FORMULATION AND EVALUATION OF BILAYER TABLET OF SUSTAINED RELEASE GLIBENCLAMIDE AND IMMEDIATE RELEASE ENALAPRIL MALEATE

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Abstract: *The purpose of this study was to formulate and evaluate bilayer tablets of immediate release Enalapril maleate for hypertension and sustained release of Glibenclamide for diabetes. Direct compression method was used to formulate bilayer tablets, which contained hydrophilic HPMC K- 100 and hydrophobic Ethyl cellulose as a sustained release polymer and super disintegrating agent such as Croscarmellose sodium in different proportion from batch F1-F6. Formulation of Bilayer tablets was prepared by the FEM1-FEM6 and FG1-FG6 powder blend for different parameters of formulated bilayer tablets were hardness, friability, thickness, drug content, weight variation, and the in-vitro drug release rate pattern results indicated that the formulation F3 was high as compared to other formulations. In formulation F3, percentage drug release of Glibenclamide sustained release layer was* ***99.98%*** *at 12 hrs. and* ***98.91%*** *at 90 min for Enalapril Maleate Immediate release layer.*

Keywords: *Glibenclamide, Enalapril Maleate, Bilayer Tablets, Sustained Release, Immediate Release, Co-morbidity.*

1. INTRODUCTION

The drug Glibenclamide is antidiabetic agent which comes under BCS class II sulfonylureas oral hypoglycemic is used to treat type -2 diabetes and Enalapril maleate is antihypertensive agent which comes under BCS class III used to treat high blood pressure (Hypertension). Glibenclamide (GLB) has elimination half-life is approximately 2-5 h after oral administration, and it is 84±9% absorbed from GIT, but its bioavailability is low due to its poor solubility and extensive first-pass metabolism in liver.[1] It is used to treat people with Non-Insulin Dependent Diabetes Mellitus (NIDDM). It has a strong yet slow-acting initial insulinemic effect. [1]

Diabetes mellitus is a condition of insulin-controlled metabolic balance that causes abnormalities in lipid and carbohydrate metabolism. There are two fundamental abnormalities that define type 2 diabetes mellitus. Type 2 diabetes occurs when your body becomes resistant to insulin, and sugar builds up in your blood. Insulin deficiency is a symptom of type 2 diabetes, which is characterized by pancreatic-cell failure and insulin resistance in target organs. When insulin secretion is compromised, type 2 diabetes mellitus results because the body is unable to meet the increasing demands placed on it by the insulin-resistant condition. Therefore, a lack of insulin is the only known cause of diabetes mellitus in Type 2 diabetes mellitus has a relative deficiency while type 1 diabetic mellitus has an absolute deficiency.[2]

Enalapril Maleate is the maleate salt of enalapril, a derivative of two amino acid , L-alanine and L-proline. Enalapril maleate is angiotensin converting enzyme (ACE) inhibitor. It lower blood pressure by reducing peripheral vascular resistance without relatively increasing cardiac output, rate or contractility. Hypertension is when blood pressure is too high. Narrow blood vessels, also known as arteries, create more resistance for blood flow. The narrower your arteries are, the more resistance there is, and the higher your blood pressure will be. Over the long term, the increased pressure can cause health issues, including heart disease.[3]

Studies have shown that the use of angiotensin converting enzyme (ACE)inhibitors can prevent the progression of renal damage and delay progression to end stage renal disease in addition to lowering blood pressure.[4] These are the novel drug delivery systems where combination of two drugs in a single unit having different release profiles Immediate release Enalapril Maleate and Sustained release Glibenclamide. Bilayer tablets are the medicines which consist of two same or different drugs combined in a single dose for effective treatment of the disease.[4]

The need for bilayer tablet is to treat Co-morbidity condition in same patients with same pill or tablet at a same time. It reduces the dose frequency and pill burden. An of reducing the lag time and providing faster onset of action to reduce the blood pressure immediately.[5] Bilayer tablet has patient compliance and is beneficial for sequential release of two drugs in combination. Bilayer tablet is an advanced technology that helps in overcoming the limitations of a single-layered tablet. In order to successfully treat a condition, bilayer tablets are prescription drugs that contain two of the same or distinct medications in a single dose. Bilayer tablets, which are excellent for the sequential delivery of numerous drugs, have high patient compliance. These are innovative drug delivery systems that combine two medicines with various release profiles into a single unit. [5]

2. MATERIALS AND METHOD

2.1. Materials

Glibenclamide an Antidiabetic agent was provided by Arti Pharmaceuticals and Enalapril Maleate an Antihypertensive agent was provided by Yarrow Chem Pharmaceuticals(India). HPMC and Ethyl Cellulose polymer as a free sample. Research Fine Chem Ltd, (India) supplied Croscarmellose sodium, Microcrystalline cellulose (Avicel pH 102), Lactose, Magnesium stearate, Talc. All of the reagents used in this experiment was analytical quality grade.

2.2 Methods Of Formualtion Of Bialyer Tablets Of Enalapril Maleate And Glibenclamide

The Direct Compression method is used for formulation of bilayer tablet of Enalapril Maleate and Glibenclamide in which tablets are formulated by direct compressed method from a powder blend of suitable excipients and API. Pre-treatment of blended of powder by dry or wet granulation procedure is not necessary. It provides merits mostly in terms of speedy production, as it's requires less machinery, reduced number of personnel, fewer unit operations and significantly less processing time along with improved product stability.

2.2.1Preparation of Immediate Release powder

Mixing all the powdered polymer ingredients with Enalapril Maleate passing through sieve no.40 using lactose as lubricant and magnesium stearate as binder to get fine smooth powder.

2.2.2 Preparation of Sustain Release powder

The drug Glibenclamide along with polymers like HPMC and Ethyl Cellulose and other exicipients mixing or blending them properly and passing through sieve by using binder to get fine smooth powder.

3. Formulation Table

Formulation table of Bilayer Tablet of IR Enalapril Maleate and SR Glibenclamide. The tablet blends for different batch formulation (FEM1-FEM6) and (FG1-FG6) are prepared and further studied for Pre-compression properties and subjected for tablet punching by direct compression.

Table 1: Formulation of Immediate Release layer of Enalapril Maleate

Formulations	**FEM1**	**FEM2**	**FEM3**	**FEM4**	**FEM5**	**FEM6**
Ingredients		Unit formula (mg per tablet)				
Enalapril Maleate	5	5	5	5	5	5
Croscarmellose	2	4	6	8	10	12
Lactose	92	90	88	86	84	82
Magnesium Stearate	1	1	1	1	1	1
Total	100	100	100	100	100	100

Table 2: Formulation of Sustain Release layer of Glibenclamide

Formulations	**FG1**	**FG2**	**FG3**	**FG4**	**FG5**	**FG6**
Ingredients		Unit formula (mg per tablet)				
Glibenclamide	10	10	10	10	10	10
HPMC K-100	40	60	80	-	-	-
Ethyl Cellulose	-	-	-	40	60	80
Magnesium Stearate	8	8	8	8	8	8
Talc	8	8	8	8	8	8
Microcrystalline Cellulose	134	114	94	134	114	94
Total	200	200	200	200	200	200

5. Evaluation Of Tablets

A)Pre-compression study

1) Angle of Repose

It is determined by funnel method. The funnel is fixed at a particular height (2.5 cm) on a burette stand. The sample powder was allowed to pass through the funnel allowing it to form a pile. This area is encircled to measure radius. This similar procedure repeated 3 times and the average value all 3 observation is taken. The angle of repose can be calculated by using equation.

Angle of Repose (θ)= Tan^{-1} (h/r)

Where, h=height of pile,

θ = angle of repose,

r= radius of the base of the powder pile.

2) Bulk Density

Accurately weighed quantity of the powder(W) is taken in measuring cylinder and volume (V_0) is measured, Bulk density is calculated using the formula.

Bulk density = Weight of the powder / Volume of powder

3)Tapped density determination

Accurately weighed quantity of the powder (W) is taken in a measuring cylinder and the volume occupied by powder is measured. The cylinder is fixed in Tapped Densitometer and is tapped for 500, 750 and 150 times till the difference in the volume after successive tapping was less than 2%. The final reading was denotes by (V_f).

Tapped density = W/V_f g/ml

4) Hausner's Ratio

Hausner found that the ratio was related to inter particle friction and as such, could be used to predict powder flow properties.
Hausner's factor = Tapped bulk density/Loose bulk density

5)Carr's Index

Carr's Index is fast and popular method of predicting powder flow characteristics
Carr's index was calculated using the formula:
Carr's index=(Tapped Density- Bulk density)×100/Tapped Density

B) Post compression studies

1) Appearance

All tablets were inspected visually and found white colored round shaped and biconvex.

2) Thickness and Diameter

Thickness and diameter of tablets was determined using Vernier caliper. Five tablets from each batch were used, and average values were calculated.

3) Weight variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

4) Hardness

For each type of formulation, the hardness values for 3 tablets were determined using Monsanto hardness tester.

5) Friability

For each type of formulation, the friability was determined as follows
Twenty tablets were weighed accurately and placed in Roche friabilator. The speed rotation of Roche friabilator was kept 25 rpm for 4 min. The tablets were removed and weighed. The percentage friability was determined using following formula
% Friability = [Initial weight - Final weight] X 100/Initial weight)
Evaluation of prepared tablet blends for pre-compression study: The mass-volume relationship characteristics of a mixed blend were determined by characterization. Angle of repose, bulk density, and tapped density were all examined, with Hauser's ratio and compressibility index.

5) Disintegration time

The measured disintegration time of tablets of each batch ranged between 5 Min to 8 Min.

6)In- Vitro Dissolution Study

Speed of Paddle: 50 rpm.
Temperature of Dissolution Medium: 37°C ± 0.5°C.
All of the formulated tablets were disintegrated in vitro using the USP II Paddle technique at 50 rpm in 0.1 N HCL for the first 2 hours and 6.8 pH buffer solution for the remaining 10 hours. The temperature of the dissolving media was kept constant at 37.50°C. After 1, 2, 4, 6, 8, and 12 hours, 1 ml of the sample was extracted. To keep the volume consistent throughout the experiment, 1 ml of 0.1 N HCL and 6.8 pH buffer solution was employed. The samples were appropriately diluted, and the percentage of drug release from each formulation was determined using a UV- Spectrophotometer at 210 nm and 230 nm.

7) In vitro Release Kinetics Studies

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from SR was described by using zero order kinetics or first order kinetics. The mechanism of drug release from SR was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

1. Zero Order Release Kinetics:

It defines a linear relationship between the fractions of drug released versus time.
$Q=k_0t$.
Where, Q is the fraction of drug released at time t and k, is the zero-order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

2. First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during as tablets could be described dissolution process suggested that the drug release from most of the slow adequately by the first-order kinetics. The equation that describes first order kinetics is

Log C= Log C_0-kt/2.303

Where C is the amount of drug dissolved at time t,

Co is the amount of drug dissolved at t=0 and

k is the first order rate constant.

A graph of log cumulative of log % drug remaining Vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

3. Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$Q=K_2t^{1/2}$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

4. Peppa's-Korseymere equation (Power Law)

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's-Korseymere equation (Power Law).

$Mt/M_2=K.t^n$

Where, Mt is the amount of drug released at time t

Mα is the amount released at time a.

$M_t/M\alpha$ is the fraction of drug released at time t,

K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release upto 60% against log of time will be linear if the release obeys Peppa's-Korsemeye equation and the slope of this plot represents "n" value the kinetic data of the formulations were included. Nature of release of the drug from the designed tablets was inferred based on the correlation coefficient obtained from the plots of the kinetic models. The data were processed for regression analysis using PCP Disso1.

Table 3: Drug Release kinetics mechanism

Diffusion Exponent	Mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous(Non- Fickian) Diffusion
0.89	Case II transport
n>0.89	Super Case II transport

6.RESULT AND DISCUSSION

1. Pre-compression Studies

The values of angle of repose (<30) indicates good flow properties of the powder. The bulk density and tapped density were found to range from 0.30±0.03 to 0.33±0.5 and 0.33±0.2 to 0.36±0.08 respectively. These results were satisfactory and may further influences the properties of the tablets. The hausner's ratio and carr's index results were also satisfactory.

Table 4: Evaluation of Powder Blend IR Enalapril Maleate

Batch	Angle of Repose(θ°)	Bulk Density(gm/ml)	Tapped Density(gm/ml)	Hausner's ratio	Carr's Index(%)
FEM1	27.88±0.42	0.31±0.02	0.33±0.02	1.06±0.031	6.42±1.12
FEM2	28.30±1.66	0.33±0.05	0.36±0.08	1.09±0.082	8.33±1.78
FEM3	27.10±1.03	0.31±0.04	0.35±0.02	1.12±0.071	11.42±1.32
FEM4	28.12±0.38	0.30±0.03	0.33±0.03	1.11±0.041	9.09±1.79
FEM5	26.34±0.45	0.31±0.02	0.34±0.04	1.09±0.012	8.82±1.61
FEM6	28.60±0.88	0.30±0.08	0.35±0.07	1.16±0.032	14.28±1.87

Table 5: Evaluation of Powder Blend SR Glibenclamide

Batch	Angle of Repose(θ°)	Bulk Density(gm/ml)	Tapped Density(gm/ml)	Hausner's ratio	Carr's Index
FG1	30.26±0.73	0.28±0.02	0.32±0.04	1.14±0.03	12.5±1.12
FG2	29.93±0.83	0.29±0.03	0.32±0.05	1.10±0.05	9.37±1.34
FG3	28.40±0.67	0.30±0.02	0.34±0.02	1.13±0.06	13.3±1.30
FG4	29.76±0.62	0.29±0.01	0.32±0.02	1.10±0.07	11.76±1.54
FG5	30.72±0.17	0.28±0.03	0.30±0.03	1.07±0.05	6.66±1.33
FG6	28.98±0.81	0.32±0.02	0.36±0.05	1.12±0.04	11.23±1.32

2. Post – Compression Studies

The average percentage deviation for all tablet formulation was found to be with in specified limit and all the formulation complied the weight variation test. All tablets showed hardness and thickness values were found the range between 6.0±0.43 to 7.99±0.77 and 4.13±0.003 to 4.23±0.09 respectively. The friability of all tablet formulations was found to be <1%, indicating that the friability is within the prescribed limits.

Table 6: Post-compression studies of Bilayer Tablet

Batch	Weight Variation	Thickness	Hardness	Friability
F1	296.24 ± 1.12	4.13±0.003	6.0±00.4	0.50±0.02
F2	298.39 ± 1.18	4.34±0.006	7.5±0.28	0.57±0.03
F3	297.50 ± 1.14	4.23±0.009	6.8±0.20	0.34±0.019
F4	299.36 ± 1.04	4.15±0.0012	6.8±0.56	0.45±0.45
F5	296.66 ±1.15	4.23±0.0012	6.0±0.40	0.50±0.20
F6	298.11±1.02	4.28±0.003	7.99±0.77	0.13±0.11

These table show the results of batches of F1-F6 IR Enalapril Maleate and SR Glibenclamide

Table 7: Disintegration Time of Enalapril Maleate Immediate Release Layer

Formulations	Disintegration Time
F1	**70 sec**
F2	**72 sec**
F3	**79 sec**
F4	**85 sec**
F5	**80 sec**
F6	**90 sec**

Dissolution Study

All of the formulated tablets were subjected to In vitro dissolution using the USP II Paddle technique at 50 rpm in 0.1 N HCl for the first 2 hours and 6.8 pH buffer solution for the remaining 10 hours. The temperature of the dissolving media was kept constant at 37°C. For Immediate release layer sample extracted after 5,10,15,30,45,60,90 minutes and for sustained release layer After 1, 2, 4, 6, 8, and 12 hours, 1 ml of the sample was extracted. To keep the volume consistent throughout the experiment, 1 ml of 0.1 N HCl and 6.8 pH buffer solution was employed. The samples were appropriately diluted, and the percentage of drug release from each formulation was determined using a UV-Spectrophotometer at 210 nm and 230 nm.

Table 8: Dissolution study of Immediate Release Layer of Enalapril Maleate

Time (Min)	F1 %	F2%	F3%	F4%	F5%	F6%
0	0	0	0	0	0	0
5	10.21 ± 0.12	12.15 ± 0.25	14.04 ± 0.32	16.78 ± 0.51	19.02±0.87	22.08±0.67
10	16.11 ± 0.31	18.02 ± 0.65	27.65 ± 0.78	30.72 ± 0.36	34.62±0.13	35.66±0.21
15	29.99 ± 0.63	34.11 ± 0.52	41.77 ± 0.55	49.82 ± 0.62	54.3±0.23	59.41±0.12
30	40.25 ± 0.52	45.91 ± 0.33	56.21± 0.44	65.22 ± 0.47	69.29±0.89	88.41±0.16
45	55.77 ± 0.11	60.21 ± 0.98	71.01± 0.21	89.36 ± 0.34	91.44±0.22	99.43±0.76
60	68.17 ±0.28	72.01 ± 0.17	90.22 ± 0.16	99.4±0.11	99.44± 0.41	-
90	79.59± 0.10	83.35± 0.91	98.91± 0.32	-	-	-

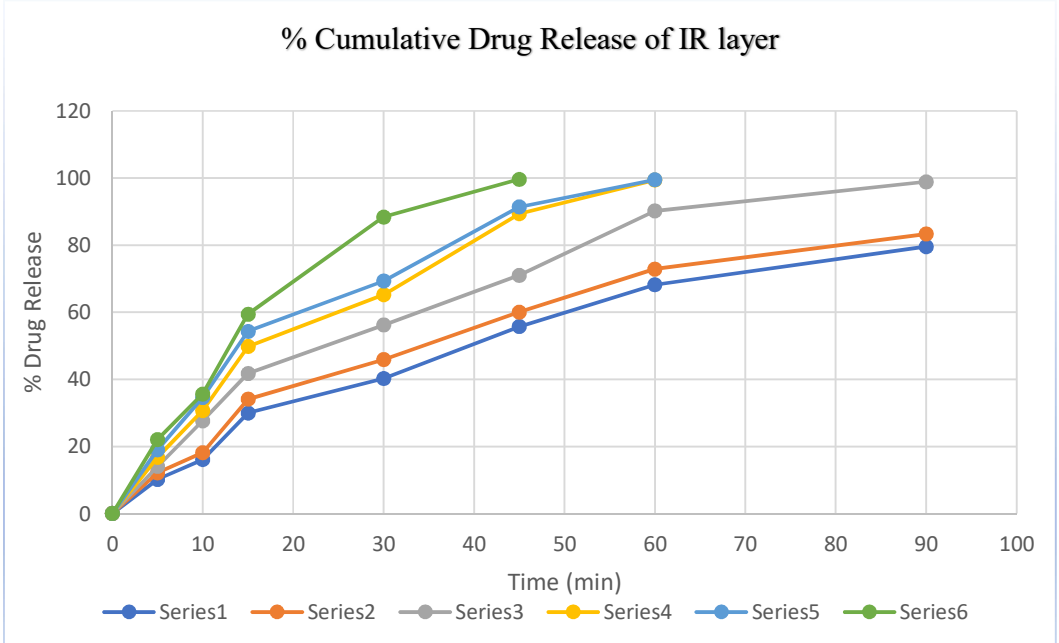


Fig 11: Cumulative Dissolution study of Batch FEM1 to FEM6

Table 9: Dissolution Study of Sustained Release Layer of Glibenclamide

Time (Hour)	FG1	FG2	FG3	FG4	FG5	FG6
0	0	0	0	0	0	0
1	15.44±0.88	13.73±0.83	16.76±0.11	16.76±0.98	17.71±023	20.33±0.22
2	36.32±0.26	32.73±0.89	38.99±0.32	34.07±0.76	35.15±0.76	40.11±0.10
4	69.22±0.89	62.89±0.32	49.99±0.21	63.61±0.85	64.87±0.44	59.13±0.12

6	88.38±0.28	85.99±0.54	61.78±0.65	82.31±0.31	85.45±0.32	70.22±0.33
8	99.43±0.89	90.21±0.43	78.88±0.43	99.12±0.39	90.06±0.98	80.54±0.54
10	-	99.90±0.98	89.65±0.11	-	99.98±0.31	91.11±0.88
12	-	-	99.98±0.34	-	-	97.22±0.23

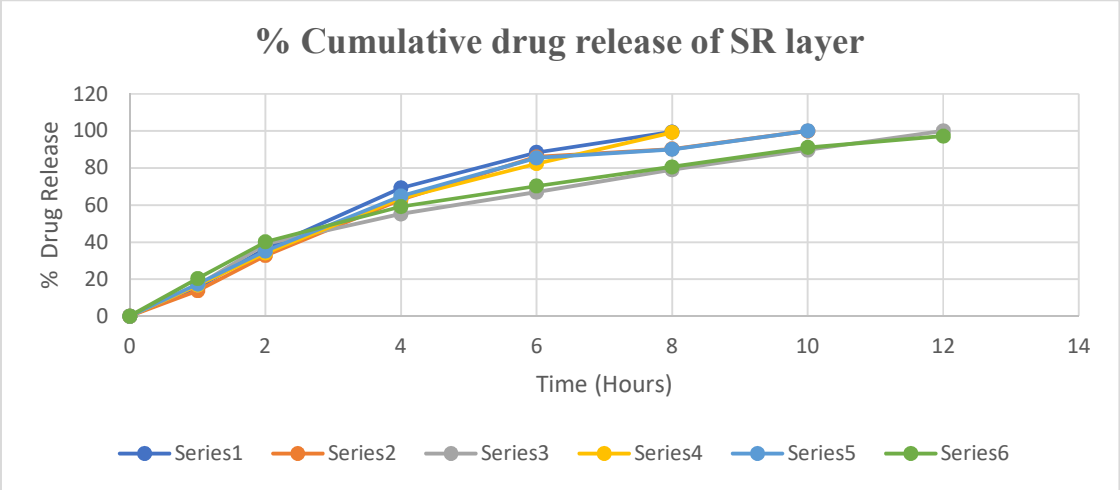
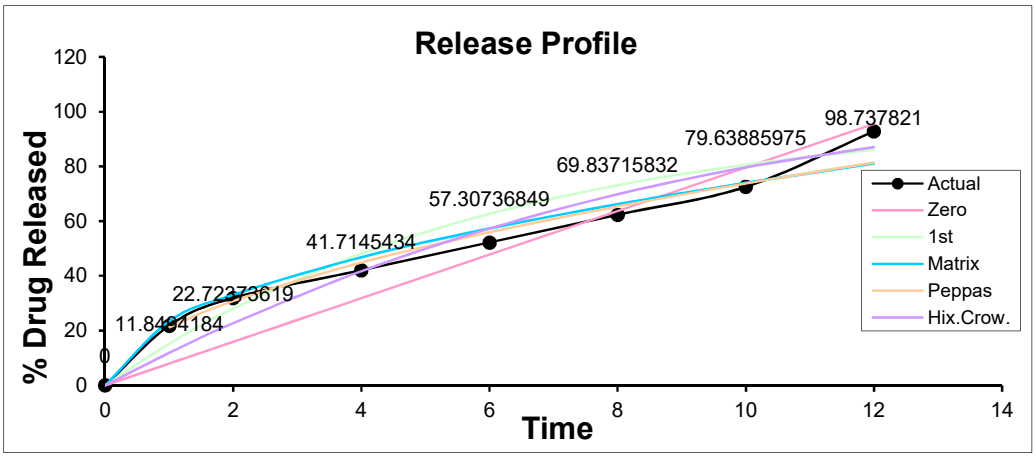


Fig 11: Cumulative Dissolution study of Batch FG1 to FG6

The formulation F3 as an optimized formulation because of these batch showed satisfactory result of the tablets parameter. Result of Glibenclamide and Enalapril Maleate in vitro 99.98% and 98.91 % drug release profile an indicated that formulation (F3) was the most promising formulations as the drug release from this formulation was high as compared to other formulations.

4.4. In-Vitro Release Kinetics Studies

• The In -vitro dissolution data of Glibenclamide SR formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer- Peppas models to assess the mechanism of drug release. It was observed from the above, that dissolution of all the tablets followed zero order kinetics with co-efficient of determination (R^2) values above 0.9834. Kinetic data also treated for Peppas equation, the absorbed slope (n) value is that shows 0.9874 • Non-Fickian diffusion mechanism. The kinetic result reveals that, the best fit model for F3 formulation is Korsmeyer- Peppas models with highest correlation coefficient (r2) value i.e. 0.9525.



Model Fitting (Average)-		
	R	k
Zero order	0.9834	7.4632
T-test	13.275	(Passes)
1st order	0.9072	-0.1502
T-test	5.282	(Passes)
Matrix	0.9525	21.5373
T-test	7.658	(Passes)
Peppas	0.9874	14.3904
T-test	15.278	(Passes)
Hix.Crow.	0.9535	-0.0381
T-test	7.747	(Passes)

5.5 Stability Study

Formulation Batch F3 for Enalapril Maleate is 98.91% and for Glibencamide is 99.98 % Stability study: Stability study for the developed formulation F3 were carried out as per ICH guideline by storing at 40°C/75% RH up to three months. The formulation F3 was selected on the basis of their high cumulative percentage drug release.

Table 10: Stability study of Bilayer tablet

Parameters	Initial Release	Final Release
Hardness	5-6	5-6
% of Drug Release (Batch F3)	99.98 SR 98.91 IR	97.98 SR 96.01 IR

The stability study showed that the formulation F3 was physically stable when stored at 40±20°C and 75±5% RH for three months and there was no significant difference in dissolution parameters of optimized formulation.

CONCLUSION

In the present study, Glibenclamide is Sulphonylureas agent, an antidiabetic agent Enalapril Maleate is Angiotensin Converting enzyme inhibitor agent was successfully prepared in the form of Bilayer. Glibenclamide and Enalapril maleate was prepared by using HPMC, Ethyl cellulose sustain release polymer and Croscarmellose as Super disintegrating polymer by using Direct Compression method, The Results of the Formulation F3 were was also satisfying was stable in compared to Formulation kept in Room Temperature as no significant growth in particle size was found in the Optimized batch. Comparison of in-vitro % Drug Release of pure drug and optimized Batch Bilayer of Glibenclamide and Enalapril Maleate was also carried out. Optimized Batch F3 Enalapril Maleate showed 99.89% at 90 mins and Glibenclamide showed 98.22 % Drug Release in 12 hr.

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