ejpmr, 2023, 10(11), 351-357

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND EVALUATION OF LISINOPRIL AS IMMEDIATE RELEASE AND METFORMIN AS SUSTAINED RELEASE BILAYERED TABLETS

Eepuri Meshak[1]*, A. Siva Kumar[2], Dr. A. Yasodha[3] and Dr. D. Avinash[4]

[1]Department of Pharmaceutics, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001.

[2]Associate Professor, Department of Pharmaceutics, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001.

[3]Professor, Principal, Department of Pharmaceutical Chemistry, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001.

[4]Professor, Department of Pharmaceutics, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001.

***Corresponding Author: Eepuri Meshak**
Department of Pharmaceutics, Dhanvanthri College of Pharmaceutical Sciences, Thirumala Hills, Centre City, Appannapally, Mahabubnagar, Telangana 509001.

Article Received on 14/09/2023 **Article Revised on 04/10/2023** **Article Accepted on 24/10/2023**

ABSTRACT

The present investigation was focused on formulation and in-vitro evaluation of a fixed dose bilayer tablet of two prominent antihypertensive agent and antidiabetic agents Lisinopril and Metformin. The tablets were designed to immediately release Lisinopril by using different percentage of sodium starch glycolate as super-disintegrant for prompt blood pressure lowering activity and sustain release metformin by varying the percentage of hydroxy propyl methylcellulose (HPMC) for prolonged activity. After evaluation of the physical and chemical parameters of the formulations according to United States Pharmacopoeia (USP) guidelines, both Lisinopril and Metformin parts were successfully compressed into bilayer tablets and post-compression parameters were evaluated. In 0.1 N HCl medium, the release of Lisinopril and Metformin it was found 98.76% 6.8 phosphate buffer medium after 8 hours.

KEYWORDS: Bilayer tablet, Lisinopril, Metformin, FTIR Studies, Polymers, In vitro drug release studies.

INTRODUCTION

Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly patient compliance.[1] Bilayer tablets are a novel drug delivery system that improves patient compliance, prolongs drug action and avoids serrated kinetics by combining two or more drugs with different release profiles into one entity, resulting in effective therapy and improved plasma drug control.[2] Bilayer tablets are suitable for combining two drugs for separate and sequential release from two miscible substances.[3] It is also suitable for sustained release tablets, where one layer is the initial dose for immediate release and the second layer is the maintenance dose. Therefore, the current study attempted to prescribe a bilayer tablet of Lisinopril and metformin as a bimodal delivery system to treat hypertension and diabetes mellitus.[4] Lisinopril is a synthetic peptide derivative, is an oral long acting angiotensin converting enzyme inhibitor (ACE).[5] It is widely used in treatment of hypertension; it has the biological half-life of 12.6 hr. Its bioavailability is 25% and it is mainly excreted in urine.[6] Metformin hydrochloride obtained from natural sources as a drug for the treatment of type II diabetes mellitus 21. It shows low bioavailability and a shorter half-life.[7] The aim of this study was to formulate the Bilayered tablets of Metformin and Lisinopril by using direct compression technique.

MATERIALS

Metformin and Lisinopril were obtained from Alkem Pvt Mumbai, Polymers and superdisintegrants procured from SD fine chemicals Mumbai. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Compatibility Studies of Drug and Polymers[8]

API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between drugs and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation Development[9]

Preparation of Bilayer Tablets

1. Step 1: Weigh all the ingredients in required quantity.

2. Step 2: Transfer all ingredients into a mortar, triturate for 10minutes until to get fine powder and sieve the material. (#60)
3. Step 3: then transfer the material into blender for proper distribution of drug in blend for 10minutes.
4. Step 4: then addition of lubricant, mix well.
5. Step 5: Perform the Micromeritics properties (Precompression studies).
6. Step 6: Compression.

Table 1: Composition of Bilayered Tablets.

S.No.	Ingredients	F1 (mg)	F 2 (mg)	F 3 (mg)	F 4 (mg)	F 5 (mg)	F 6 (mg)	F 7 (mg)	F 8 (mg)
1	Lisinopril	10	10	10	10	10	10	10	10
2	Metformin HCL	500	500	500	500	500	500	500	500
3	HPMC k 15M	50	100	150	200	-	-	-	-
4	Ethyl Cellulose	-	-	-	-	50	100	150	200
5	Croscaramellose	5	10	15	20	-	-	-	-
6	Sodium Starch Glycolate	-	-	-	-	5	10	15	20
7	Lactose	220	165	125	55	220	165	125	55
8	Microcrystalline Cellulose	10	10	10	10	10	10	10	10
9	Talc	2	2	2	2	2	2	2	2
10	Magnesium Stearate	3	3	3	3	3	3	3	3
11	Total Weight	800	800	800	800	800	800	800	800

EVALUATION STUDIES

Evaluation of Tablet

Weight Variation[10]

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.

Thickness[11]

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

Hardness[12]

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/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability[13]

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.

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[14]

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Bilayered tablet. Dissolve the weighed quantity of powder into 100 ml of 6.8 phosphate solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask, to it 1 ml of 5% Ninhydrin solution was added and boil this solution for 3 min, cool it and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at Suitable wavelength using reagent blank.

In- Vitro Release Study[15]

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±1. 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, to it add 1 ml of 5% Ninhydrine solution and 1 ml of 0.1 N NaOH solution, boil for 3 min at water bath, cool it at room temperature and make the volume with distilled water. The diluted samples were assayed at Suitable wavelength.

Drug Release Kinetics[16]

The data from the in vitro release investigation were fitted into different kinetic models, including the zero-order, first-order, Higuchi's, and Korsmeyer-Peppas

models, to clarify the method and mechanism of drug release.

Stability Studies[17]

The success of an effective formulation can be evaluated only through stability studies. The prepared Bilayered tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 90 days.

RESULTS AND DISCUSSION

Drug compatibility Studies

Fourier Transformation Infra-Red (FTIR) Analysis

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan). The instrument was calibrated by using polystyrene film.

Fourier Transformation Infra-Red (FTIR) Analysis of Lisinopril

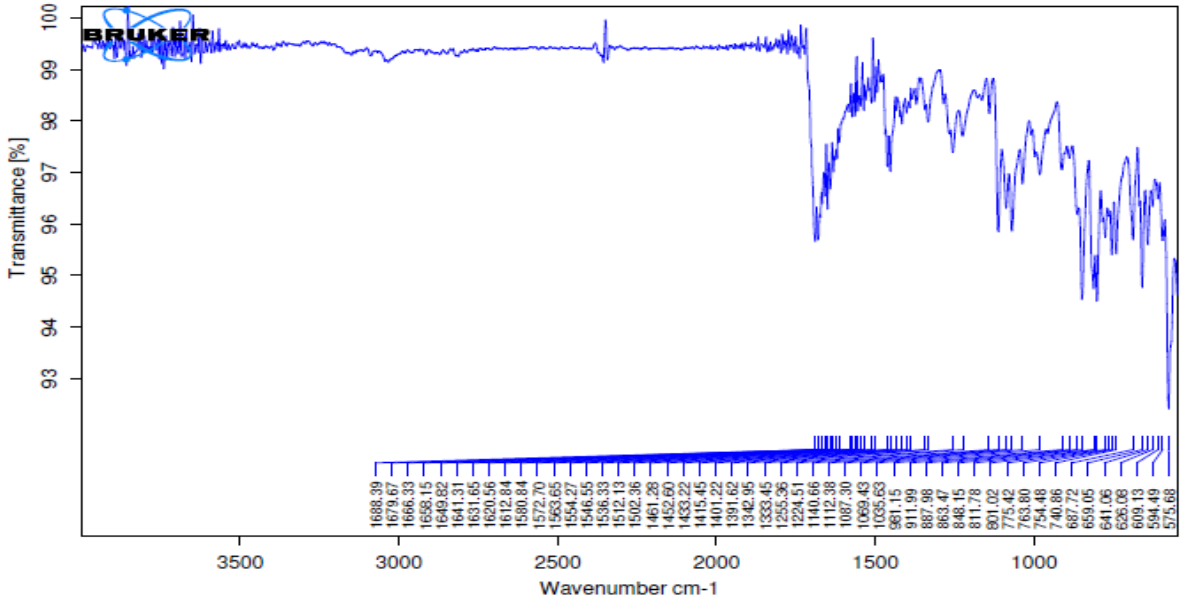

Fig-1: FTIR Studies of Lisinopril.

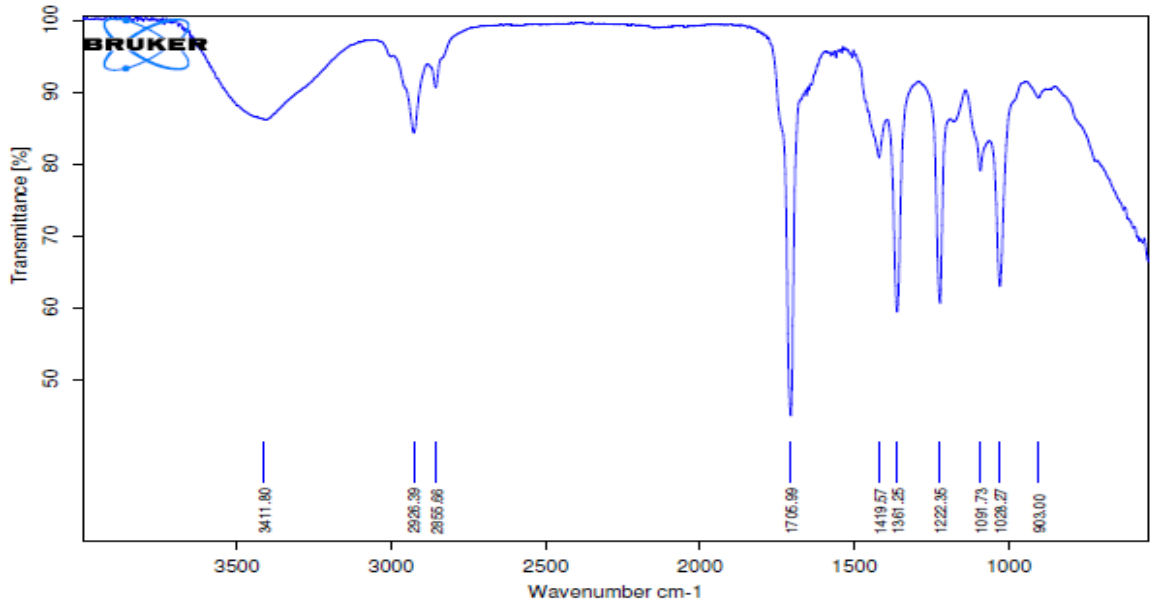

Fig-2 : FT-IR Graph for Metformin.

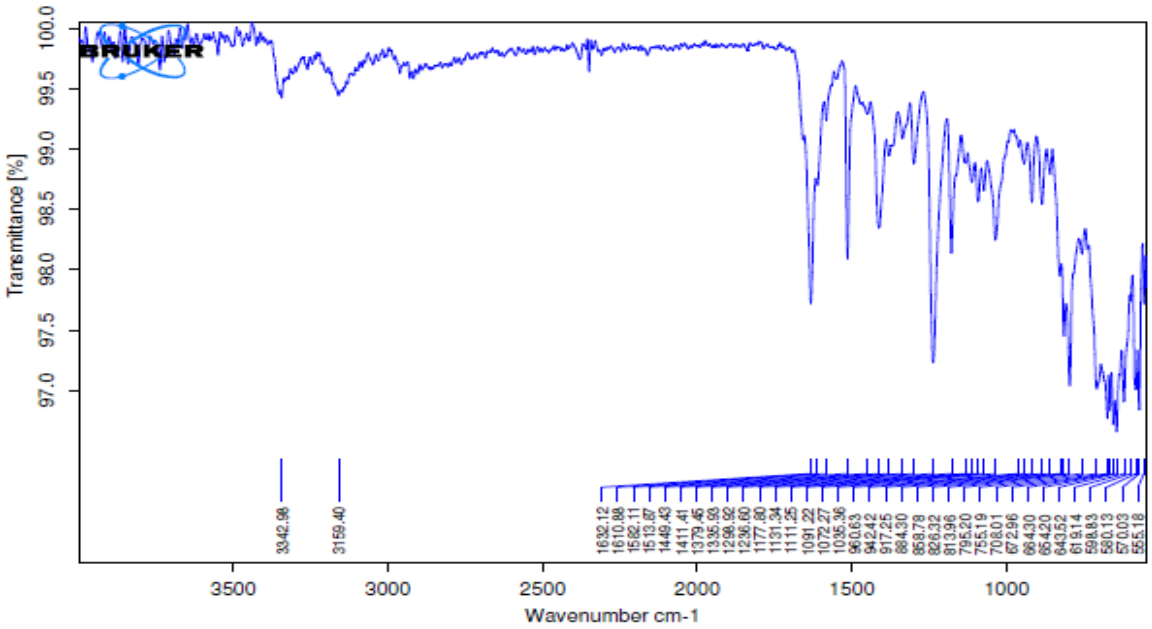

Fig-3 : FT-IR Graph for Bilayer Optimised Formulation.

Formulation of Bilayer Tablets: Optimized batch of Immediate Layer (F5) and different formulations of Bilayer tablets used to formulate Bilayer tablets of Metformin and Lisinopril.

The powder Sustain layer powder was blended for 20 min. to obtain uniform distribution of the drug in formulation. Powder mix was accurately weighed and fed into the die of single punch tablet press and compressed at 1.5 N compression force using 10-mm concave punches. The Immediate layer mix was blended for 20 min to obtain uniform distribution of the drug in formulation. 100 mg of the powder mix was accurately weighed and manually fed into the die on controlled release layer and compressed at a compression pressure of 3 N using 10-mmconcave punches.

Evaluation of Prepared Bilayered Tablets for Post Compression Parameters

Table 2: Evaluation of Post Compression Parameters for Bilayered Tablets.

Parameter	LM1	LM2	LM3	LM4	LM5	LM6	LM7	LM8
Weight Variation	800	799	800	798	800	799	800	800
Thickness (mm)	3.2	3.2	3.5	3.4	3.4	3.1	3.0	3.2
Hardness (kg/cm^2)	6.2	6.4	6.2	6.4	6.2	6.3	6.1	6.2
Friability (%)	0.12	0.13	0.14	0.11	0.16	0.14	0.13	0.16
Assay of Metformin	92.42	93.40	92.15	94.18	95.31	92.46	96.89	94.25
Assay of Lisinopril	92.50	94.89	91.47	93.49	95.89	95.89	98.31	97.16

In Vitro Dissolution Studies: The dissolution conditions used for studying the drug release from Bilayered tablet:

Apparatus : USP apparatus II (Paddle)
Agitation speed (rpm) : 50rpm
Medium : 0.1N HCl (1.2 pH) and 6.8pH Phosphate buffer
Volume : 900 ml
Temperature : 37.0 ± 0.5 ^{0}C
Time : 5, 10, 15, 30 Min's for immediate release & 1, 2, 3, 4, 5, 6, 7 and 8hrs for Sustain layer.
Wavelength : 230 nm and 265 nm

The samples were withdrawn at predetermined time points, and were analyzed spectrophotometrically at 230 nm and 265 nm.

Table 3: In-Vitro Dissolution Data of Bilayer Tablets.

Time (Hrs)	LM 1	LM 2	LM 3	LM 4	LM5	LM 6	LM 7	LM 8
0	0	0	0	0	0	0	0	0
1	12.15	15.96	17.25	15.24	14.96	16.94	18.59	15.96
2	23.28	27.10	25.18	22.65	20.19	24.21	30.32	25.63
3	40.22	32.21	40.17	37.21	36.59	32.28	44.45	33.51

4	50.37	45.17	51.28	45.31	42.35	41.5	50.75	43.29
5	61.32	53.24	63.74	61.52	60.31	52.25	62.86	54.52
6	72.59	65.42	78.25	74.32	68.93	66.54	73.42	68.28
7	82.32	73.1	87.32	86.21	79.32	73.28	86.37	78.25
8	92.49	97.56	93.28	94.84	93.10	91.70	98.76	93.58

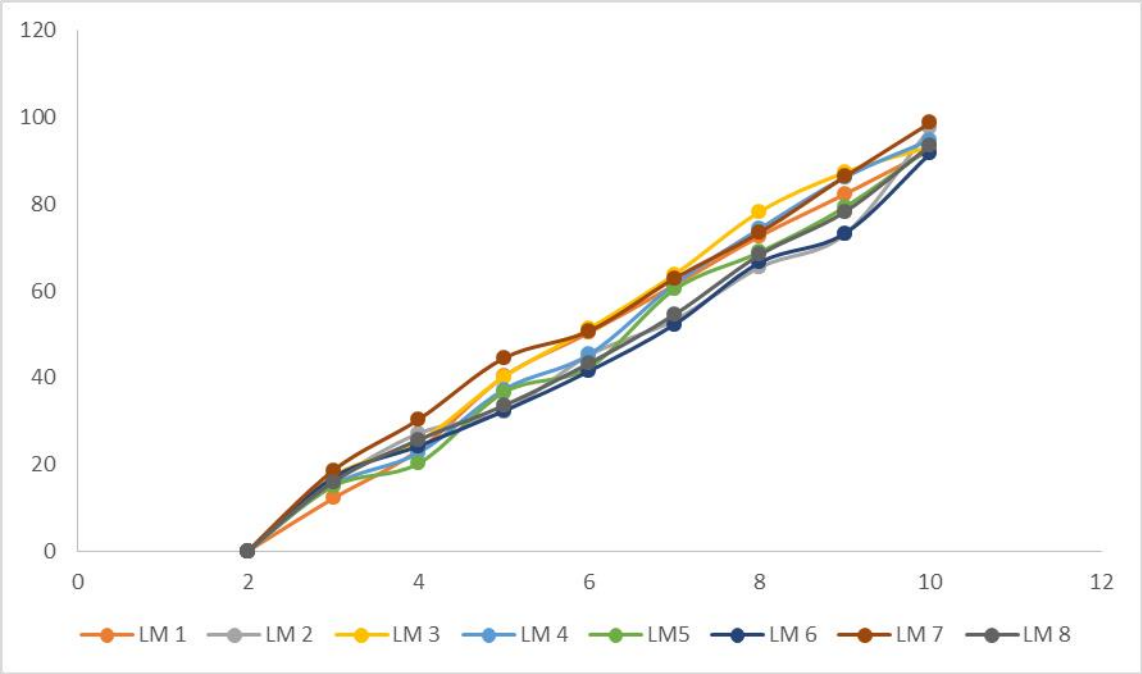

Fig-4: An Overview of In-Vitro Dissolution Profiles for Bilayer Tablet of All Formulations.

Among all formulations, Lisinopril and Metformin show better drug release of (98.32%) at the end of 8 hrs, when compared with all other formulations. So formulation Lisinopril and Metformin LM7 selected as optimized formula.

DRUG RELEASE KINETICS

Zero Order Kinetics

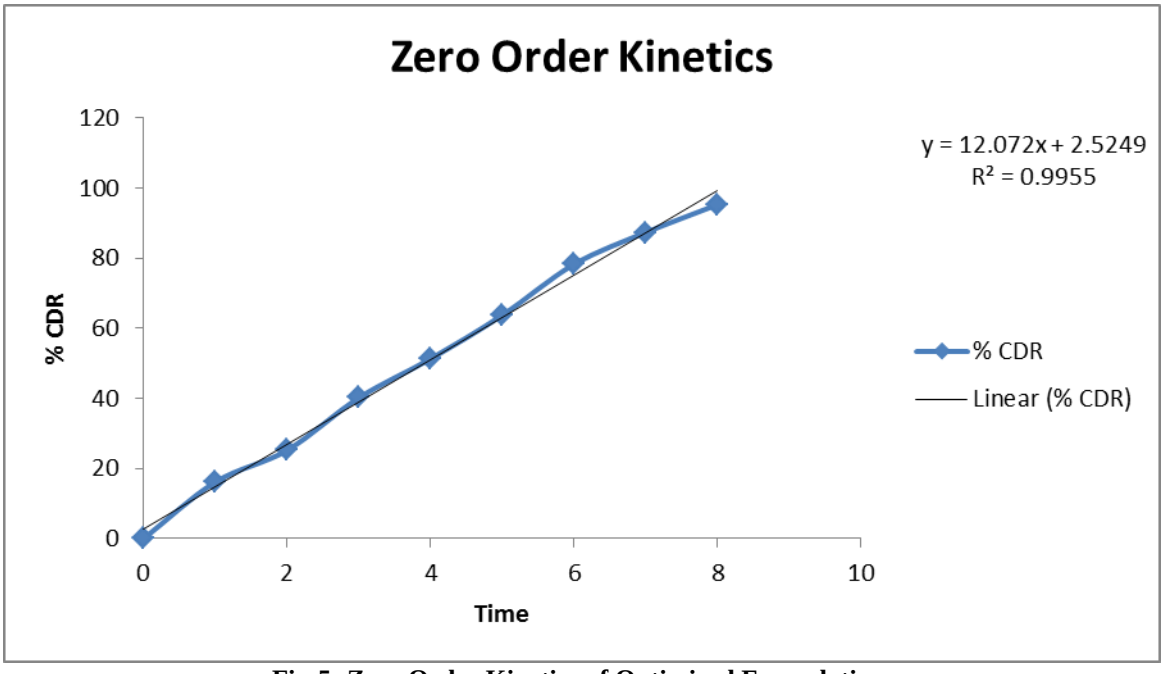

Fig-5: Zero Order Kinetics of Optimized Formulation.

First Order Kinetics

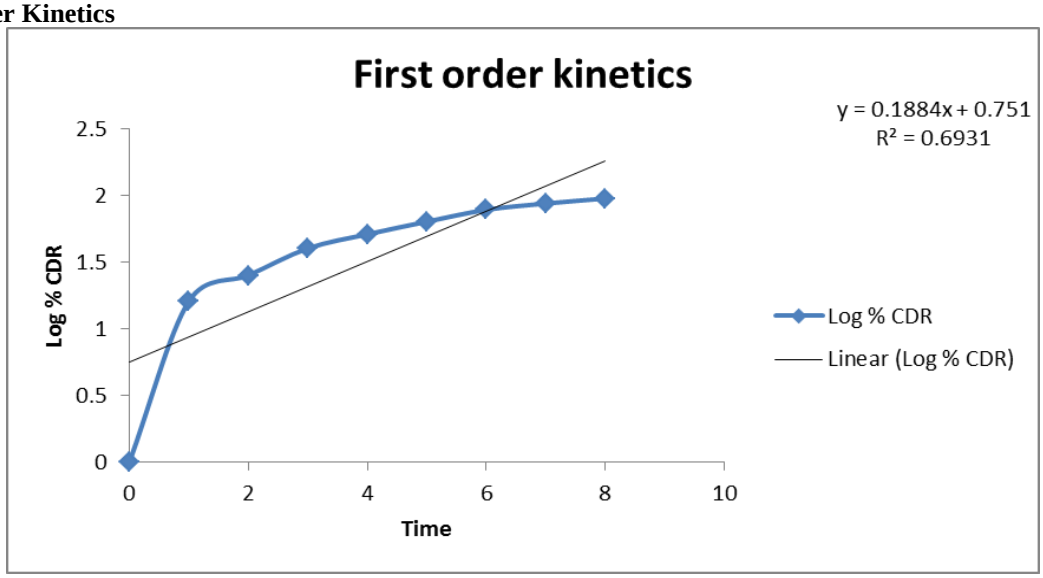

Fig-6: First Order Kinetics of Optimized Formulation.

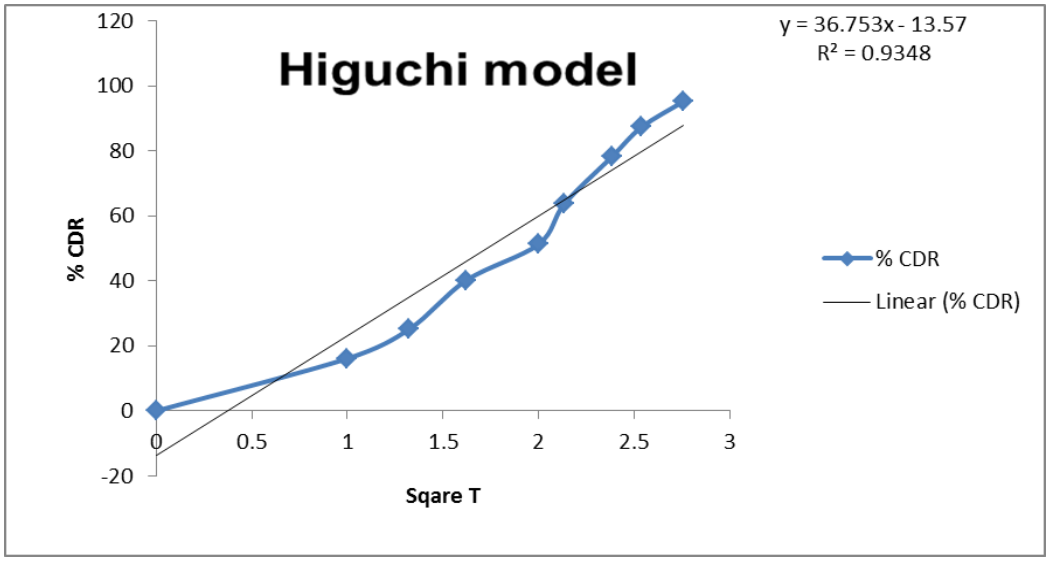

Fig-7: Higuchi Model of Optimized Formulation.

Korsmeyer Peppas

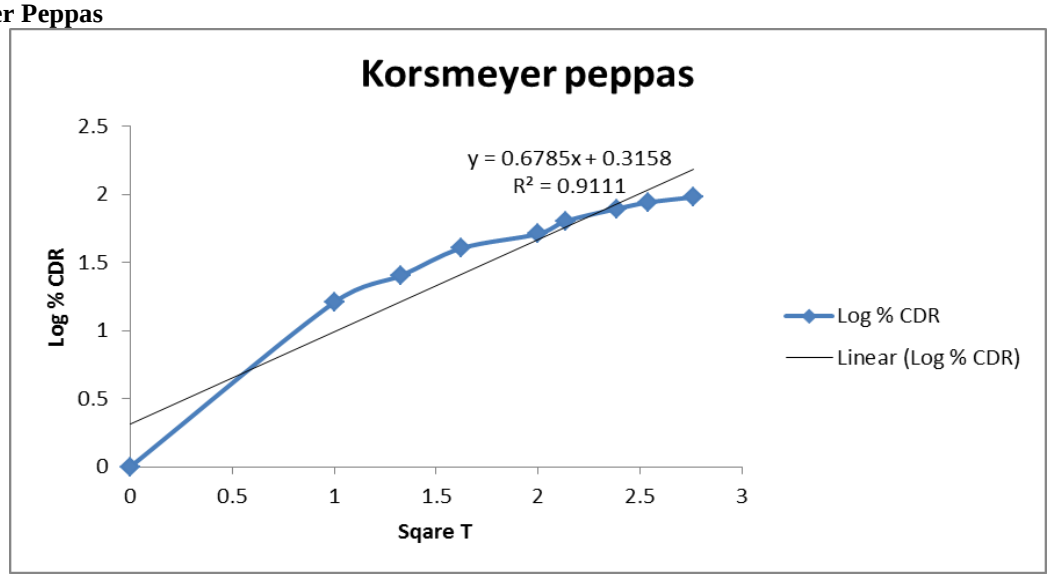

Fig-8: Korsmeyer Peppas of Optimized Formulation.

Stability Studies

Table 4: Stability Studies Data of Optimized Formulation.

S.No.	Time in Days	Physical Changes	Mean % Drug Content ± SD		
			Optimized Formulation		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	98.76	97.56	96.14
2.	30	No Change	98.76	96.35	96.02
3.	60	No Change	98.76	95.15	95.46
4	90	No Change	98.76	94.02	94.32

There was no significant change in physical and chemical properties of the tablets of formulation LM7 after 3 Months, for parameters like % drug release and assay values at various conditions (at 40^0C/ 75% RH) was observed as per ICH guidelines.

CONCLUSION

The chosen formulation conformed to Pharmacopoeial requirements, and the manufactured granules produced the necessary flow qualities. First order kinetics was followed by the release rate. Diffusion is the drug release mechanism. The formulation LM7 has exhibited higher in-vitro dissolution release, hence it was considered as better formation. The drug release was discovered to be reliant on the polymer used in the manufacture of the sustained release layer. As a result, the investigation's main goals were accomplished.

REFERENCES

1. Chein Y W, "Oral Drug Delivery and Delivery Systems" second edition, New York: Marcel Dekker, 1992.
2. Nagaraju, R. and Rajesh Kaza, 'Formulation and Evaluation of Bilayer Sustained Release Tablets of Salbutamol and Theophylline, International Journal of Pharmaceutical Sciences and Nanotechnology, 2009; 2(3): 638-646.
3. Narendra, C. et al. 'Optimisation of Bilayer Floating Tablet Containing Metoprolol Tartrate as a Model Drug for Gastric Retention. American Association of Pharmaceutical scientists Pharmascitech, 2006; 7(2): 1-7.
4. Naeem, M.A. et al. ‹Development and Evaluation of Controlled Release Bilayer Tablets Containing Microencapsulated Tramadol and Acetaminophen, Tropical Journal of Pharmaceutical Research, 2010; 9(4): 347-354.
5. Gudas GK, Bingi M, Subal D, Rajesham VV. Design and evaluation of controlled release mucoadhesive buccal tablets of Lisinopril. Int. J. pharma. Res., 2010; 2(4): 24-27.
6. Viswanadhan P V, Padole A, Abraham A. Buccal tablets of Lisinopril by direct compression method for buccal drug delivery. International Research Journal of Pharmaceuticals, 2012; 2(02): 30-38.
7. Ganesh S Andhale, Giles D, Amit K Das, Basavraj Metikurk and Gurubasav Raj Swamy PM: Design Synthesis and Chemical Hydrolysis Study of Co-drugs of Metoprolol with metformin. Int J Pharm Sci Drug Res., 2018; 10(2): 95-102.
8. Sinodukooeziuzookafo, Christian arerusuoghenealalor, John ikechiordu: Design and in-vitro evaluation of sustained release matrix tablets of metformin produced using detar iummicrocarpum gum, Int J App Pharm, 2020; 12(5): 131-37.
9. Patel Mehul, Ganesh *et al*, Nanjan Sockan *et al*, Challenges in the Formulation of Bilayered Tablets: A Review, International Journal of Pharma Research and Development, 2010, ISSN 0974 – 9446.
10. Rudnic EM et al, Kottke et al MK Tablet dosage form. In Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 3rd ed., vol 72. New York: Marcel Dekker Inc. p 369.
11. Breech AJ et al, Lucisano L J et al, Franz RM et al Investigation into substrate cracking of a film coated Bilayered tablet. J. Pharm. Pharmacol, 1998; 40: 282- 283.
12. Li S.P. et al, Karth M.G. et al, Feld K.M. et al, Pendharkar C.M. et al, Williams R.O. et al, Evaluation of Bilayer tablet machines. A Case study. Drug Dev. Ind. Pharm., 1995; 21(5): 571 590.
13. N. Deattu Formulation and evaluation of bilayer tablets of Metformin hydrochloride and Ramipril, Article January 2012.
14. Vishwakarma A.G. Bi-Layer Tablet -A New Ways in Oral Drug Delivery System, International Journal of PharmTech Research CODEN (USA): IJPRIFISSN: 0974-4304, Sept-Oct 2014; 6(5): 1416-1428.
15. Krishnaiah YSR, Karthikeyan RS, Satyanarayana V. A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate. Int. J. Pharm., 2002; 2(41): 353–366.
16. Nakhat PD, Yeole PG, Galgatte UC, Babla IB. Design and evaluation of Xanthum gum based sustained release matrix tablets of diclofenac sodium. Ind. J. Pharm. Sci., 2006; 2: 185-189.
17. Juslin M, Turakka L, Puumalainen P. Controlled release tablets. Pharm Ind., 1980; 42: 829–32.
18. Nithin kumar p., Elango k., Devi Damayanthi, Formulation and Evaluation of Bilayer Tablets of Losartan Potassium for Immediate Release (IR) and Metformin Hydrochloride for Sustained Release (SR), IJPI'S Journal of Pharmaceutics and Cosmetology, 2012; 2(8): 37-42.