

Controlled Release Tablets of Zileuton by Using Gum Based and HPMC Polymers

Ayesha Haseena*, Asfia Kauser, Faheem Unnisa Begum, Taiyaba Fatima

*Assistant Professor, Shadan Women's College of Pharmacy,
Khiartabad, Hyderabad, Department of Pharmaceutics

ABSTRACT: The aim of the present study was to develop Controlled release formulation of Zileuton to maintain constant therapeutic levels of the drug for over 12 hrs. Sodium alginate, Guar gum and HPMC K15M were employed as polymers. Zileuton dose was fixed as 300 mg. Polymers were used in the concentration of 100, 200 and 300 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 98.86 % in 12 hours. It contains the natural polymer Zileuton as controlled release material. It followed zero order release kinetics mechanism.

Keywords: Zileuton, Guar gum, HPMC K15 M, Sodium alginate and controlled release tablets.

I. Introduction

Controlled Drug Delivery System

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.

Advantages of Controlled Drug Delivery System

1. Reduction in frequency of drug administration.
2. Improved patient compliance.
3. Improvement in bioavailability of some drugs because of spatial control.

Disadvantages Of The Drug Delivery Systems

1. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
2. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
3. Stability problems.

Classification

1. Dissolution controlled release
 - a) Matrix dissolution control
 - b) Reservoir dissolution control
2. Diffusion controlled release
 - a) Matrix diffusion control
 - b) Reservoir diffusion control
3. Dissolution and Diffusion controlled systems
4. Water penetration controlled systems
 - a) Osmotic controlled release
 - b) Swelling controlled release
5. Hydrogels
6. Ion exchange resins
7. pH independent formulation
8. chemically controlled system

II. Materials

Name of the material
Zileuton
HPMC
Guar gum
Sodium alginate
MCC pH 102
Magnesium stearate
Talc

III. Methodology

3.1 Analytical Method Development

3.1.1 Determination Of Absorption Maxima

A solution containing the concentration 10 µg/ml drug was prepared in 0.1N HCl and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

3.1.2 Preparation Calibration Curve

100mg of Zileuton pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with 100ml by using 0.1 N HCl (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 2, 4, 6, 8 and 10µg/ml of Zileuton per ml of solution. The absorbance of the above dilutions was measured at 230 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line. Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

3.2 Drug – Excipient Compatibility Studies

Fourier Transform Infrared (Ftir) Spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 4000 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

3.3. Preformulation Parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of Repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was calculated using the following formula;

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

Tan θ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Bulk Density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm³.

The bulk density was calculated using the formula;

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped Density

The cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 taps per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures Of Powder Compressibility

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these influence the compressibility index. The simple method for measurement of free flow of powder is Carr's Index, a sign of the easiness with which a material can be induced to flow is given by Carr's Index (CI) which is calculated as follows;

$$CI (\%) = [(Tapped\ density - Bulk\ density) / Tapped\ density] \times 100$$

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$Hausner's\ Ratio = Tapped\ density / Bulk\ density$$

3.4 Formulation Development Of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Zileuton. Total weight of the tablet was considered as 800mg.

Procedure

- 1) Zileuton and all other ingredients were individually passed through sieve no = 60.
- 2) All the ingredients were mixed thoroughly by triturating up to 15 min.
- 3) The powder mixture was lubricated with talc.
- 4) The tablets were prepared by using direct compression method.

TABLE 1: Formulation composition for tablets

Formulation No.	Zileuton	Sodium alginate	Guar gum	HPMC K15M	Mag. Stearate	Talc	MCC pH 102
F1	300	100			8	8	384
F2	300	200			8	8	284
F3	300	300			8	8	184
F4	300		100		8	8	384
F5	300		200		8	8	284
F6	300		300		8	8	184
F7	300			100	8	8	384
F8	300			200	8	8	284
F9	300			300	8	8	184

All the quantities were in mg

3.5. Evaluation Of Post Compression Parameters For Prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight Variation Test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1-W2) / W] \times 100$$

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

3.6 Determination Of Drug Content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml media and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV – Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In Vitro Drug Release Studies

Dissolution Parameters

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl , p H 6.8 Phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°C ± 0.5°C

Procedure

Drug release from formulated controlled tablets was determined by using USP dissolution test apparatus II (Paddle apparatus). The tablets were place in 900 ml of dissolution medium as pH 1.2(0.1N HCl) for 2 hours then replace the gastric fluid with pH 6.8 phosphate buffer maintained at 37 ± 0.5 °C and 50 rpm. At appropriate intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours) 5ml of the samples were taken and the dissolution media was then replaced by 5ml of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were then analyzed at 230nm by UV-spectrophotometer. The concentration was calculated by using calibration curve.

3.7 Application Of Release Rate Kinetics To Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero Order Release Rate Kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_0 t$$

Where, 'F' is the drug release at time 't', and 'K₀' is the zero order release rate constant. The plot of % drug release versus time is linear.

First Order Release Rate Kinetics

The release rate data are fitted to the following equation

$$\text{Log} (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi Release Model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k t^{1/2}$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer And Peppas Release Model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release

calculated through the slope of the straight Line.

$$M_t / M_\infty = K t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process.

Hixson-Crowell Release Model

$$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

IV. Results And Discussion

The present study was aimed to developing Sustained release tablets of Zileuton using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

4.1. Analytical Method

Graphs of Zileuton were taken in Simulated Gastric fluid (pH 1.2) and in pH 6.8 phosphate buffer at 238 nm and 234 nm respectively.

TABLE 2: Observations for graph of Zileuton in 0.1N HCl (230nm)

Conc [µg/l]	Abs
0	0
2	0.231
4	0.428
6	0.66
8	0.925
10	1.155

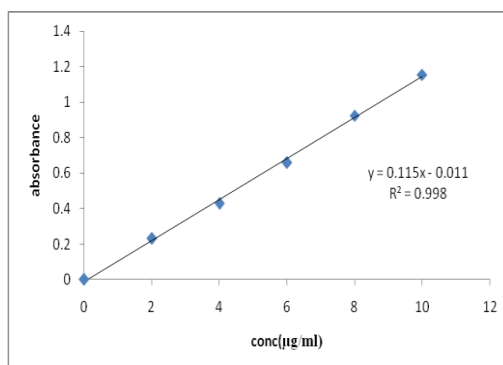


Fig: Standard graph of Zileuton in 0.1N HCl

TABLE 3: Observations for graph of Zileuton in pH 6.8 phosphate buffer (229nm)

Conc [µg/l]	Abs
0	0
2	0.157
4	0.299
6	0.411
8	0.57
10	0.71

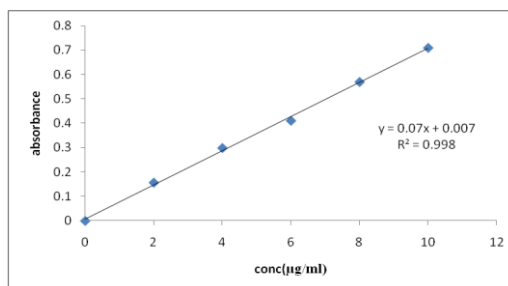
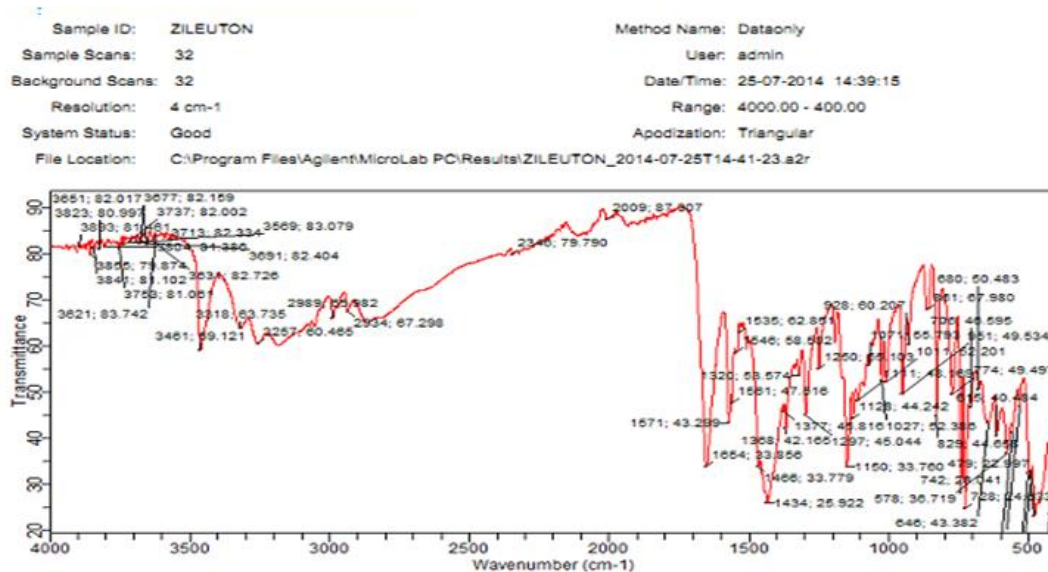
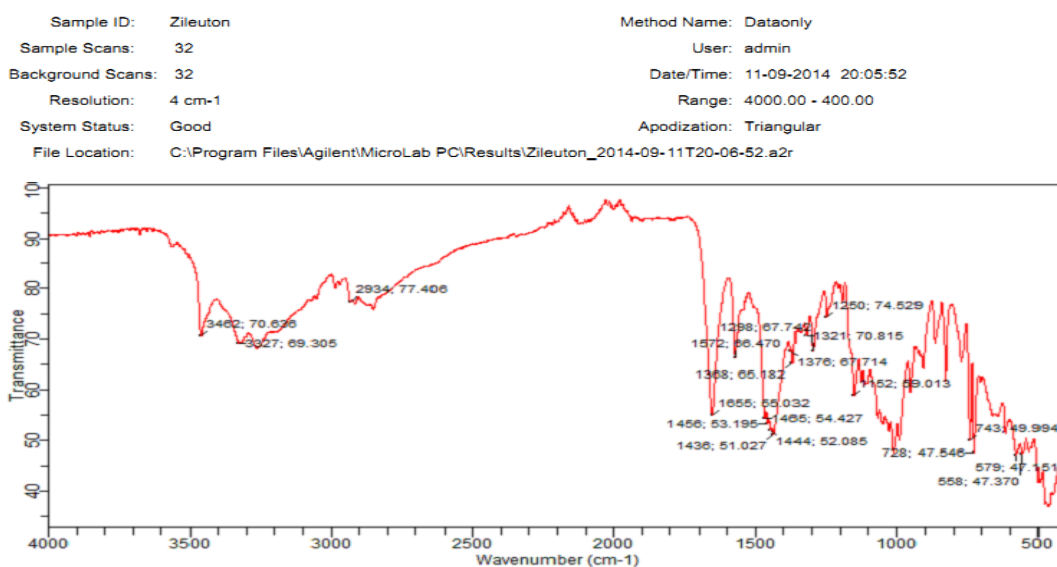


Fig: Standard graph of Zileuton pH 6.8 phosphate buffer (229 nm)

4.2 Drug – Excipient Compatability Studies Fourier Transform-Infrared Spectroscopy



FT-TR Spectrum of Zileuton pure drug



FT-IR Spectrum of Optimised Formulation

4.3 Preformulation Parameters Of Powder Blend

TABLE 4: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49	0.57	14.03	1.16
F2	24.8	0.56	0.67	16.41	1.19
F3	22.74	0.52	0.64	18.75	1.23
F4	25.33	0.54	0.64	15.62	1.18
F5	26.24	0.53	0.65	18.46	1.22
F6	26.12	0.56	0.66	15.15	1.17
F7	27.08	0.58	0.69	15.94	1.18
F8	25.12	0.48	0.57	15.78	1.18
F9	25.45	0.54	0.65	16.92	1.2

4.4 Quality Control Parameters For Tablets

TABLE 5: Invitro quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm ²)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	812.5	4.5	0.50	3.8	99.76
F2	805.4	4.5	0.51	3.9	98.45
F3	818.6	4.4	0.51	3.9	99.34
F4	810.6	4.5	0.55	3.9	97.87
F5	809.4	4.4	0.56	3.7	99.14
F6	810.7	4.5	0.45	3.7	98.56
F7	802.3	4.5	0.51	3.4	98.42
F8	801.2	4.3	0.49	3.7	99.65
F9	798.3	4.5	0.55	3.6	98.12

4.5. In-Vitro Drug Release Studies

TABLE 6: Dissolution Data of Zileuton Tablets Prepared With Sodium alginate In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F1	F2	F3
0	0	0	0
0.5	27.51	20.17	16.45
1	48.74	39.45	26.73
2	74.53	55.33	34.64
3	99.48	75.32	42.45
4		87.35	55.43
5		99.44	67.48
6			85.43
7			91.55
8			97.37

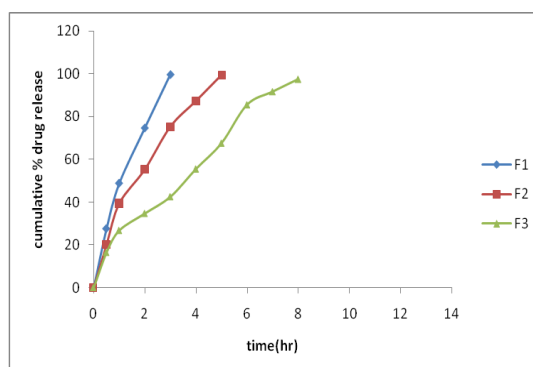


Fig : Dissolution profile of Zileuton (F1, F2, F3 formulations).

TABLE 7: Dissolution Data of Zileuton Tablets Prepared With Guar gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F4	F5	F6
0.5	17.25	14.42	12.62
1	38.26	23.73	19.86
2	56.16	36.63	23.35
3	72.01	45.04	30.45
4	85.26	58.25	39.80
5	97.10	65.33	45.25
6		76.41	53.24
7		84.84	61.73
8		97.80	69.34
9			75.52
10			82.17
11			89.10
12			98.86

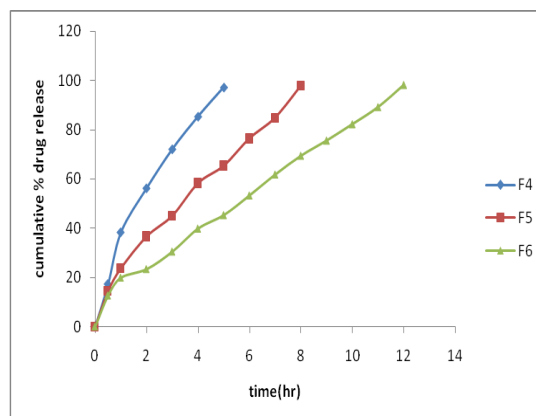


Fig7.6: Dissolution profile of Zileuton (F4, F5, F6 formulations)

TABLE 8: Dissolution Data of Zileuton Tablets Prepared With HPMC K15M In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F7	F8	F9
0.5	14.4	11.4	8.5
1	18.5	17.6	14.5
2	26.6	23.4	18.4
3	32.5	30.7	23.4
4	44.5	38.4	28.2
5	50.4	44.6	34.8
6	67.2	52.3	40.2
7	76.5	61.3	44.8
8	88.3	70.8	50.4
9	97.78	79.52	63.34
10		86.65	69.27
11		97.56	74.86
12			82.97

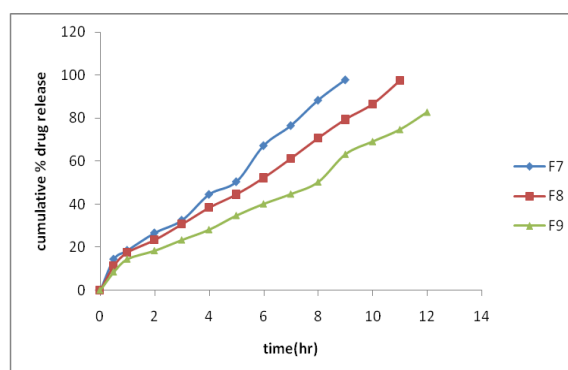


Fig : Dissolution profile of Zileuton (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Sodium alginate as polymer were unable to retard the drug release up to desired time period i.e., 12 hours.

Whereas the formulations prepared with Guar gum retarded the drug release in the concentration of 300 mg (F6 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.86% in 12 hours with good retardation.

The formulations prepared with HPMC K15M showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application Of Release Rate Kinetics To Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

TABLE 9: Release kinetics data for optimised formulation

CUMULATIVE RELEASE (%)	TIME (T)	ROOT (T)	LOG(% RELEASE)	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM % RELEA SE	PEPPA S log Q/100	% Drug Remaining
0	0	0			2.000				100
12.62	0.5	0.707	1.101	-0.301	1.941	25.240	0.0792	-0.899	87.38
19.86	1	1.000	1.298	0.000	1.904	19.860	0.0504	-0.702	80.14
23.35	2	1.414	1.368	0.301	1.885	11.675	0.0428	-0.632	76.65
30.45	3	1.732	1.484	0.477	1.842	10.150	0.0328	-0.516	69.55
39.8	4	2.000	1.600	0.602	1.780	9.950	0.0251	-0.400	60.2
45.25	5	2.236	1.656	0.699	1.738	9.050	0.0221	-0.344	54.75
53.24	6	2.449	1.726	0.778	1.670	8.873	0.0188	-0.274	46.76
61.73	7	2.646	1.790	0.845	1.583	8.819	0.0162	-0.210	38.27
69.34	8	2.828	1.841	0.903	1.487	8.668	0.0144	-0.159	30.66
75.52	9	3.000	1.878	0.954	1.389	8.391	0.0132	-0.122	24.48
82.17	10	3.162	1.915	1.000	1.251	8.217	0.0122	-0.085	17.83
89.1	11	3.317	1.950	1.041	1.037	8.100	0.0112	-0.050	10.9
98.86	12	3.464	1.995	1.079	0.057	8.238	0.0101	-0.005	1.14

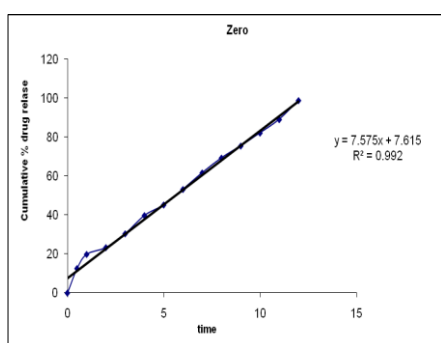


Fig : Zero order release kinetics graph

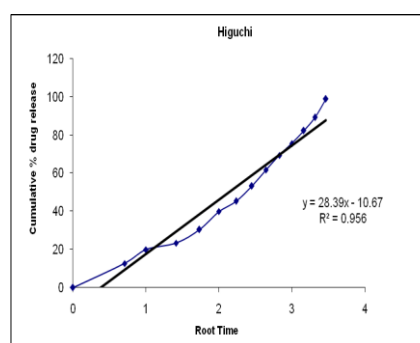


Fig : Higuchi release kinetics graph

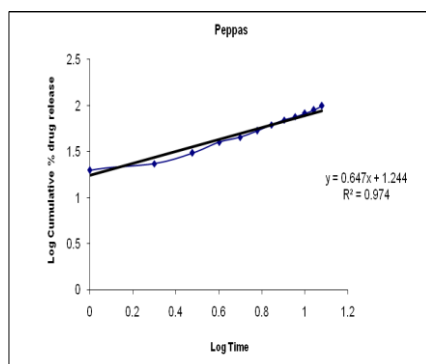


Fig: Kars mayer peppas graph

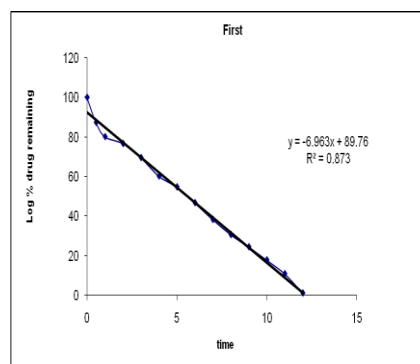


Fig : First order release kinetics graph

From the above graphs it was evident that the formulation F6 was followed Zero order release kinetics.

V. Conclusion

The aim of the present study was to develop Controlled release formulation of Zileuton to maintain constant therapeutic levels of the drug for over 12 hrs. sodium alginate, guar gum and HPMC K15M were employed as polymers. Zileuton dose was fixed as 300 mg. Polymers were used in the concentration of 100, 200 and 300 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 98.86 % in 12 hours. It contains the natural polymer Zileuton as controlled release material. It followed zero order release kinetics mechanism.

Bibliography

- [1]. 1Nokhodchi, Shaista Raja, Priya Patel, Kofi Asare-Addo. The Role Of Oral Controlled Release Matrix Tablets In Drug Delivery Systems. *Bioimpacts*. 2(4);175-187:2012.
- [2]. 39Amir Badshah, FazalSubhan, Khalid Rauf, Nadeem Irfan Bukhari, Zia Ahmed. Development Of Controlled-Release Matrix Tablet Of Risperidone: Influence OfMethocel®-And Ethocel®-Based Novel Polymeric Blend On In-Vitro Drug Release And Bioavailability. *AAPS Pharm. sci.tech.* 12(2);525-533:2011.
- [3]. Anil K. Anal. Time-Controlled Pulsatile Delivery Systems For Bioactive Compounds. *Recent Patents On Drug Delivery & Formulation*. 1;73-79:2007.
- [4]. Anne B Chang, John G Widdicombe. Cough throughout life: children, adults and the senile. *Pulmonary Pharmacology & Therapeutics*. 20;371-382:2007.
- [5]. Ansel HC, Allen LV, Popvich NG. *Pharmaceutical Dosage Forms And Drug Delivery System*. 2000;7th :229-243.
- [6]. [6] 2Aravind Singh Rathore, Jat RC, Narendra Sharma, Rahul Tiwari. An Overview: Matrix Tablet As Controlled Drug Delivery System. *International Journal Of Research And Development In Pharmacy And Lisfe Sciences*. 2(4);482-492:2013.
- [7]. 31Ashtamkar Joel, Nangude Shantaramand Chugh Naresh. Formulation And Evaluation Of Controlled Release Tablets Of Labetalol Hydrochloride Using Hydrophobic Polymers. *International Journal Of Research in Pharmaceutical And Biomedical Sciences*. 4(1);380-384:2013.
- [8]. Avgoustakis K, Nixon JR. Biodegradable Controlled Release Tablets: Effect Of Polymer Characteristics On Drug Release From Heterogeneous Poly (Lactide-co-Glycolide) Matrices. *Int. J. Pharm.* 99;247-252:1993.
- [9]. Bala Ramesha Chary R, Madhusudan Rao Y. Formulation And Evaluation Of Methocel K15M Bioadhesive Matrix Tablets. *Drug Development And Industrial Pharmacy*. 26(8);901-906:2000.
- [10]. 26Banker GS, Rhodes CT. *Modern Pharmaceutics. Sustained and Controlled Release Delivery Systems*. Marcel Dekker. 2002;4th :501-528.
- [11]. 3Bhalla Neetika, Deep Arsh, Goswami Manish. An Overview On Various Approaches To Oral Controlled Drug Delivery System Via Gastoretentive Drug Delivery System. *Int. Res. J. Pharm.*3(4);128-133:2012.
- [12]. Bonny JD, Leuenberger H. Matrix Type Controlled Release Systems: Effect Of Percolation On Drug Dissolution Kinetics. *Pharm. Acta. Helv.* 66(5-6);160-164:1991.
- [13]. 19Borguist P, Korner A, Larsson A. A model for the drug release from a polymeric matrix tablets-effect of swelling and dissolution. *J Control Release*. 113;216-225:2006.
- [14]. 7Bramhanker DM, Jaiswal SB. *Controlled Release Medications. Biopharmaceutics And Pharmacokinetics a Treatise*. Vallabh Prakashan, 1995;2nd.:335-375.
- [15]. 53Catena E, Dafton Chio. Efficacy And Tolerability Of Levodropropizine In Adult Patients With Non Productive Cough: Comparison With Dextromethorphan. *Pulmonary Pharmacology And Therapeutics*.10;89-96:1997.
- [16]. Chang KT, Coffin MD, McGinity JW. Properties Of Controlled Release Matrix
- [17]. Tablets Containing DL- Polylactic acid as the Retardant Polymer. *J. Pharm. Sci.* 76(11);259:1987.
- [18]. 35Charulatha R, Kumaravel Rajan R. Design And Evaluation Of Carbamazepine Controlled Release Drug Delivery System. *International Journal Of Pharm Tech Research*. 4(1);25-34;2012.
- [19]. Chidambaram N, Porter W, Flood K, Qiu Y. Formulation And Characterization Of New Layered Diffusional Matrices For Zero-Order Sustained Release. 52(1-2);149-158:1998.
- [20]. 13Chien YW, *Controlled Drug Delivery Systems. Novel Drug Delivery Systems*, Marcel Dekker, 1992;2nd:139-196.
- [21]. 41Chitta Suresh Kumar, Pilli Yesupadam, Harika B, Deepika D, Chandra Sekhar A. Formulation And Evaluation Of Once-Daily Sustained Release Aceclofenac ProsopisJuliflora Gum Matrix Tablets. *International Journal Of Pharmaceutical Sciences Review And Research*. 1(2);23-27:2010.
- [22]. 25Christian Nordqvist. Cough and Causes of cough. 6;1-3:2011.
- [23]. Chung KF, Pavord ID. Cough, en.wikipedia.org.1;1-7:2013.
- [24]. 24Collett J, Morenton C. *Pharmaceutics: The Science And Practice Of Pharmacy*. Churchill livingstone. 2002;2nd.: 295-299.
- [25]. Colombo P. Swelling Controlled Release In Hydrogel Matrices For Oral Route. *Adv. Drug Del. Rev.* 11;37-57:1993.