- **Granulation:** Granulate the intra granular portion by using purified water used as granulating agent
- **Drying:** dried at 50°C ± 5°C till its LOD reaches to NMT- 3% w/w. (LOD @105°C Auto mode).
- **Milling:** After milling the milled granules are divided into two parts (IR layer 25% and ER layer 75%)
- **Pre-Lubrication:** Pre-lubricate the both IR layer blend and ER layer blend separately.
- **Lubrication:** Lubricate the both IR layer blend and ER layer blend separately.
- **compression**

RESULTS AND DISCUSIONS

❖ **PREFORMULATION STUDIES:**

- PHYSICAL CHARACTERIZATION OF API:

Table No: 02 PHYSICAL CHARACTERIZATION OF API

S.NO	Description	Result
1	Colour	White
2	Odour	Odourless
3	Taste	Bitter
4	Appearance	Crystalline Powder
5	LOD	0.31% L

- **SOLUBILITY STUDIES OF API:**

Table No: 03 SOLUBILITY STUDIES OF API

Solvent system	Solubility (mg/ml)
Purified Water	0.069
0.1 N HCl	0.065
pH 4.5 Acetate buffer	0.068
pH 4.8 phosphate buffer	0.063
Water +0.1 M SLS	2.121
0.1 N HCl +0.1 M SLS	1.669
pH 4.5 Acetate buffer +0.1 M SLS	2.010
pH 4.8 phosphate buffer +0.1 M SLS	1.860

- **FLOW PROPERTIES OF API:**

Bulk density and Tapped density was found to be 0.40 g/ml and 0.82 g/ml. Hausner's ratio and Compressibility index were found to be 51.21 % and 2.05 respectively.

- **Drug and Excipient compatibility studies (Physical observation):**

Table No: 04 Drug and Excipient compatibility

S.No	Ingredients	Ratio	Description		
			Initial	50°C (1Month)	40±2°C /75±5% RH (1Month)
1	API	1	White	No change	No change
2	Microcyrstalline cellulose	1	White	No change	No change
3	Mannitol	1	Off white	No change	No change
5	Crosspovidone	1	White	No change	No change
6	Sodium starch glycolate	1	Off white	No change	No change
7	Starch	1	White	No change	No change
8	Hydroxy propyl cellulose	1	Off white	No change	No change
8	Colloidal silicon dioxide [Aerosil]	1	White	No change	No change
9	HPMC K 15 M Premium Cr	1	Off white	No change	No change
10	HPMC K 4 M Premium Cr	1	Off white	No change	No change
11	Magnesium Stearate	1	White	No change	No change
12	Ferric oxide	1	Off white	No change	No change
13	API + Microcyrstalline cellulose	1 :1	White	No change	No change
14	API + Mannitol	1 :1	Off white	No change	No change
15	API + Crosspovidone	1 :1	White	No change	No change
16	API + Sodium starch glycolate	1 :1	Off white	No change	No change
17	API + Starch	1 :1	White	No change	No change
18	API + Hydroxy propyl cellulose	1 :1	Off white	No change	No change
19	API + Colloidal silicon dioxide	1 :1	White	No change	No change

20	API + HPMC K 15 M Premium Cr	1 :1	Off white	No change	No change
21	API + HPMC K 4 M Premium Cr	1 :1	Off white	No change	No change
22	API + Magnesium Stearate	1 :1	White	No change	No change
23	API + Ferric oxide	1 :1	Off white	No change	No change
24	Placebo excipients without drug	5 g	Off White	No change	No change
25	Composite sample	5 g	Off white	No change	No change

➢ **FLOW PROPERTIES OF LUBRICATED BLEND:**

- **Flow properties of ER Layer:**

Table No: 05 Flow properties of ER Layer

Evaluation Parameters	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
F1	0.45± 0.04	0.56± 0.02	1.24± 0.03	19.64± 0.04	27º59'± 0.05
F2	0.46± 0.06	0.58± 0.03	1.26± 0.02	20.68± 0.02	28º10'± 0.02
F3	0.47± 0.01	0.64± 0.01	1.36± 0.05	26.56± 0.04	30º38'± 0.01
F4	0.46± 0.02	0.51± 0.02	1.10± 0.04	9.80± 0.03	26º51'± 0.06
F5	0.47± 0.02	0.54± 0.03	1.14± 0.01	12.96± 0.05	26º53'± 0.03
F6	0.52± 0.03	0.66± 0.05	1.26± 0.05	21.21± 0.01	28º10'± 0.04
F7	0.58 ± 0.05	0.70± 0.03	1.20± 0.01	17.14± 0.06	26º34'± 0.04
F8	0.56± 0.01	0.71± 0.02	1.26± 0.03	21.12± 0.03	28º33'± 0.02
F9	0.49± 0.06	0.58± 0.01	1.18± 0.04	15.51± 0.07	28º49'± 0.01

(n=3**)**

Flow properties of IR Layer:

Table No: 06 Flow properties of IR Layer

Evaluation Parameters	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
F1	0.43± 0.03	0.56± 0.03	1.30± 0.01	23.21± 0.02	$27^0$59'± 0.03
F2	0.52± 0.04	0.60± 0.04	1.15± 0.04	13.33± 0.01	$28^0$10'± 0.03
F3	0.46± 0.03	0.63± 0.02	1.36± 0.03	26.98± 0.02	$30^0$38'± 0.04
F4	0.47± 0.01	0.52± 0.03	1.10± 0.02	9.61± 0.01	$26^0$51'± 0.04
F5	0.47± 0.04	0.55± 0.01	1.17± 0.03	14.54± 0.01	$26^0$53'± 0.02
F6	0.51± 0.02	0.60± 0.04	1.17± 0.02	15.00± 0.01	$28^0$10'± 0.01
F7	0.59± 0.06	0.69± 0.04	1.16± 0.02	14.49± 0.03	$26^0$34'± 0.03
F8	0.55± 0.03	0.70± 0.01	1.27± 0.04	21.42± 0.02	$28^0$33'± 0.01
F9	0.46± 0.04	0.54± 0.02	1.17± 0.02	14.81± 0.03	$28^0$49'± 0.03

(n=3)

- **Particle size distribution of ER Layer blend:**

Table No: 07 Particle size distribution of ER Layer blend

Sieve No:	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8(%)	F9(%)
#30	41.01	28.39	21.22	19.76	25.4	29.37	27.92	26.25	21.65
#40	60.65	42.68	41.71	43.35	40.27	44.59	42.67	47.12	36.87
#60	73.01	61.24	58.92	66.17	66.37	64.85	68.93	64.37	59.29
#80	87.66	82.55	77.36	85.17	79.87	78.81	80.04	77.33	83.68
#100	95.64	88.14	86.38	80.81	87.68	89.23	88.65	86.39	85.74
#200	98.56	95.61	95.55	97.47	98.12	98.64	99.04	97.45	98.97
Receiver	100	100	100	100	100	100	100	100	100

- **Particle size distribution of IR Layer blend:**

Table No: 08 Particle size distribution of IR Layer blend

Sieve No:	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
#30	40.01	27.36	19.85	18.56	26.01	30.37	28.11	25.95	23.15
#40	58.65	41.5	39.89	39.89	43.55	47.58	43.58	48.82	35.46
#60	72.01	59.18	60.91	60.19	65.88	63.77	69.01	65.01	58.44
#80	85.66	81.2	76.33	87.52	80.8	79.52	79.98	78.2	82.97
#100	93.64	80.09	87.32	83.89	88.58	90.69	89.15	87.1	86.69
#200	97.56	93.24	95.57	98.54	97.91	98.7	99.14	98.33	98.41
Receiver	100	100	100	100	100	100	100	100	100

- **ASSAY:**

Assay percentage of the Innovator product was 99.6±1.82, Assay percentage of optimized formulation F09 showed assay percentage of 99.2±1.39 which is in limit and matches the marketed product.

Table No: 09 Particle size distribution of ER Layer blend

TEST	Assay (98-101% USP)
RLD	99.6±1.82
F1	97.2±1.46
F2	97.3±1.15
F3	96.5±2.51
F4	98.1±1.42
F5	97.3±1.19
F6	98.1±1.33
F7	96.1±2.11
F8	96.9±2.31
F9	99.2±1.39

(n=3**)**

POST COMPRESSION PARAMETERS:

Table No: 10 Post Compression Parameters

Parameters	Weight variation (mg)	Hardness (Kp)	Thickness (mm)	Friability (%w/w)
F1	1012±1.32	19 ±2	6.90± 0.01	0.07± 0.05
F2	1010.1 ±1.69	21±1	6.90± 0.02	0.09± 0.03
F3	1009.5 ±1.44	19±2	6.90± 0.01	0.08± 0.02
F4	1011.0 ±1.92	19±2	6.90± 0.01	0.10± 0.05
F5	1009.4 ±1.99	20±1	6.90± 0.03	0.15± 0.02
F6	1010.7 ±1.63	19±2	6.90± 0.02	0.09± 0.01
F7	1012.1 ±2.05	21±1	6.90± 0.01	0.11± 0.03
F8	1010.6 ±1.59	20±1	6.90± 0.02	0.08± 0.03
F9	1010.1 ±1.33	21±1	6.90± 0.02	0.12± 0.01

(n=3**)**

DISSOLUTION:

The drug release profiles are obtained for the innovator drug and various formulations F1, F2, F3, F4, F5, F6, F7, F8, F9 and the optimized formulation trail F9 shows the cumulative % drug release 0, 21±0.12, 43±1.05, 55±1.63, 85±1.01 & 99±1.03 respectively shown in table no.22. The innovator drug shows drug release 0, 22.1, 43.8, 56.3, 85.7 & 99.6 respectively. These are carried out at certain intervals of time duration 1, 2, 4, 8, 12(hours). Of all the formulations held trail F9 shows cumulative % drug release after 12th hour similar to that of innovator.

Table No:11 Percentage (%) drug release of formulations

Trials	Time(hr)					
	0	**1**	**2**	**4**	**8**	**12**
F1	0	34±1.21	56±1.78	74±3.12	99±1.36	100±2.01
F2	0	28±1.82	58±2.74	76±1.15	78±1.85	81±1.97
F3	0	32±1.34	53±1.63	67±1.97	94±1.52	97±1.01
F4	0	27±1.19	42±1.71	62±2.01	91±2.47	97±3.06
F5	0	26±3.36	34±1.37	39±4.12	42±2.01	63±2.56
F6	0	28±2.72	35±1.23	41±1.37	53±1.28	71±1.08
F7	0	29±1.39	40±1.21	51±1.21	67±1.65	86±2.01
F8	0	31±1.01	45±1.55	63±1.83	88±1.07	94±1.32
F9	0	21±0.12	43±1.05	55±1.63	85±1.01	99±1.13

(n=3**)**

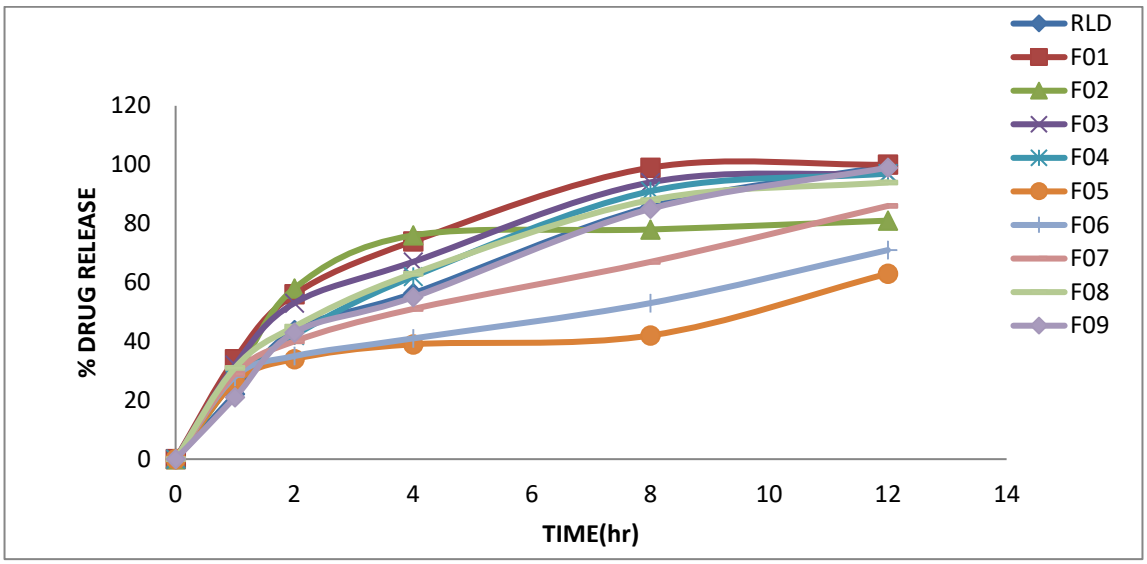

Figure 01: In-Vitro dissolution profile of all formulations

Table No: 12 Percentage (%) drug release of RLD and F09

TIME (hrs)	RLD	F9
0	0	0
1	22.1±1.01	21±0.12
2	43.8±2.10	43±1.05
4	56.3±3.30	55±1.63
8	85.7±1.23	85±1.01
12	99.6±1.13	99±1.13

(n=3)

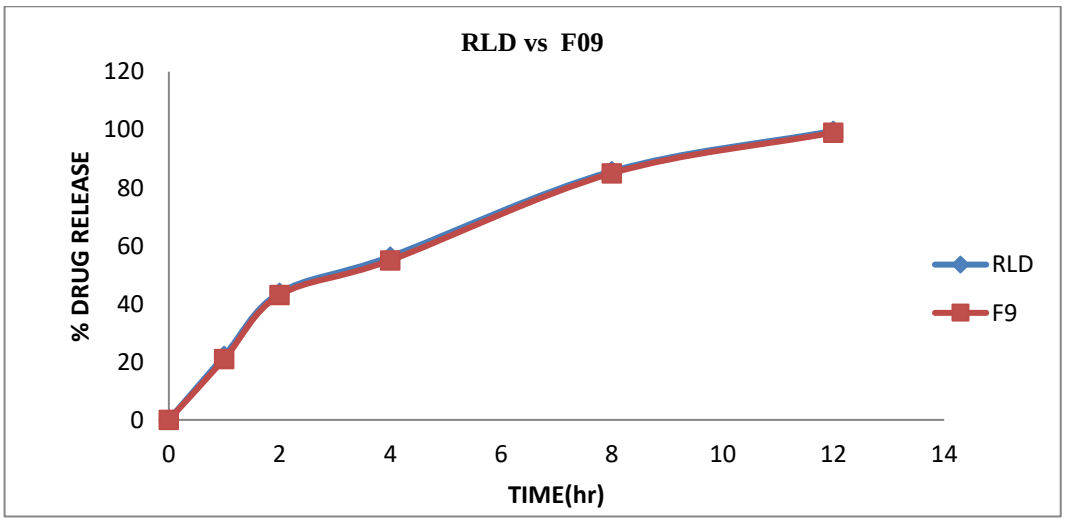

Figure No 02: *In-Vitro* dissolution profile of RLD and optimized formulation (F09)

➢ **Results of stability loaded batch (F09):**

Assay:

Table No:13 Assay of stability batch

Trial	Condition	Duration	Assay average (%)
F09	Initial	0	99.21±1.39
	40°C/75%RH	1 Month	99.05±1.71
		2 Months	99.09±0.81
		3 Months	98.22±1.75
		6 Months	98.45±1.69

(n=3)

***In-vitro* Dissolution studies:**

Table No.14: % drug release of stability batch

Batch	Stage	Time points (min)					
		0	1	2	4	8	12
		% Drug Release					
RLD	Initial	0	22.1± 1.01	43.8± 2.10	56.3± 3.30	85.7± 1.23	99.6± 1.13
F09	40°C/75%RH 1M	0	19.6± 1.10	41.9± 2.12	54.8± 3.20	83.6± 1.29	98.8± 1.06
	40°C/75%RH 2M	0	20.2± 1.01	44.8± 2.13	58.2± 3.11	83.8± 1.09	97.4± 1.03
	40°C/75%RH 3M	0	20.7± 1.21	43.6± 2.31	54.9± 3.27	86.6± 1.13	99.2± 1.18
	40°C/75%RH 6M	0	20.5± 1.03	45.1± 2.07	53.8± 2.27	83.8± 1.15	98.5± 1.07

(n=3)

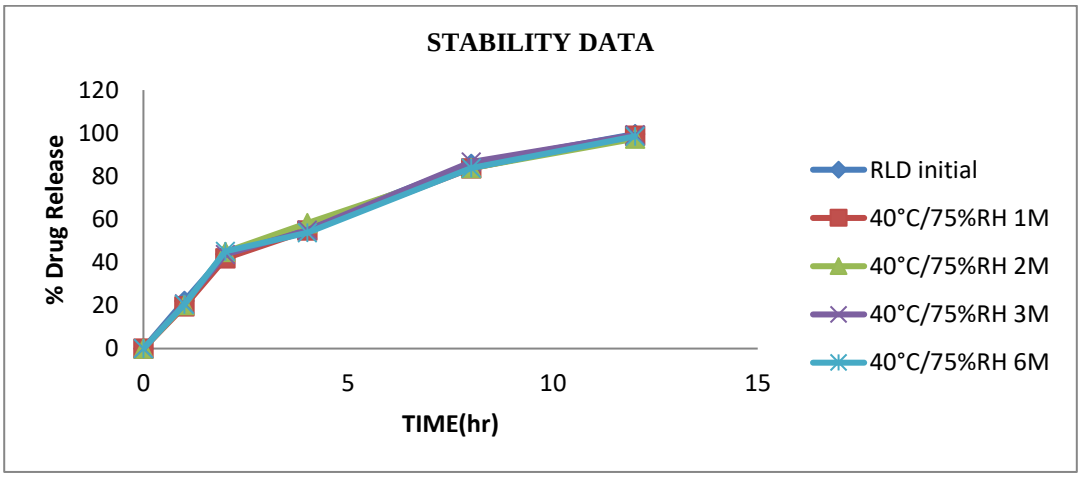

Figure No 03: *In-Vitro* dissolution profile of innovator and stability loaded batch (F09)

CONCLUSION:

The drug Zileuton was found to be suitable for the method of formulating into the bilayer tablets. The release of the drug was comparable to the RLD. For the optimization of the formula various excipients and their effects on the formulation was evaluated. The evaluation tests which include pre-compression parameters, weight variation test, Hardness, thickness, assay, dissolution, particle size distribution. All the formulations were evaluated and the formulation F09 was found to be the optimized formulation and the batch was loaded for the stability at accelerated stability condition (40 ± 2°C /75 ±5% RH). The initial drug release was 99.6±1.13% and it was found to be 98.10 ± 1.02 % at the end of the 6th month.

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