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Formulation and In Vitro Evaluation of Acyclovir Sustained Release Tablets

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ABSTRACT

The aim of the present work is to Formulate and Evaluate controlled release of Acyclovir matrix tablets used for treatment of viral infections. Development of SR Acyclovir is proposed considering the adverse event profile and high fluctuation index of Acyclovir observed with SR dosage forms. In the present work, attempts were made to formulate and evaluate controlled release of matrix tablets of Acyclovir. Acyclovir was subjected to preformulation studies, based on the results obtained Acyclovir controlled release tablets were successfully formulated. Formulations prepared by direct compression technique using sodium alginate and Xanthan gum as control release polymers. Set of trials were formulated for which Acyclovir evaluated parameters (bulk density, tapped density, compressibility index, Hausner's ratio, weight, thickness, and hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in 0.1 HCL for 2 hours followed by pH 1.2 and pH 6. 8 phosphate buffer. From the results of the invitro study it appears that the release of the Acyclovir was significantly influenced by the characteristics of the polymer used.

Key Words: Acyclovir, Polymers, Direct compression technique, in vitro drug release studies, Zero order kinetics.

INTRODUCTION

Oral administration of drugs is the most common and preferred route for delivery of therapeutic agents. Oral route of drug administration is the ideal, convenient and preferred route.[1] Sustained drug contains loading dose and maintenance dose. In that loading dose is quickly released to form speed drug on site if action and maintenance dose is released at a sustained release rate so that the plasma concentration persist continual above minimum effective concentration.[2] A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. [3]Aciclovir triphosphate competitively inhibits viral DNA polymerase and competes with the natural deoxyguanosine triphosphate, for incorporation into viral DNA.[4] Aciclovir is used for the treatment of herpes simplex virus and varicella zoster virus infections.[5]

MATERIALS

Acyclovir was obtained from Alkem Pvt Mumbai, Xantham gum and Sodium alginate was procured from SD fine chemicals Mumbai. Other chemicals and the reagents used were of analytical grade.

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METHODOLOGY

Drug-Excipient Interaction Studies[6]

This type of interactions was studied with the help of Shimadzu FTIR spectrophotometer, in which KBR pellet method used to determine the interactions.

Preparation of Acyclovir Tablets

Table-1: Formulation Table

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	200	200	200	200	200	200	200	200
Tragacanth	100	-	-	50		-	50	50
Sodium alginate	-	100		-	50	50	-	50
Xanthan gum	-	-	100	-	-	50	50	-
Microcrystalline cellulose	195	195	195	245	245	195	195	195
Talc	2	2	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3	3	3
Total Wt.	500	500	500	500	500	500	500	500

Preparation of Matrix Tablets by Direct Compression Method:

Different matrix embedded formulations of Acyclovir were prepared by direct compression method using varying proportion of polymers. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, polymer and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant, the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 10-mm flat-faced punches at a compression force required to produce tablets of about 5–8 kg/cm2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.[7]

Post Compression Parameters

Weight Variation:

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table and none deviate by more than twice the percentage shown.[8]

Thickness:

Twenty tablets were randomly selected form each batch and there thickness was measured by using Vernier Caliper. Thickness of three tablets from each batch was measured and mean was calculated.[9]

Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined. [10]

Friability:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets

were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not lose more than 1% of their weight.[11]

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Acyclovir. Dissolve the weighed quantity of powder into 100 ml of 0.1 N NaOH solution by stirring it for 15 min. 01 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at 225 nm using reagent blank.[12]

In- Vitro Release Study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37 ± 5. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask and make the volume with distilled water. The diluted samples were assayed at 225 nm against reagent blank.[13]

Drug Release Kinetics[14]

(i) Zero Order Kinetics

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (that is, a constant release rate). The following equation is used to express the model:

$$Qt = Qo + Kot$$

Where,

Qt is the amount of drug dissolved in time t.

Qo is the initial amount of drug in the solution.

Ko is the zero order release constant.

For practical purposes the equation is rearranged.

$$\text{Percent drug released} = Kt$$

This is applicable to dosage forms like transdermal systems, coated dosage forms, osmotic systems as well as matrix tablets with low soluble drugs.

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(ii) First Order Kinetics

First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior; in such a way that amount of drug released by unit time diminish. The following equation is used to express the model:

$$\log Qt = \log Qo + Kt/2.303$$

Where,

Qt is the amount of drug dissolved in time t.

Qo is the initial amount of drug in the solution.

K is the first order release constant.

For practical purposes the equation is rearranged:

$$\text{Log \% of drug unreleased} = Kt/2.303$$

This model is applicable to dosage forms such as those containing water soluble drugs in porous matrices.

(iii) Higuchi Model

Higuchi describes drug release as a diffusion process based in Fick's law, square root dependent. The following equation is used to express the model:

$$Qt = Kht1/2$$

Where, Qt is the amount of drug dissolved in time t.

Kh is the first order release constant.

For practical purposes the equation is rearranged:

$$\text{Percent drug released} = Kt1/2$$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drugs.

(iv) Peppas-Korsmeyer Model

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

The following equation is used to express the model:

$$Qt/Q\infty = Ktn$$

Where, Qt is the amount of drug dissolved in time t.

Q∞ is the amount of drug dissolved in infinite time.

n is the release exponent indicative of drug release mechanism.

K is the kinetic constant.

For practical purposes the equation is rearranged:

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Log percent drug released = log k +n log t

Stability Studies: [15]

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Matrix tablets of Acyclovir were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2oc and refrigerator 2-8ºc for a period of 3 months.

RESULTS AND DISCUSSION

Drug - Excipient Compatibility Studies

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

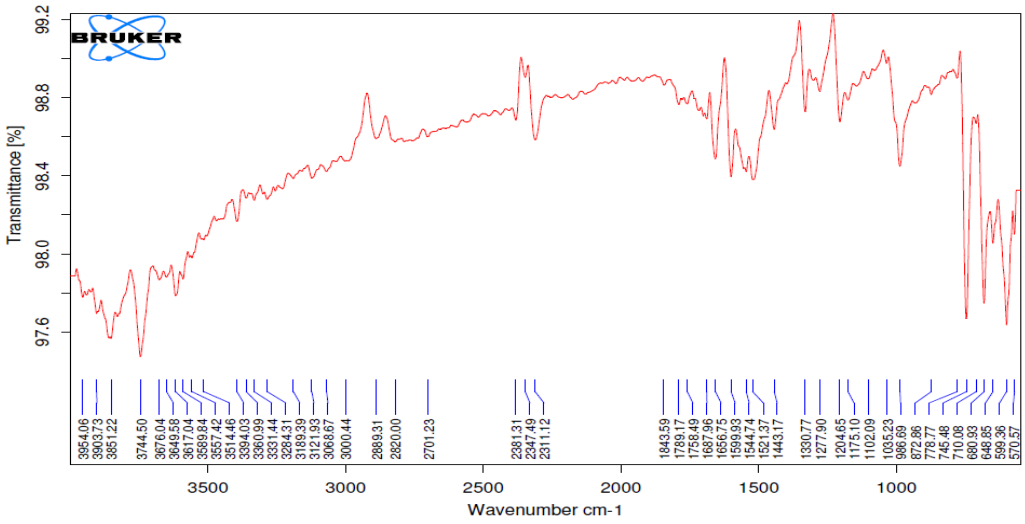

Fig-1: FTIR Spectra of Pure Drug

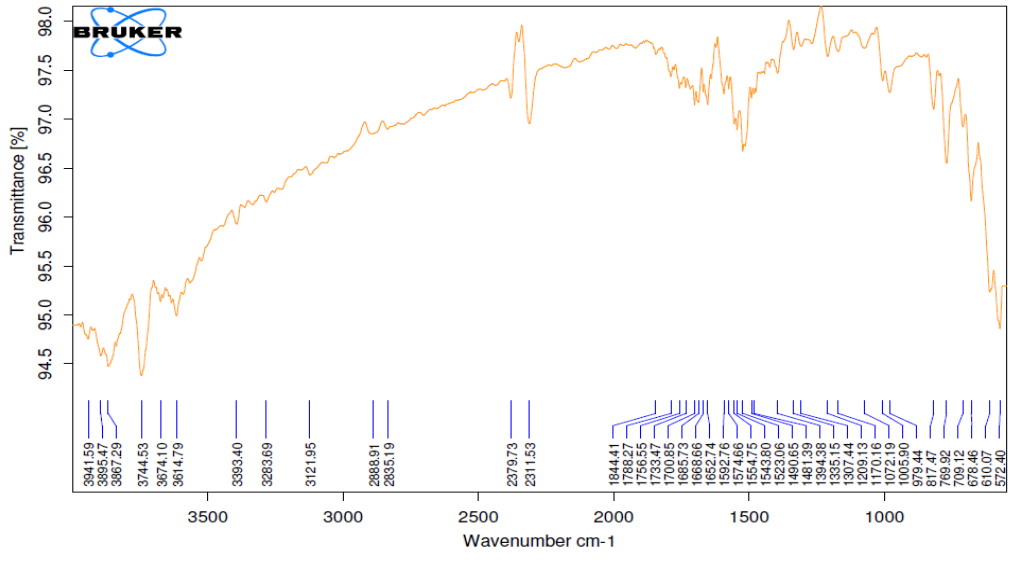

Fig-2: FTIR Spectra of Optimized Formulation

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Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Post Compression Parameters

Weight Variation:

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the Pharmacopeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 4.56 mm to 4.88 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 5.17 to 5.28 kg/cm^2 .This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F8 was found to be between 89.55% and 98.92 % of Acyclovir, it complies with official spec.

Table-2: Physical Parameters of Tablets of Each Batch

F. No.	Weight Variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug Content (%)
F1	500	4.86	5.28	0.45	91.85
F2	499	4.78	5.19	0.51	97.20
F3	498	4.59	5.25	0.48	96.22
F4	500	4.78	5.21	0.46	91.88
F5	499	4.56	5.19	0.43	93.89
F6	500	4.86	5.17	0.50	89.55
F7	499	4.75	5.20	0.51	92.55
F8	500	4.88	5.22	0.49	98.92

***In-Vitro* Dissolution Study**

All the eight formulation of prepared matrix tablets of Acyclovir were subjected to in-vitro release studies these studies were carried out using dissolution apparatus.

The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for the 8 hrs.

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Table-3: Dissolution Profile of F1 to F8

Time (hrs)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	29.12	28.20	27.11	28.09	27.89	26.94	25.19	29.18
2	32.45	35.30	33.11	31.45	32.28	36.15	35.14	36.95
3	42.80	45.32	43.76	49.90	41.28	43.69	42.16	48.16
4	52.63	54.65	53.23	59.70	50.71	52.18	50.31	57.16
5	68.21	69.28	62.11	65.16	61.46	62.17	63.18	62.18
6	73.35	78.55	75.22	71.22	70.25	71.28	70.19	78.16
7	88.26	83.10	85.16	80.26	82.19	83.14	82.15	82.28
8	92.25	92.99	95.12	93.50	92.17	93.18	91.18	95.12

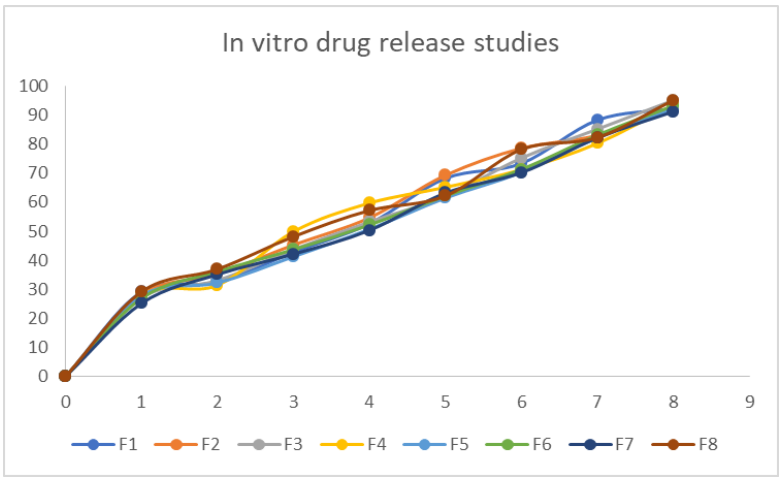

Fig-3: Dissolution Profile of all Formulations (F1-F8)

Kinetic Models:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

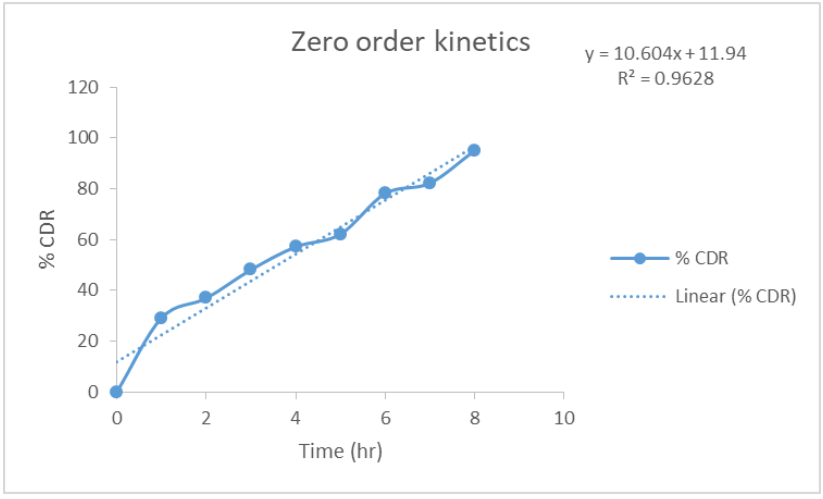

Fig-4: Zero Order Plot for Optimized Formula

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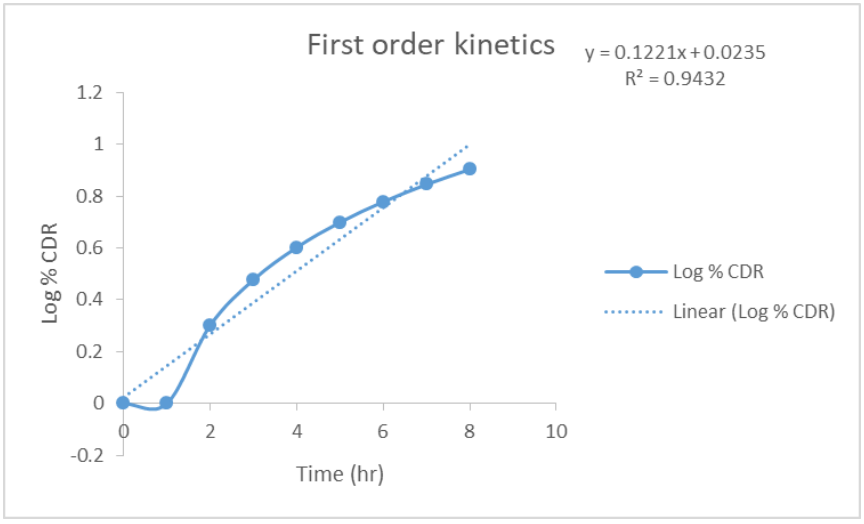

Fig-5: First Order for Optimized Formula

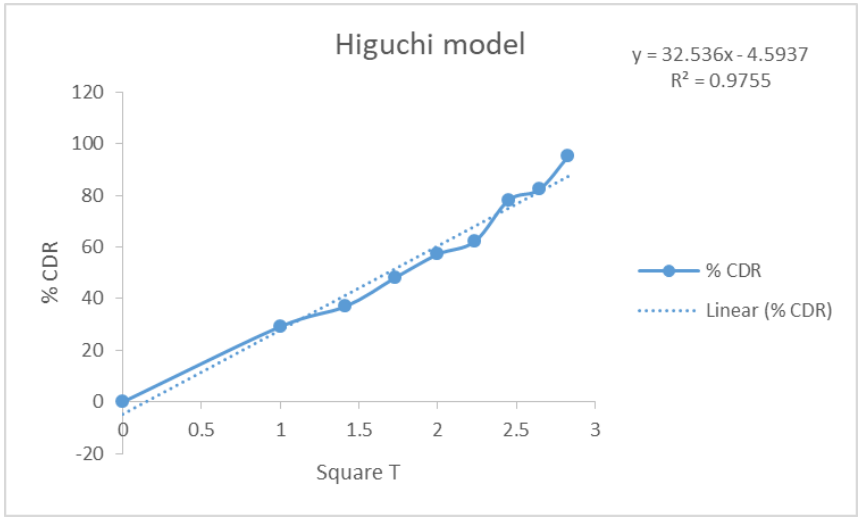

Fig-6: Higuchi Plot for Optimized Formula

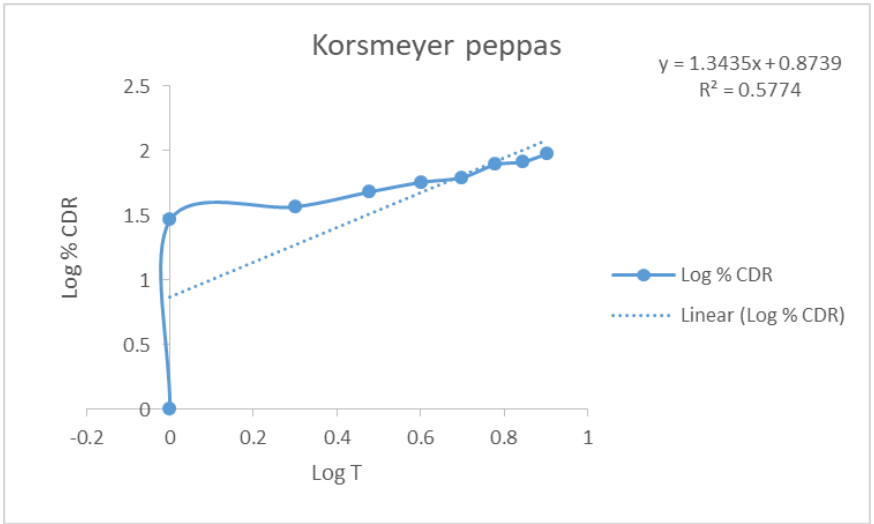

Fig-7: Korsmeyer Peppas Plot for Optimized Formula

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Stability Studies

Sustained release matrix tablets of Acyclovir formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40°c and 2-8°c for a period up to 90 days.

The results revealed that no significant changes in appearance, drug content, hardness, friability, and in vitro release for F8 formulation. When it was stored at the three storage conditions. However there was slight variation in invitro release when it is stored at 2-8°c, there was no change when it is stored at 40°c and room temperature.

Table-4: Results of Stability Studies of Optimized Formulation F-8

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-8	**25^0C/60%RH % Release**	95.12	94.11	93.10	92.08	**Not less than 85 %**
F-8	**30^0C/75% RH % Release**	95.12	94.10	93.09	92.06	**Not less than 85 %**
F-8	**40^0C/75% RH % Release**	95.12	94.10	93.08	92.01	**Not less than 85 %**

CONCLUSION

Various formulations of sustained release tablets of Acyclovir were prepared by using different polymers viz Tragacanth, sodium alginate and Xanthan gum in different proportions by Direct compression technique. The tablets were evaluated for physical parameters, in vitro release study and stability studies.

In-vitro release indicated that the formulation F8 had better dissolution profile along with sustained action as compare to other formulations. Stability study was conducted on tablets of Batch F8 stored at room temperature, 400C, and 2-80C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. No significant changes were observed in any of the studied parameters during the study period (90days), thus it could be concluded that formulation was stable.

REFERENCES

1. Liberman HA, Lachman L, Schwartz JB. Pharmaceutical dosage forms: Tablets. 2nd edition (Volume-2), New York (USA); Marcel Dekker, 2005; 165-67.
2. Vishwakarma Swati, Formulation and Evaluation of Controlled Release Tablet of Lamotrigine, International Journal of Pharmaceutical & Biological Archives 2018; 9(3):151-156.
3. Hoyashi T, Kanbe H, Okado M. Suzuki M, Sonobe T. "formulation study and drug release mechanism of a new theophylline Sustained Release preparation" Int. J. Pharm**,** 2005,304, p.no. 91-101.
4. Solinis M.A, Cruz Y. De, Gascon A, Calvo B, Pedraz J. L "Release of Ketoprofen enantiomers from HPMC K100M matrices –Diffusion studies" Int. J. Pharm., 2002,239, p.no. 61-68.
5. Qiu Y. Chidambaram N, Porter W. Flood K., "Formulation and characterization of new diffusional matrices for Zero – order sustained release" J. Cont. Rel**.,** 1998, 52, p.no.149-158.
6. Dinda SC, Durga P, Pattanayak, Narayan UL, Design and evaluation of a fixed Dose combination formulation of Valsartan and Metformin HCl for biphasic drug release: A novel approach to increase therapeutic efficacy, International Journal of Pharmaceutical Science and Technology, 6, 2011, 44-63.
7. Shivakalyani Adepu, Controlled Drug Delivery Systems: Current Status and Future Directions, Molecules. 2021 Oct; 26(19): 5905
8. Ali, The Role of Oral Controlled Release Matrix Tablets in Drug Delivery Systems, Bioimpacts.2012; 2(4): 175–187
9. Manish Wani , Controlled Released System - A Revie, January 2008, Pharmaceutical Reviews
10. Shailesh, Formulation and Evaluation of Controlled-Release Tablet of Zolpidem Tartrate by Melt Granulation Technique, International Scholarly Research Notices,2012
11. Pradeep Kumar, preparation and evaluation of saquinavir mesylate oral suspension, international journal of drug formulation & research, VOL. 1; 2; 2012.
12. Mahajan P, Mahajan SC, Mishra DK, Valsartan release from sustained release matrix tablet and effect of cellulose derivatives, International Journal of Pharmacy and Life Science, 2, 2011, 521

13. Lachman L, Liberman HA and Kanig JL. The Theory and Practice of Industries Pharmacy, 3rd edition. Varghese publishing house, 2008; 296-303,430-456.
14. Venkatesh DN, Jawahar N, Ganesh GNK, Kumar RS, Senthil V, Samanta MK, Sankar S and Elango K. Development and In Vitro evaluation of sustained release matrix tablet of theophylline using hydrophilic polymer as release retardant. Int J Pharm Sci Nano. 2009; 2(1): 34-38.
15. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pg 505 Fourth Edition, 2002.

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Conflict of Interest Statement: All authors have nothing else to disclose.