

Formulation And Evaluation Of Bilayer Tablet Of Eplerenone For The Treatment Of Hypertention

Sakshi Sharad Aher¹, Sujit A. Jadhav^{2*}, Khanderao Jadhav³, Rishikesh Bachhav⁴, Nilesh Chitte⁵, Pravin P Gadakh⁶, Kapil Phulwani⁷

¹Research Scholar, Department of Pharmaceutics, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik Maharashtra, India.

^{2,3}Associate Professor, Department of Pharmaceutics, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.

⁴Professor, Department of pharmacology, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.

^{5,7}Assistant professor, Department of Pharmaceutics, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.

⁶Assistant professor, Department of pharmaceutical Quality Assurance, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India

*Corresponding Author: Dr. Sujit Appasaheb Jadhav

*Department of Pharmaceutics, KCT's R.G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.
Email- sujitpharma29@gmail.com

Abstract

The purpose of the current work is to prepare and evaluate the immediate and continuous release of Eplerenone for the treatment of high blood pressure. The Eplerenone Bilayer tablet was prepared by wet granulation using the tablet superdisintegrants (CCS, SLS) and binder (PVPK 30). To expand the release of Eplerenone for a long-term Eplerenone release using hydrophilic polymer (HPMC K10M and HPMC E5) for extended periods, especially for low-soluble drugs. The original purpose is to reduce the frequency of drug administration and reduce the cost of production.

The purpose of the current research is to develop bilayer tablet of immediate release level using superdisintegrants and continuous release levels using hydrophilic polymers. Both immediate and continuous release levels were optimized using 3² factorial designs. For the IR layer selected independent variables are HPMC E3 (X1) and CCS (X2) and for SR layer HPMC K 100M (X1) and HPMC E5 (X2). In both levels, the % of the drug release (Y1) was selected as a dependent variable. Pre-compress and post compression parameters are evaluated. The in-vitro dissolution study was done for 12 hours using a pH 6.8 phosphate buffer. F8 formulation shows 96.9 % drug release at the end of 12 hours and the formulation IR5 showed 96.9 % drug release in 30 minutes. In the vitro release, various release was analyzed according to the kinetic model.

Customized formulation follows the Higuchi equation drug release activities. The regression coefficient value (r^2) was found to be 0.994.

Keywords- Bilayer tablet, Immediate release, Sustained release, Eplerenone.

INTRODUCTION

For many years, oral drug distribution has been considered the most preferred way for the administration of drugs. It is often due to its convenience and general assumption that oral drugs are absorbed just like everyday food intake. While parenteral administration plays an important role during the crisis, local distributors have recently attracted attention to targeting specific areas of the body for systemic effects. Most drugs are in solid form they are usually given as solid dose forms. Of those, traditional tablets are especially favored due to their portability and relatively low production costs. Oral administration is about 50-60% of all drug distribution methods. [1]

The quality characteristics of the tablet: The tablet should include the correct amount of the drug. The presence of the tablet should be elegant and it should be consistent with weight, size and appearance. High blood pressure or hypertension can be defined as a stress placed inside the artery walls for flowing blood. Blood pressure is

measured by two numbers, which are displayed on each other. The World Health Organization (WHO) supports countries to reduce high blood pressure as a public health problem. In 2021, who issued a new guide to high blood pressure medic treatment in adults. Release provides evidence-based recommendations for the onset of high blood pressure treatment, and recommended intervals for follow-up. The target includes information about who can start treatment in the blood pressure and health care system obtained for control. The term is defined as a Bilayer Tablet that has two layers that may contain the same drug or two different drugs.

Advantages [2]

1. With the option of converting a single layer to a single layer if needed, all of the dual-layer functionality.
2. Economic compared to many other dosage forms.
3. A two-layer pill is ideal for keeping two drugs apart to avoid direct interaction, which increases the effectiveness of their joint use.
4. Better chemical and microbial stability than other oral forms.
5. Taste and smell can be effectively masked using coating methods.
6. Eliminates a versatile and adaptable fractional approach.
7. High dose accuracy and minimum variation in materials.

MATERIALS AND METHODS

Materials

Eplerenone was a gift sample from Glenmark pharmaceuticals, Nashik .HPMC K100M,HPMC E3,HPMC E5,SLS,MCC102,CCS,Carbopol 974,PVP K30 from Research Lab Fine Chem Industry, Mumbai. Lactose, Ferric Red Oxide ,Colloidal Silica, Starch 1500, Magnesium Stearate used from college laboratory.

Preparation of Eplerenone immediate release layer [1] [3]

All ingredients were accurately weighed and passed through a sieve with mesh size #80 and the powder mixture was mixed for 10 minutes. The mixture was granulated with water- HPMC E3 and SLS and sieve passed through 18.The coloring agent is passed through a sieve #100 and is used in wet granulated and lubrication in the hot air oven for 15-20 minutes The dry ribs between 50 ° C to 60 ° C had to pass through the # 22 mesh. The mixture was mixed with talc and magnesium for 2 minutes and placed in a desiccator until further used .

Preparation of Eplerenone sustain release layer

Eplerenone continuous release tablet were prepared by wet granular technology with a variety of hydrophilic polymer. In this process, the amount of accurate drug mixture was mixed with a separate concentration polymer in the mortar and slightly mixed with pastel.

The drug-polymer mixture received to achieve the size of a uniform particle was rusted by a sieve # 44 and was collected in a polyethylene bag to ensure homogeneous mixture and was mixed for about 3 minutes. It was granular with PVP K30 with water and dries the granules between 50 ° C and 60 ° C in the hot air oven for 15-20 minutes. After drying, granules were received # 22 mesh. The accurate weight magnesium stearate was raided by sieve #60 and was equally mixed with the mixture, and lubricated for 5 minutes in a polythene bag.

Compression of Bilayer Tablet - [1] [4]

In the current study, the bilayer tablet manually was prepared using a station punching machine. A certain amount of SR powder mixture was fed manually in the cavity of death. The SR layer was compressed by the Light Compression Force using a 9mm circular shape concave punch. The accurate weight IR layer was then fed to die and compressed to make the bilayer tablets. Both layers were identified on the basis of color because the IR layer has a pink color, and the SR layer is white.

Dose calculations [5]

In order to achieve continuous drug release in 12 hours, the immediate release (IR) of the eplerenone was calculated based on the total dosage in extended-release (ER) formusation, which is 35 mg. According to pharmacokinetic principles, the IR dose can be determined using the formula:

$$DT = AD \times [1 + (0.693 \times t / t_{1/2})]$$

Where the DT is total dose, AD is adult dose, T is a period for continuous release, and $T_{1/2}$ is the half life of the drug. Eplerenone has half a life of 4 to 5 hours.

For example, using a 4-hour half life:

$$35 = \text{dose} \times [1 + (0.693 \times 12/4)]$$

$$\text{Loading dose} = 1 + (8.316/4)/35$$

$$= 3.079/35$$

$$= 11.40 \text{ mg}$$

5-hour half-life:

$$35 = \text{dose} \times [1 + (0.693 \times 12/5)]$$

$$\text{Dose} = 13.14 \text{ mg}$$

Based on this calculation, the immediate release can be based on the selected half life, dose between 11.40 mg and 13.14 mg. The dose was rounded to 13 mg.

Calculation of dose of drug in bilayer sustain release tablet containing single drug-

The total dosage of the eplerenone for the bilayer tablets was calculated using the available pharmacokinetic data. The total dosage of eplerenone in a bilayer continuous release tablet - both were determined by using four equations - an immediate release (loading dose) and a continuous release (maintenance dose) layer. These equations were obtained from pharmacokinetic data based on one-compartment model, which releases loading and maintenance doses with a zero order release described by Robison and Eriksen. [3]

D_M = maintenance dose

T = time for continuous action

Initial dose (D_I) = 25 mg

K^0R = Drug Input Rate

Half life of Eplerenone ($T_{1/2}$): 4 hours

Time to reach peak plasma concentration (T_{max}): 1.5 hrs.

Elimination rate constant $K_E = 0.693 / t_{1/2}$

$$= 0.693 / 4h$$

$$= 0.173 \text{ h}^{-1}$$

Zero order release constant $K_0 = D_I \cdot K_E$

$$= 25 \times 0.173$$

$$= 4.32 \text{ mg/h}$$

$$K^0R = K_E \cdot DL = 0.1732 \times 11.40$$

$$= 1.98$$

$$D_M = (K^0R \cdot H) = 1.98 \times 12$$

$$= 23.76 \text{ mg}$$

Total dose = loading dose + maintenance dose

$$= 11.40 + 23.7$$

$$= 35 \text{ mg}$$

Therefore, the total dose of Eplerenone was 35mg, maintenance dose has been rounded off to 24mg and Loading dose is 11mg.

Mathematical and Statistical Analysis [6]

Given the concentration of CCS (X_1) and HPMC E3 (X_2), 3^2 the full factorial design were used as two independent variables for immediate release levels. HPMC E5 (X_1) and HPMC K100M (X_2) concentration as two independent variables for sustained release level. Based on this design, 9 batches were prepared for each level. The percentage response of the drug release (Y_1) was chosen as variable to Evaluate the impact of independent variable on Related formulations.

Anova was analyzed to determine the numerical importance of the main effects and their interactions. The multi-term equation was obtained for response variables. A numerical and mathematical assessment was designed using Design Expert Software (version 21.1.8.0).

Table No. 1 A- Formulation of Immediate Release Layer

Ingredients Mg/Tablet	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
Eplerenone	11	11	11	11	11	11	11	11	11
HPMC E3	5.5	6	5.5	6	6.5	5.5	6.5	6.5	6
CCS	9	9	8.5	8	9	8	8.5	8	8.5
SLS	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
MCC PH102	32.75	32.75	32.75	32.75	32.75	32.75	32.75	32.75	32.75
Lactose	48.15	47.65	48.65	48.65	47.15	49.15	47.65	48.15	48.15
Mg. stearate	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Talc	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Ferric red oxide	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Total weight	110mg/tablet								

Table No.1 B- Formulation of Sustained Release Layer

Ingredients Mg/tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eplerenone	24	24	24	24	24	24	24	24	24
CMCS	52.5	49.5	50.5	51	50.3	51.5	52.5	49.5	51.8
HPMC E5	39	41.4	41	40	40	39	38.5	41	40
HPMC K100	61	61.5	61	61.5	62.2	62	61.5	62	60.7
Colloidal silica	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Starch 1500	5	5	5	5	5	5	5	5	5
PVP K30	10	10	10	10	10	10	10	10	10
Mg.sterate	2	2	2	2	2	2	2	2	2
Carbopol 974	15	15	15	15	15	15	15	15	15
Total weight	210 mg/tablet								

Factorial Design for Eplerenone immediate release layer [6]

The selection of factors was informed by preliminary investigation. Independent variables included concentration of CCS (X_1) and HPMC E3 (X_2). The dependent variable was the percentage of the drug release at 30 minutes (Y_1). Coded level -1, 0, and +1 for CCS (X_1), corresponding to 8mg, 8.5mg and 9mg respectively, while for HPMC E3 (X_2), levels 5.5%, 6%

Factorial Design for Eplerenone Sustained release layer

The selection of factors was informed by preliminary investigation. Independent variables included concentration of HPMC E5 (X_1) and HPMC K100m (X_2). The dependent variable was the percentage of drug release for 12 hours (Y_1). HPMC E5 (X_1), coded level -1, 0 and +1 for HPMC K100m(X_2).

Evaluations of Pre compression parameters [7]**Bulk Density**

The exact weight of the dried granules was transferred to a 100 ml graduate -measuring cylinder. The volume captured by the granules was recorded, and the bulk density was calculated using the formula :

Bulk density = weight of untapped granules / proportion of untapped granules .

Tapped Density

Tapped density was determined by placing a well -known weight of dry rhetoric in 100 ml graduate cylinders. The cylinder was then left at regular intervals with a height of 10 cm, allowing it to tap 100 times to get a constant volume. The final volume was recorded, and the taped density was calculated:

Tapped Density = Weight of Weight / Taped Granules

Carr's Compressibility Index

The flow of granules was evaluated using Carr's compressed index (%), which was determined by the formula:

Carr's index (%) = (tapped density - bulk density) / tapped density × 100

Hausner's Ratio

Hausner's ratio, another for granules flowability, considered using the following formula:

Hausner's ratio = tapped density / bulk density

Moisture content

The moisture required for tablet grains ranges from 1.00% to 2.50% W/W. Maintaining moisture in this range promotes strong granules and best compression properties, while preventing problems such as excessive viscosity and weak condensation

Angle of repose

The angle of powder mixture was determined according to the fixed funnel and free standing cone system. The angle of Repose (Θ) was calculated using the following equation.

$\tan \Theta = h/r$; $\Theta = \tan^{-1} h/r$

Where; h = height of the heap, r = the radius of the heap Θ = the angle of repose

Evaluation of Post-Compression Parameters

In-Process Quality Control Tests

Weight Variation

Twenty tablets from the batch were chosen in a mess and weighed individually to evaluate the weight variation. The average tablet weight was calculated, and personal weight was compared to determine positive and negative deviations. According to the USP specifications, the batch adheres to the batch if more than two tablets do not exit the specified percentage limit and no more than double the percentage of neglect permits.

Thickness

The thickness of the tablet is an important parameter to ensure uniformity in the size of the tablet. It was measured using a digital vernier caliper immediately after compression.

Hardness

The hardness of the tablet reflects the ability of tablets with mechanical shocks during handling before use, storage, transport.

Friability

Friability measures the mechanical strength of tablets. The test was performed using an ELECTROLAB friability tester (model EF -2). The tablets weighing 6.5 grams were accurately weighed and placed in a friabilator, operating at 25 rpm for 4 minutes. During this time, the tablets were subjected to a six-inch collapse with each rotation. After completing 100 revolutions, the tablet was removed, cut, re-performed, and weight loss percentage was calculated.

Disintegration Time

The disintegration time of the tablet was evaluated in vitro ($37 \pm 2^\circ \text{C}$) using 900 ml distilled water in the disintegration test (Electrolab -ED -2L). Six tablets were chosen in a mess and placed individually in each basket. The devices were executed, and the time taken for the complete disintegration of each tablet was recorded.

Drug content (Assay)

Prepare a Standard Solution:

Dissolve pure Eplerenone (35 mg) in methanol and dilute up to 100 ml. Make dilutions to get $\sim 10 \mu\text{g/ml}$ solution. Measure absorption at $\sim 240 \text{ nm}$ (check $\lambda \text{ Max}$).

Prepare a sample solution:

Powder tablets and weight amount of 35 mg. Measure absorption on the same wavelength.

In-vitro Drug Release (Dissolution) Study [8]

All tablets drug release profile was determined using the USP Type -2 dissolution method operated at 50 rpm. The dissolution medium includes 900 mL phosphate buffer (pH 6.8), ($37 \pm 0.5^\circ \text{C}$), 5 ml samples were withdrawn, were filtered, filtered, properly thin, and analyzed to measure the dose of the illuminated drug.

Kinetic release modeling – [4] [5]

The release of optimized formulation was compared to zero order, first order, Higuchi model, Peppas model. Data was processed for regression analysis using MS-Excel statistical functions

Stability Study –

Stability studies were performed in accordance with the ICH guidelines. The formulation was packed in aluminum foil and was subjected to rapid stability at $40^\circ \text{C} / 75\% \text{ RH}$ for a period of 2 months. Samples that were placed from each positive were withdrawn at certain time intervals. The tablet prepared during the stability study was analyzed for the hardness, friability, drug content, the vitro drug release.

Comparative In-vitro release profile with competitor formulation [9] [4]

In-vitro release profile studies were done using the dissolution test mechanism. f1 and f2 values for various brands are evaluated compared to the innovator brand. Equality factor (f2) was introduced by FDA (1997) and European agency to assess the comparison of disintegration profiles via proprietary products (CPMP) through the committee for evaluation of medicinal products. The two dissolution profiles are considered to be the same and bioequivalent when the f1 values range from 0 to 15 and the f2 value comes between 50 and 100. [6] Comparative drug release profiles were made by calculating the similarity factors f1 and f2 between Competitive Formulation.

RESULT AND DISCUSSION

Pre-formulation Evaluation

Compatibility studies by FTIR

Compatibility was studied to know the potential interaction between the drugs and excipients used in formulation. Physical mixtures of drugs and excipients were prepared to study compatibility. Drug polymer compatibility was performed using FT-IR spectroscopy. The IR spectrum of pure drug and polymer in a revolution of 4 cm^{-1} , ranging between $600\text{-}4000 \text{ cm}^{-1}$. FT-IR shows same absorption bands as pure drug and formulation, indicating absence of interaction.

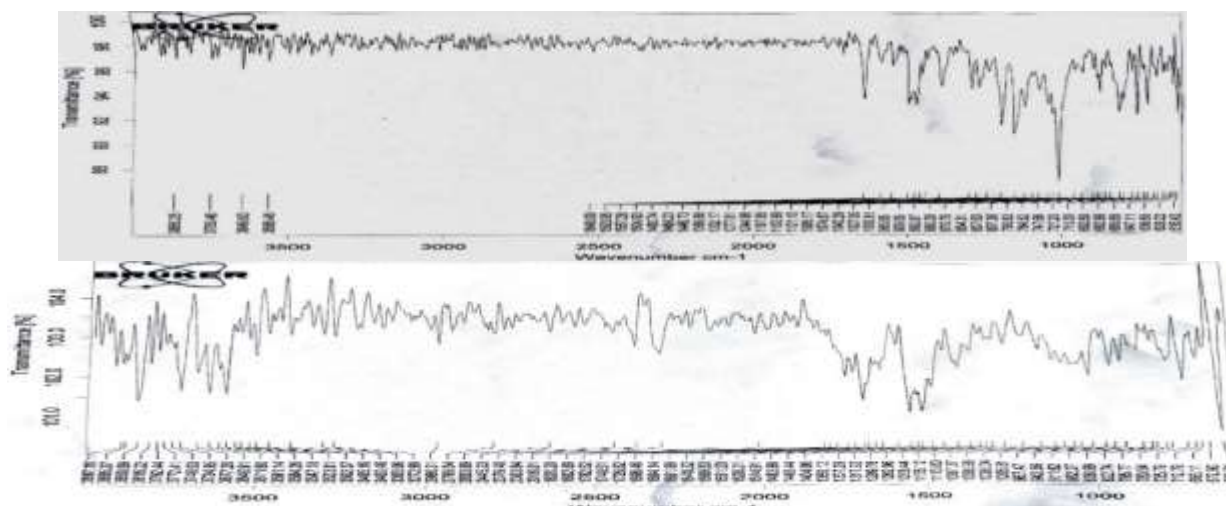




Fig no.1. FTIR of pure drug , Eplerenone IR layer, Eplerenone SR layer.

Pre-compression evaluation

Table No.2. Evaluation of Eplerenone sustain release layer granules

code	Bulk Density(g/ml)	Tapped density(g/ml)	Compressibility Index(%)	Hausners ratio	Angle of repose(°)	LOD(%)
F1	0.61	0.86	29.07	1.40	25.4	0.43
F2	0.68	0.81	16.04	1.19	28.2	0.54
F3	0.70	0.89	17.34	1.27	24.1	0.56
F4	0.71	0.86	17.44	1.21	25.3	0.67
F5	0.75	0.90	16.88	1.17	26.6	0.65
F6	0.72	0.93	15.25	1.17	24.6	0.50
F7	0.73	0.90	15.89	1.23	27.3	0.51
F8	0.62	0.71	15.7	1.14	27.3	0.50
F9	0.66	0.87	17.64	1.12	26.5	0.52

Table No.3.Results of dependent factors for IR layer(IR1-IR9)

Batch	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
% drug Release	88.9	91.9	88	90.5	94.9	86.8	94	92.7	91
%RSD	+1.76	+1.32	+2.32	+1.21	+2.43	+2.08	+3.50	+2.76	+1.54

Post compression evaluation

Table No.4. Evaluation of bilayer tablet

code	Hardness (kg/cm ²)	Weight variation(mg)	Thickness (mm)	Friability (%w/w)	Drug content(%)	Disintegration time (min)
F1	6.1	320	3.40	0.60%	95.20	3.12
F2	4.8	318	3.28	0.87%	95.23	2.17
F3	6.0	320	3.44	0.67%	95.43	3.40
F4	5.1	318	3.43	0.57%	94.20	3.01
F5	5.6	319	3.18	0.60%	96.50	2.12
F6	6.2	318	3.47	0.54%	98.30	3.49
F7	6.1	320	3.44	0.40%	92.01	1.58
F8	4.6	320	3.43	0.38%	98.75	1.25
F9	5.3	319	3.44	0.58%	95.40	2.22

Result of Regression Analysis for IR layer Equation in term of actual factors.

$$\% \text{ drug release} = + 39.01667 + 5.96667 * \text{ HPMC E3} + 1.90000 * \text{ CCS}$$

Table.No.5.ANOVA For Determining the Significance of the variables in IR layer

Source	Sumof squares	DF	Mean Square	F Value	P-Value	
Model	58.82	2	29.41	460.30	<0.0001	Significant

A-HPMC E3	53.40	1	53.40	835.85	<0.0001	
B-CCS	5.41	1	5.41	84.76	<0.0001	
Residual	0.3833	6	0.0639			
Cor Total	59.20	8				

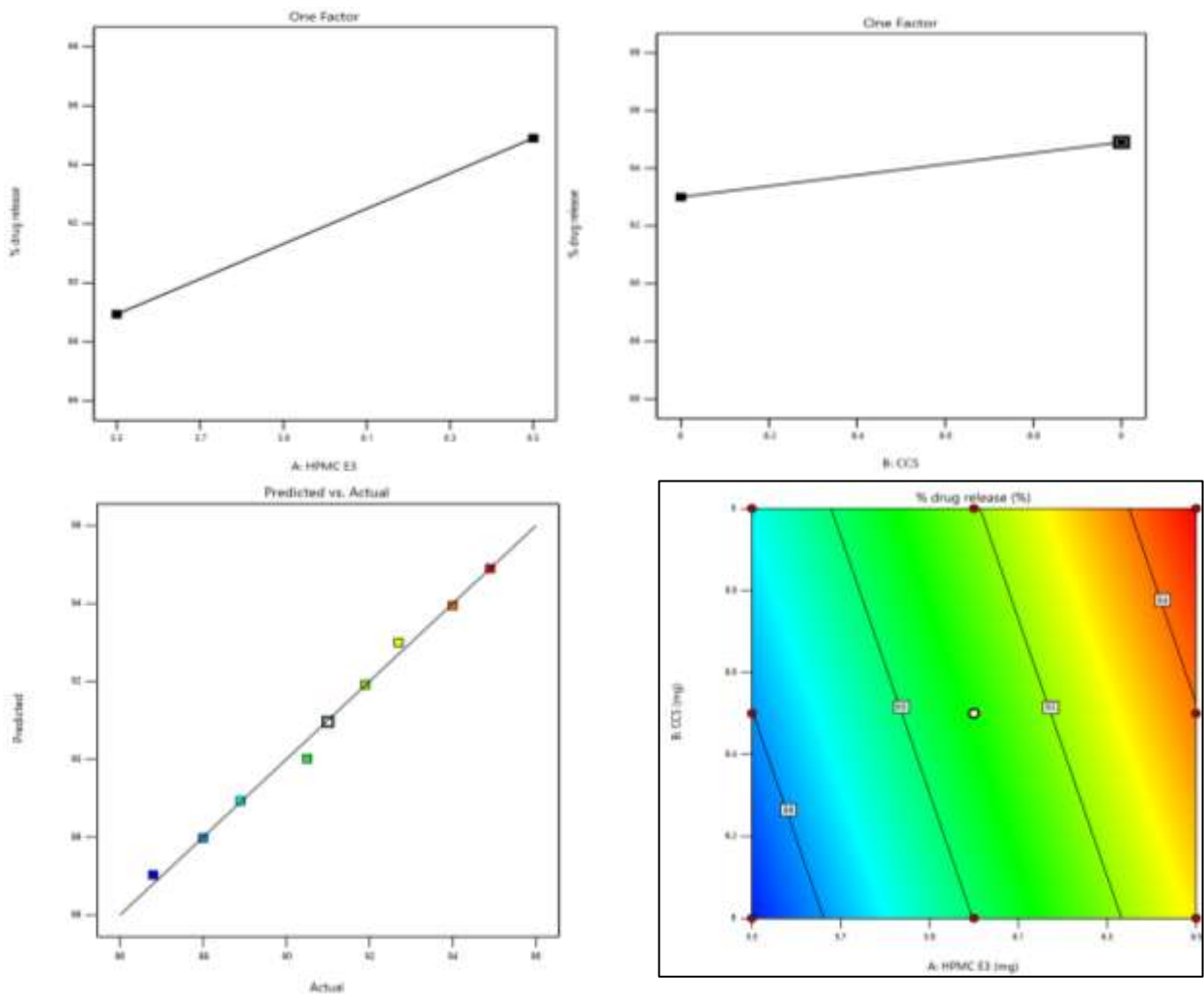
The ANOVA results of the experimental model for percentage release in the form of reaction are summarized in Table No.5

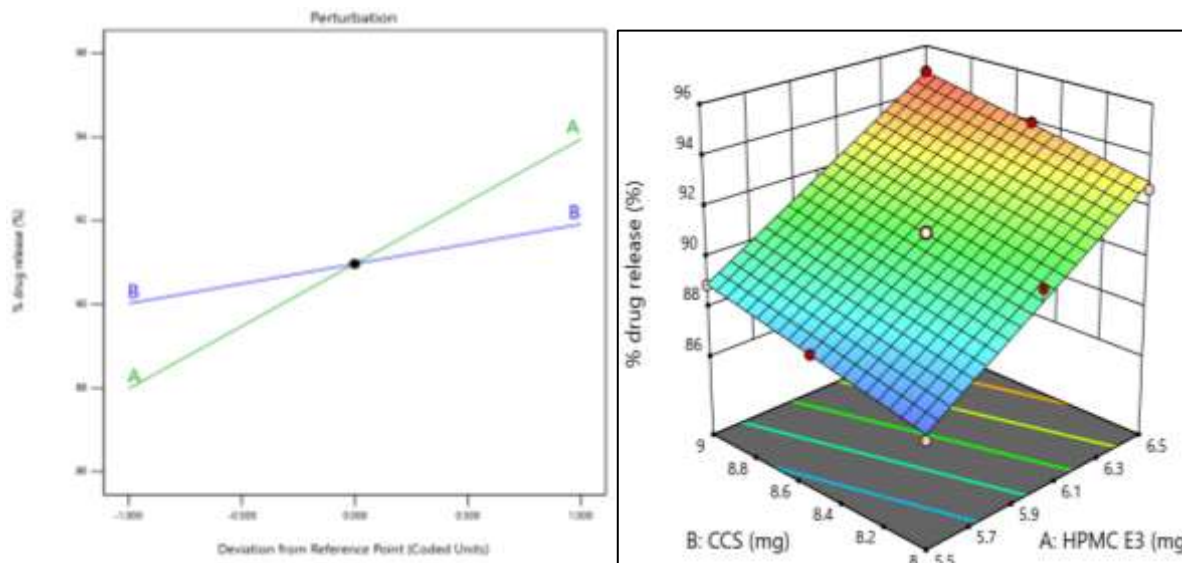
Model for dependent variables for eplerenone IR layer

Design expert 13 software using 21.1.8.0 a causative effect (HPMC E3, CCS), and (HPMC E3, CCS), conversations between counter plot and response surface plots, actual plots vs predicted, components were prepared for variables.

Model for dependent variables for eplerenone SR layer

Design expert 13 software using 21.1.8.0 was designed for a factor effect (HPMC E5, HPMC K100 M), and (HPMC E5, HPMC K100 M) interaction, counter plot and response surface plots, predictive Vs Actual plots, Perturbation plots were prepared for variables.





Figno.2.One factor effect, perturbation,predicted vs Actual plot, response surface plot showing effect of HPMCE3,CCS on % drug release.

From all figures, reflects the conversation between A and B. It was observed that the increase in% drug release depends on the concentration of CCS and HPMC E3

Table no.6 .results of dependent factor for SR layer (F1- F9)

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
% Drug release	92.7	95.8	93.9	93.4	94.9	91.9	91.5	96.9	93.3
% RSD	+1.65	+2.65	+2.43	+2.08	+1.32	+1.43	+1.29	+2.42	+1.42

Result of Regression Analysis for SR layer

Equation in term of actual factors

$$\% \text{ Drug release} = + 100010.21703 - 125.21096 * \text{ HPMC E5} - 243.17732 * \text{ HPMC K100m} + 1.90000 * \text{ AB} + 0.123761 * \text{ A}^2 + 1.36824 * \text{ B}^2$$

Source	Sum of Squares	df	Mean Square	F-Value	P-Value	
Model	25.35	5	5.07	4578.18	<0.00001	Significant
A-HPMC E5	18.87	1	18.87	17043.86	<0.00001	
B-HPMC K100M	2.49	1	2.49	2248.41	<0.00001	
AB	3.61	1	3.61	3260.38	<0.00001	
A ²	0.0439	1	0.0439	39.65	0.00081	
B ²	0.3415	1	0.3415	308.43	0.0004	
Residual	0.0033	3	0.0011			
Cor Total	25.35	8				
std deviation	0.2528		R ²		0.9935	
Mean	90.97		Adjusted		0.9914	
C.V %	0.2779		Predicted		0.9843	
			Adeq. Precision		53.9062	

Table No.7.ANOVA For Determining the Significance of the variables in sustained release layer

Percentage as a response is brief in ANOVA result table of the experimental model for drug release.

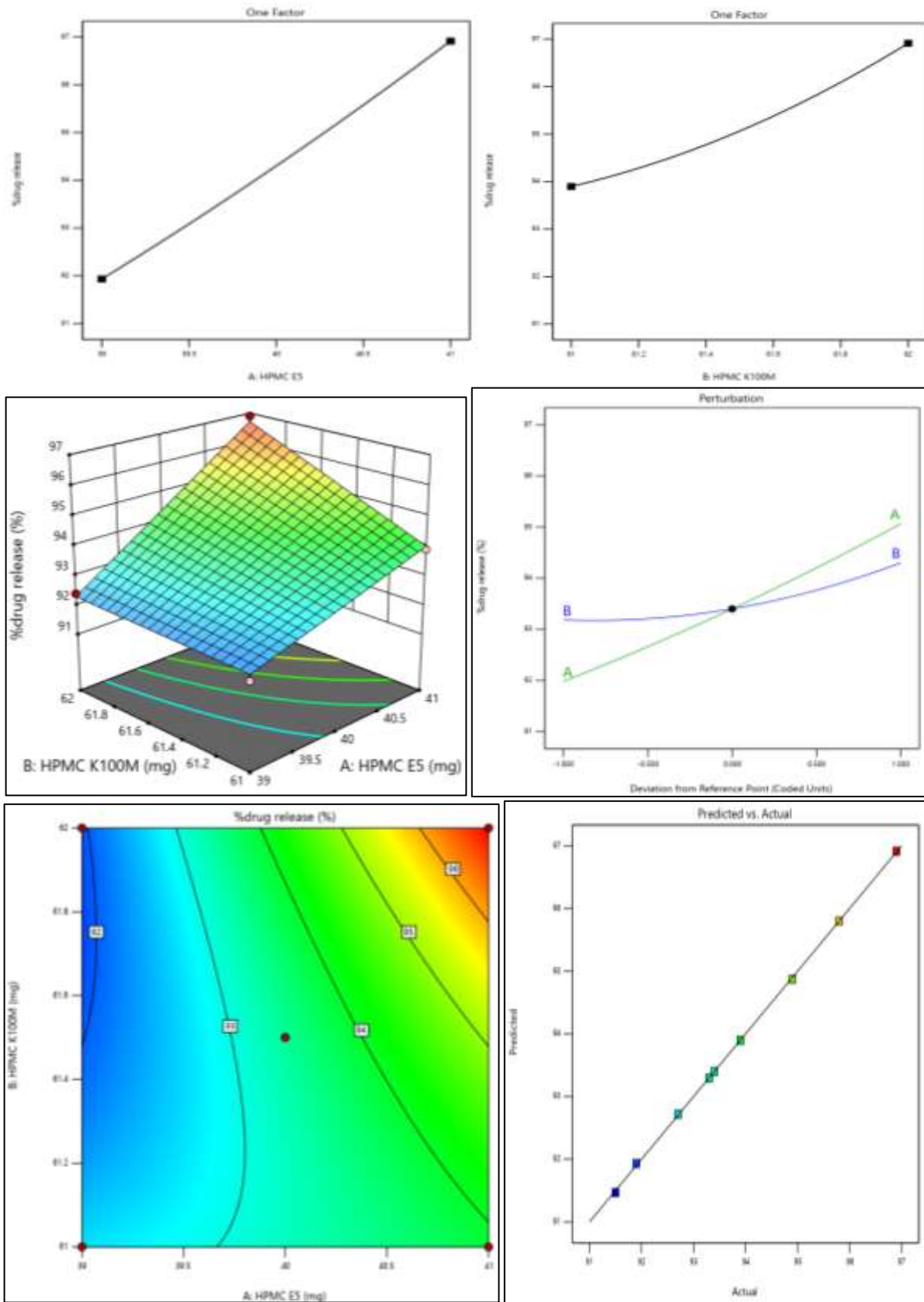


Fig no.3. One factor effect ,interaction ,counter plot ,perturbation ,predicted vs actual , response surface plots showing effects of HPMC E5 , HPMC K100M on % drug release

In vitro drug release of optimized bilayer tablet (IR5-F8)

The bilayer tablet prepared for the Eplerenone IR (IR5) and the Eplerenone SR (F8) layer from the prepared bilayer tablet was subjected to the dissolution test. The disintegration rate of the Eplerenone Bilayer Tablet (IR5-F8) is given in Table No. 8

Time	%drug release
5	09.01
10	11.03
15	16.00
20	21.10
25	29.62
30	31.10
60	40.90
120	46.1
180	50.67
240	63.29
300	67.93
360	71.88
420	76.83
480	82.60
540	87.72
600	91.20
660	95.89
720	96.9

Table no. 8 % drug release

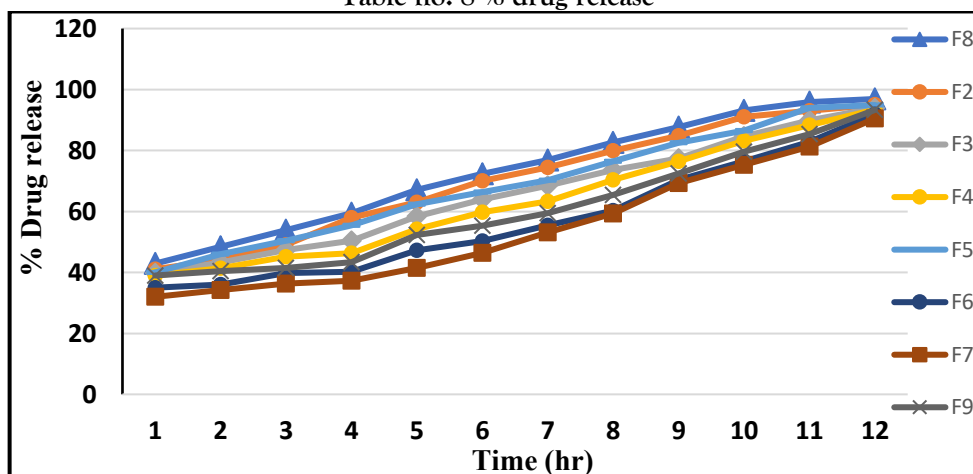


Fig.4. %Drug release of optimized batch

Pharmacokinetic modeling of optimized batch

Correlation coefficient values of trend lines indicated that all seven formulations followed the Higuchi release pattern, as clarified by the highest correlation coefficient (R^2 result = 0.9948). This suggests that the release behavior of our continuous-release formulations is affected by the initial drug concentration. As the content of the drug is reduced, the release rate decreases. The data of optimized formulation was fitted in various pharmacokinetic models. The best fit release of customized batch is shown below to the Kinetic model. [5]

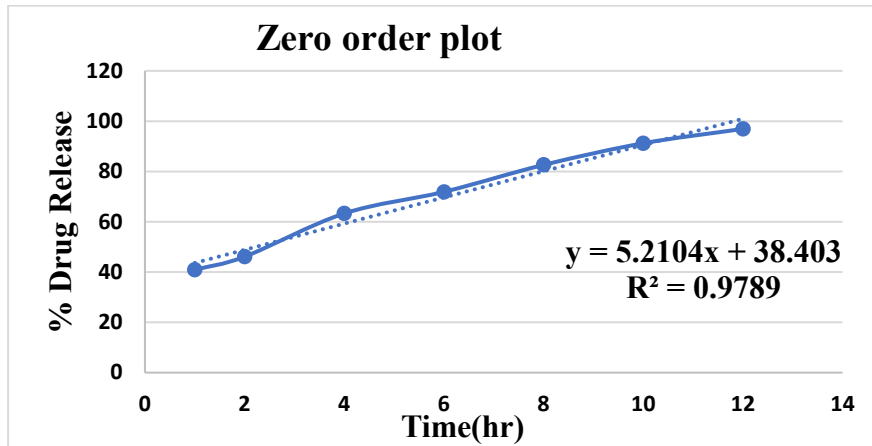


Fig 5.Zero order plot of optimized formulation

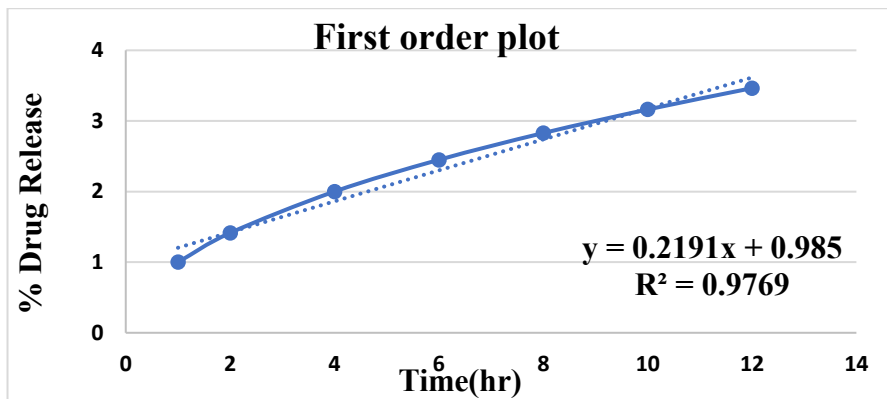


Fig. 6 .First order plot of optimized formulation

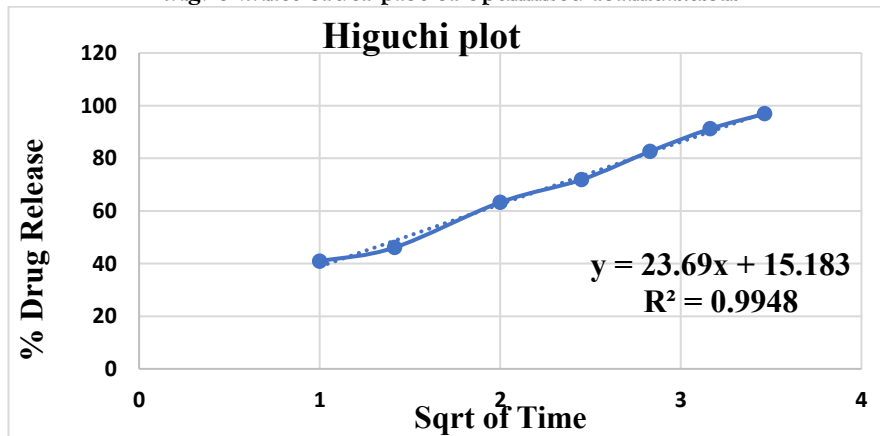


Fig . 7 . Higuchi plot of optimized formulation

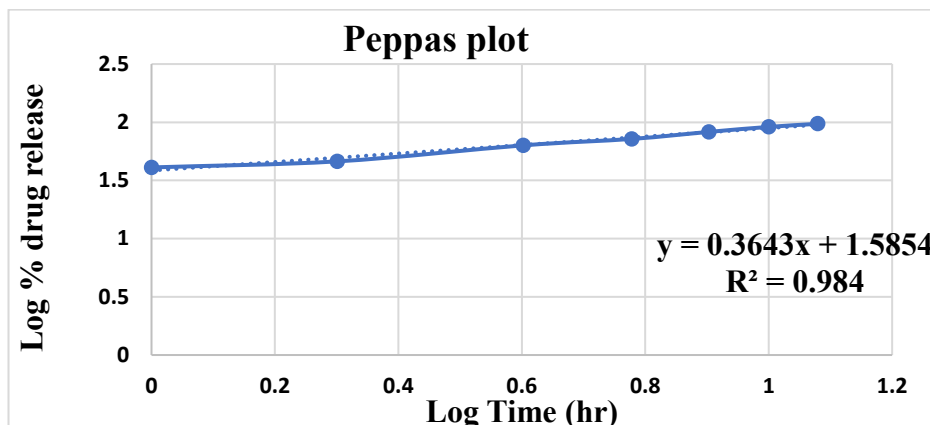


Fig. 8. Peppas plot of optimized formulation

TableNo.9.Regression coefficient values of pharmacokinetic models

Kinetics	Zero order	First order	Higuchi	Peppas
R ² values	0.9789	0.9769	0.9948	0.984

In models, the Higuchi model (R^2 and = 0.9948) shows the best correlation with experimental data, showing that the drug continues to be released from the tablet is primarily disruptions.

Comparative in- vitro release profile with competitor formulation

The comparative drug release profile was shown in the table by calculating the similarity factor f_1 and f_2 of competitor formulation (Lopressor)

Table .10 . Similarity factors between competitor formulation and optimized batch (F8)

Formulation No.	f_1	f_2	Dissolution profile
F8	3.22	73.80	Similar

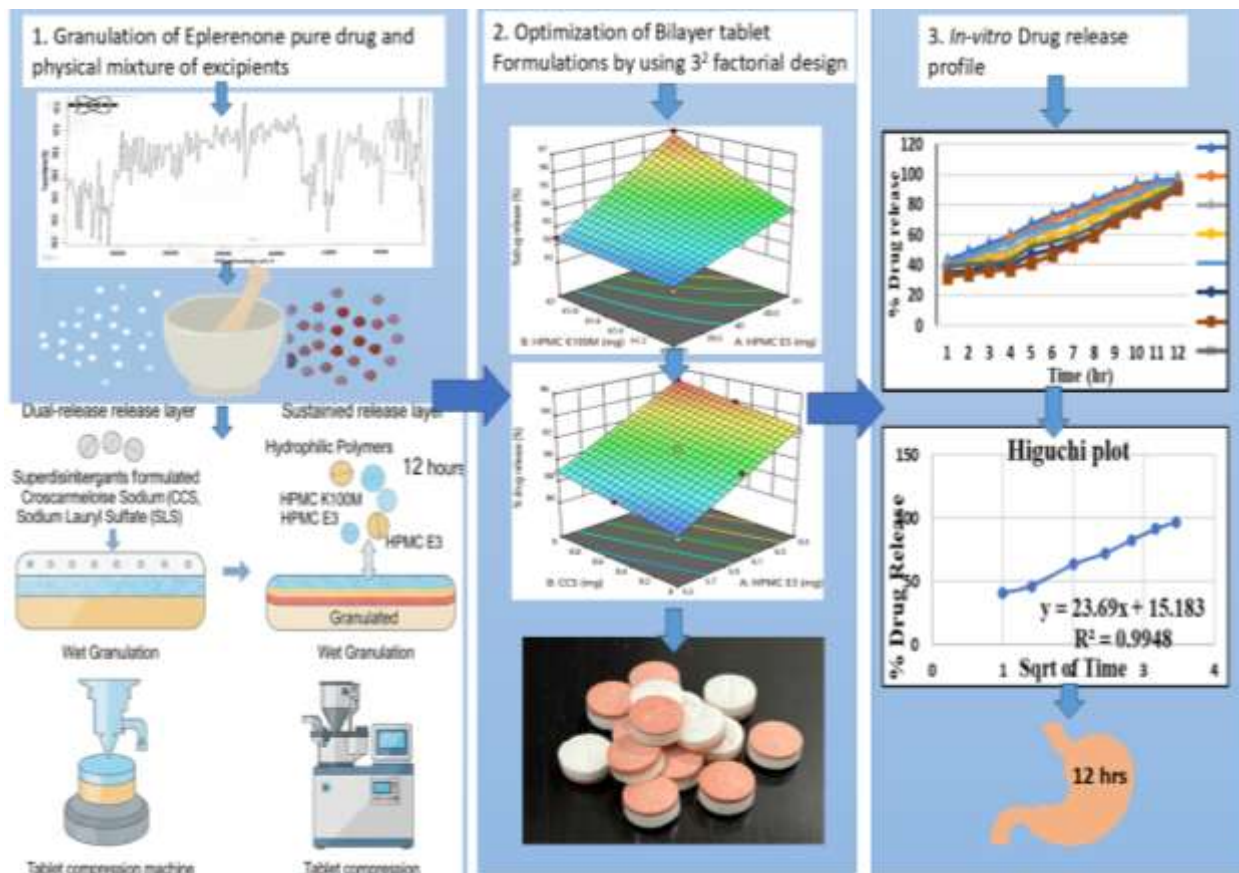
Stability studies

Stability studies for customized fractions Eplerenone Bilayer Tablet were moved to 40 + 20 °C/ 75 + 5 % RH for a period of 2 months and then the sample was tested for preaching post compression assessment.

The results of the stability study showed that there was no significant change in the parameters mentioned above after the high temperature and humidity conditions during the study of stability.

Test	Initial	1 Month	2 Month
Avg. weight (mg)	320	319	317
Hardness(kg/cm ²)	4.6	4.5	4.3
Thickness(mm)	3.43	3.43	3.41
Friability	0.38%	0.40%	0.41%
Drug content	98.75	98.03	97.45
Disintegration time	1.25	1.21	1.18
% drug release	96.9%	96%	95.2%

Table.11.Stability study data of optimized formulation



CONCLUSION

The study successfully demonstrated the effectiveness of CCS, as a carrier to increase the solubility and disintegration of the eplerenone. The SR layer compiled a combination of HPMC E5 and HPMC K100M ,with USP standards to effectively release the drug up to 12 hours. The FT-IR analysis confirmed the compatibility of the Eplerenone with the excipients used in the bilayer tablet. The final bilayer tablets, optimized IR and SR layers (batch I5 and F8) are made of better drug release than marketing products. Stability studies confirmed the strength of formulation. Therefore, bilayer tablet technology was successfully applied to give eplerenone in both immediate and continuous release forms.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. N. S. Tarun Parashar, "Formulation And In Vitro Evaluation Of Bilayer Tablet Of Atenolol For Biphasic Drug Release," Asian Journal Of Pharmaceutical And Clinical Research,2018 Pp. 115-119.
2. M. D. Sagar S. Kolhe, "Formulation And Evaluation Of Sustained Release Bilayer Tablet Of Losartan Potassium," World Journal Of Pharmacy And Pharmaceutical Science,2018 Vol. 7, No. 9, Pp. 957-970.
3. N. Panda, "Formulation Design And In Vitro Evaluation Of Bilayer Sustained Release Matrix Tablet Of Doxofylline," International Journal Of Pharmacy And Pharmaceutical Sciences , 2015 Vol.7, No. 10, Pp. 74-83.
4. S. K. Kunjan Gandhi, "Formulation ,Development And Evaluation Of Uncoated Bilayer Tablet Of Anti-Hypertensive Agent," Journal Of Drug Delivery And Therapeutics,2020 Vol. 10, No. 4(S), Pp. 100-107.

5. N. H.Mourya, "Formulation And Optimization Of Propranolol Bilayer Tablet," Indian Journal Of Pharmaceutical Science,2023 Vol. 85, No. 1, Pp. 189-198
6. S. V.Kapadi, "Formulation,Development And In Vitro Evaluation Of Fixed Dose Combination Of Hypertensive Drugs Through Bilayer Approach," World Journal Of Pharmaceutical Research,2015 Vol. 4, No. 3, Pp. 1511-1528
7. N. D. K.Himabindu, "Formulation And Evaluation Of Bilayer Tablet Of Quinapril Hydrochloride," Indo American Journal Of Pharmaceutical Research,2012 Vol. 3, No. 11, Pp. 9322-9329
8. V. K. Reddy Sunil, "Effect Of Polymers On In-Vitro Performance Of Eplerenone Sustained Release Matrix Tablet," Archives Of Pharmacy Practice,2012 Vol. 3, No. 3, Pp. 223-228.
9. P. Shrestha, "Design And Development Of Immediate And Sustained Release Tablet Of Vildagliptin," Research Jorنال Of Pharmaceutical ,Biological And Chemical Science,2014 Vol. 5, No. 4, Pp. 811-825
10. Sowmya C, Reddy Sc, Tabasum Sg, Varma V. An Overview On Bi-Layer Tablets. Int J Pharm Technol 2012;4:2143-56.
11. Parashar T, Soniya, Vishal S, Gaurav S, Satyanan T, Chirag P, Et Al. Novel Oral Sustained Release Technology: A Concise Review. Int J Res Dev Pharm Life Sci 2013;2:262-9.
12. Jadhav P, Samnani A, Panday G, Dubey Bk. Formulation And Evaluation Of Simvastatin Sustained Release Bilayer Tablet Using Hydrophilic And Or Hydrophobic Polymers. World J Pharm Pharm Sci 2012;1:621-32.
13. Yadav A, Jain Kd. Formulation Development And In Vitro Characterization Of Bilayer And Floating- Bioadhesive Tablets Of Propranolol Hydrochloride. Asian J Pharm Life Sci 2011;1:1-12.
14. Jain J, Mittal Rp, Patel M. Formulation And Evaluation Of Indomethacin Bilayer Sustained Release Tablets. Int J Pharmtech Res 2011;3:1132-8.
15. Jabbar Ms, Khalil I. Formulation Of Metoprolol Bilayer Tablets As A Ranch Km, Koli Ar, Vyas A, Parikh Rk. Formulation, Design And Optimization Of Orodispersible Tablets Of Atenolol. Int J Pharmtech Res 2009;1:1559-63.
16. Karwa P, Kasture V. Formulation And In Vitro Evaluation Of Bilayer Tablets Of Zolpidem Tartrate For Biphasic Drug Release. Int J Pharmtech Res 2011;3:1919-29.
17. Patel Sj, Thakkar P, Patel K, Patel Jk. A Review On Bilayer Tablets. J Drug Discov Ther 2013;1:40-8.
18. Roy Sk, Naskar S, Kundu S, Koutsu K. Formulation And Evaluation Of Sustained Release Bilayer Tablets Of Propranolol Hydrochloride. Int J Pharm Pharm Sci 2015;7:264-9.
19. Shinde Aj, Misale Gm, Salokhe Sv. Development And Evaluation Of Bilayer Mucohesive Gastroretentive Tablet Of Diltiazem Hydrochloride. Int J Pharm Pharm Sci 2014;6:365-701