RESEARCH ARTICLE

Development and Evaluation of Eplerenone Microbeads as Floating Drug Delivery System using Design of Experiment

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ABSTRACT

The present study was designed to formulate floating microbeads of eplerenone for decreasing dosing frequency and increasing gastric residence. The floating properties of the gastric juice were used to control the stomach stay time. Eplerenone was selected as a model bioactive which is used in lowering blood pressure by loading into floating microspheres was designed by using polymer ethyl cellulose and solvent ratio (Dichloromethane: methanol), keeping. The floating microbeads were studied for their drug entrapment efficiency, shape, percentage yield, and particle size, surface morphology, *in-vitro* drug release studies, percentage buoyancy, and formulation stability studies. Dichloromethane we used (DCM) as a constant and stirred them for hours. The study showed that fluid evaporation can be used to make floating microbeads that contain eplerenone. This method can be used to successfully make eplerenone-loaded floating microbeads. The study showed that making floating eplerenone microbeads with controlled release is a good way to cut down on how often you have to take your medicine.

Keywords: Eplerenone, Hypertension, Floating microbeads, Box-Behnken, Sustained delivery, Oral route.

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INTRODUCTION

Because biological half-lives are short, drugs need to be dosed often to keep their effective levels in the blood. To get around this problem, most of the study being done on new products is about controlling how fast drugs are released. The gastroretentive (GR) method of drug delivery has become an important tool in this area because it controls the drug's release and hence its availability in the body. A lot of new gastro-retentive technologies have been released recently. One of the most well-known is quality by design (QbD) - enabled systematic development of multiple-unit microbeads of eplerenone. This optimized gastro-retentive system used simple, effective floating microbeads to improve drug delivery and gastric residence time. A recent publication showed that QbD-based systematic development of a once-a-day gastro-retentive formulation is more desirable.

Eplerenone, pregn-4-ene-7, 21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ-lactone, methyl ester (7α, 11α, 17α), is an aldosterone blocker that is used to help treat people with long-term heart failure. Eplerenone can be used by itself or with other drugs to treat high blood pressure[1]. Eplerenone is a mineralocorticoid receptor blocker, which is a type of medicine. A natural chemical[1] in the body called aldosterone boosts blood pressure. This drug stops aldosterone from doing its job. The hormone aldosterone can't do its job because of eplerenone. It is important for blood pressure to be controlled by aldosterone.[2] Eplerenone is a class II drug. In this study, it was used as a model drug to make floating microbeads, a new way to release the drug into the body more quickly and for a longer time.

MATERIAL AND METHODS

Eplerenone was provided as a free sample by RA Chem Pharma in Hyderabad. Himedia Laboratories Pvt., Ltd. in Mumbai provided the ethyl cellulose. S.D Fine Chem., Mumbai, provided the di chloromethane, methanol, and PVA. All of the other substances included in the recipe were of analytical grade.

Box-Behnken Experimental Design

We used the Box–Behnken experimental design (Stat-Ease, Inc. Design Expert sample version 13.0.5.0) to look at the impacts of certain independent factors on the reaction to improve the floating microbeads formulation process. This approach is used to find the best way to do things with fewer testing runs by looking into quadratic response equations and making second-order polynomial models. Low, middle, and high sets (-1, 0, and +1)[3] were used to code the values of factor. The selected dependent and independent factors and their amounts and limits

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were represented in Table 1 from early studies. The separate factors that were picked were EC (X1), DCM:Methanol (X2), and stirring time (X3). We chose particle size (Y1), drug trapping rate (Y2), and *in-vitro* drug-releasing study at 12 hours (Y3) as the independent factors to measure the dependent variable. This study used a Box-Behnken design to find the best EP floating tablet recipe from a group of 17 trial mixtures with five center points. The main step is to find the values of X1, X2, and X3 that give the best possible values for Y1, Y2, and Y3 under controlled conditions (Table 2). This is done by making a polynomial equation with the dependent and independent factors. Based on the expected amounts of X1, X2, and X3, a new recipe F18 was made. Second, the observed answers Y1, Y2, and Y3 were matched. Next, the expected data, the residual, and the residual mistakes (%) were found (Table 3)[4]. Y is the variable that depends on the study plan, which is a polynomial equation.

$$Y= b_0+b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2.$$

Y = represents each response level b0 is the intercept of all the variables in the equation from b1-b33, for the variables, it was found that there are three lack of fits and four pure errors to ensure a valid lack of fit test and found smaller D-optimal criterion, standard deviation (SD).[5]

Floating Microbeads Processing

The moving microspheres method that was made was based on studies that had already been done, but with big changes. In this study, a floating nanoparticle mixture was made with a polymer that includes ethyl cellulose. The drug eplerenone was dissolved in different amounts of DCM and methanol, and the resulting solution was added drop by drop to water that had 0.75% PVA in it. The solution was stirred at definite 500 rpm for prescribed varying stirring time.[6] After the evaporation of the solvent, the emulsion was filtered with What man filter paper and washed several times in distilled water. The resulting microbeads were dried and stored in a desiccator.

The model has generated the following polynomial equation for entrapment efficiency, particle size, and cumulative% of drug releasing at 12th hours.

Response Analysis through Polynomial Equation (Figures 1-6)

$$Y_1= +244.00 + 0.4875 + 5.98B -12.35C -1.76AB -7.56AC -3.57BC +30.64A^2 +4.80 B^2 +1.57 C^2$$

In this case, B, C, AC, and A^2 were significant model term, the F-values of 18.75 implies that there is only a 0.04 % chance that the model would be significant. Lack of fit was found to be insignificant, which mould fit the model. Adequate precision was found to be 13.361 indicating that the model can navigate the design space.

$$Y_2 = +71.90 -0.5487A+ 6.26 B-7.94C +1.39AB-0.5525AC-9.96BC$$

In this case, B, C, and BC are significant model terms the F-value of 8.49 implies that there is only a 0.19 % chance that would be significant. Lack of fit was found to be non-significant which would fit the model (Tables 4 and 5). Adequate precision was 11.375, indicating that the model can navigate the design space.

$$Y_3 = + 85.33-0.2737A+ 11.84B-3.80C+ 1.01 AB+0.3775AC+0.8650BC-0.6133A^2-1.57B^2-0.3832C^2$$

In this case, B, C, AB, and B^2 were significant model terms. The F-value of 190.18 implies that there is only a 0.01% chance that would be significant. Lack of fit was found to be non-significant which would fit the model.

METHODOLOGY

Evaluation of Floating Microspheres

Determination of percentage yield

The reported method was used to figure out the percent return, with a few small changes. The made microbeads that were gathered were weighed correctly. The weighed amount was split by the total amount of all the non-volatile ingredients that were used to make the microbeads.[7]

$$\text{Percentage yield} = \frac{\text{Total weight of microbeads obtained}}{\text{Total weight of the ingredients}}$$

Drug entrapment efficiency

The effectiveness of entrapment was measured using the method described earlier, with a few small changes. To put it simply, 100 mg of eplerenone microbeads were crushed in a glass mortar and pestle. The powdered microbeads were then mixed with 100 ml of PB pH 7.4. After 24 hours, the solution was filtered, and 1-mL of the filtrate was taken out and diluted enough[8]. A UV-visible spectrophotometer was employed to

Table 1: Experimental design parameters

Factors	*Levels (coded values)*			*Actual value*		
Independent Variables	*Low*	*Medium*	*High*	*Low*	*Medium*	*High*
EC (mg) (X_1)	-1	0	+1	100	350	600
DCM: Methanol (mL) (X_2)	-1	0	+1	1:1	1:2	1:3
Stirring time (hrs) (X_3)	-1	0	+1	1	2	3
Dependent variable	Constraint/Desired response/Research goals				Importance	
Particle size (µm) (Y_1)	Minimum				5	
Drug entrapment efficiency (%) (Y_2)	Maximum				5	
In vitro drug release study at 12th hours (%) (Y_3)	Maximum				5	

Table 2: Composition of floating microbeads of eplerenone (EP)

F code	*EP (mg)*	*EC (mg)*	*DCM (mL)*	*Methanol (mL)*	*Stirring speed (rpm)*	*PVA (mg)*	*Water (mL)*	*Stirring time (hr)*
F 1	70	350	1	2	500	750	100	2
F 2	70	100	1	1	500	750	100	2
F 3	70	350	1	2	500	750	100	2
F 4	70	100	1	2	500	750	100	3
F 5	70	600	1	3	500	750	100	2
F 6	70	350	1	2	500	750	100	2
F 7	70	350	1	1	500	750	100	1
F 8	70	350	1	2	500	750	100	2
F 9	70	350	1	3	500	750	100	1
F 10	70	350	1	1	500	750	100	3
F 11	70	100	1	2	500	750	100	1
F 12	70	350	1	3	500	750	100	3
F 13	70	350	1	2	500	750	100	2
F 14	70	600	1	2	500	750	100	1
F 15	70	600	1	1	500	750	100	2
F 16	70	100	1	3	500	750	100	2
F 17	70	600	1	2	500	750	100	3

Table 3: Factors and response of experimental designed formula

		Factor 1	*Factor 2*	*Factor 3*	*Response 1*	*Response 2*	*Response 3*
STD	*Run*	*A: EC Polymers (X_1)*	*B: DCM: Methanol (X_2)*	*C: Stirring times (X_3)*	*Particle size (Y_1)*	*Drug entrapments efficiency (Y_2)*	*Cumulative% of drugs release at 12^{th} hours (Y_3)*
		Mg	(mL)	(hrs)	(µm)	%	%
15	1	350	2	2	250.61	71.87	84.03
1	2	100	1	2	267.33	69.45	72.82
17	3	350	2	2	246.09	70.15	84.96
7	4	100	2	3	276.83	61.79	80.53
4	5	600	3	2	288.02	78.38	95.51
16	6	350	2	2	242.65	75.15	87.01
9	7	350	1	1	258.49	55.34	76.11
14	8	350	2	2	239.39	70.13	85.51
10	9	350	3	1	274.29	89.71	98.47
11	10	350	1	3	233.58	67.92	66.56
5	11	100	2	1	279.06	85.09	88.66
12	12	350	3	3	235.09	62.45	92.38
13	13	350	2	2	241.26	76.89	85.16
6	14	600	2	1	290.71	85.65	87.39
2	15	600	1	2	276.28	65.02	70.21
3	16	100	3	2	286.11	77.25	94.06
8	17	600	2	3	258.22	60.14	80.77

assess the content of the drug in samples that had already been prepared. The absorption peak was set at 244 nm.

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100$$

Buoyancy percentage (Table 6)

There were separate microspheres floating on top of the 100 mL PB pH 7.4 fluid that was stirred at 50 rpm on a magnetic mixer for 6 hours straight. The pipette was used to separate the microspheres that were floating on top of the medium. Filtration

Table 4: Calculated estimates of Y_1-Y_3 responses

Source	R^2	*Lack of fit p-value*	*Adjusted R²*	*Predicted R²*	*SD*	*PRESS*	
Response (Y_1)							
Linear	0.2426	0.0033	0.0674	-0.3393	19.05	8341.12	
2FI	0.2892	0.0018	-0.1373	-1.656	21.04	16352.53	
Quadratic	0.9602	0.1671	0.9089	0.5449	5.95	2834.54	Suggested
Cubic	0.9874		0.9495		4.43	*	Aliased
Response (Y_2)							
Linear	0.5591	0.0359	0.4574	0.1045	7.05	1312.52	
2FI	0.8360	0.1160	0.7375	0.2710	4.90	1068.51	Suggested
Quadratic	0.8697	0.0666	0.7022	-0.7176	5.22	2517.52	
Cubic	0.9746		0.8983		3.05	*	Aliased
Response (Y_3)							
Linear	0.9792	0.2563	0.9743	0.9655	1.42	43.56	
2FI	0.9852	0.2659	0.9764	0.9622	1.37	47.73	
Quadratic	0.9959	0.9413	0.9907	0.9886	0.8576	14.36	Suggested
Cubic	0.9963		0.9851		1.09	*	Aliased

Table 5: ANOVA reports of Y_1-Y_3 responses

Source	Y_2	Y_3			Y_1		
	F-value	*p-value*	*F-value*	*p-value*	*F-value*	*p-value*	
Model	18.75	0.0004	190.18	< 0.0001	8.49	0.0019	Significant
A-EC	0.0536	0.8235	0.8152	0.3966	0.1002	0.7581	
B-DCM: Methanol	8.07	0.0250	1524.99	< 0.0001	13.03	0.0048	
C-stirring time	34.44	0.0006	156.98	< 0.0001	20.96	0.0010	
AB	0.3496	0.5730	5.60	0.0498	0.3214	0.5833	
AC	6.46	0.0386	0.7751	0.4078	0.0508	0.8262	
BC	1.44	0.2691	4.07	0.0835	16.50	0.0023	
A^2	111.51	< 0.0001	2.15	0.1857			
B^2	2.73	0.1423	14.13	0.0071			
C^2	0.2914	0.6061	0.8410	0.3896			
Residual							
Lack of Fit	2.87	0.1671	0.1238	0.9413	3.64	0.1160	not significant

was used to sort the microspheres that had sunk to the bottom of the jar. Each fraction was dried at 45°C until the weight stayed the same. The buoyancy was found by comparing the weight of particles that float to the weight of particles that sink.[9]

$$\% \text{ Buoyancy} = \frac{\text{Microsphere remained floating}}{\text{The total mass of microspheres}} \times 100$$

Particle size assessment

We checked the particle size of microbeads using an optical microscope (Model CH20iBIMF) and a particle size analyzer (Malvern, Model: Nano ZS90), but we made some important changes to the method that had already been described. In short, microbeads were spread out evenly on the slide, and a calibrated optical microscope was used to carefully look at them to determine the particles' size. Both the longest and smallest axes were used to measure the particle size of the microbeads. The mean measure of the particles was given as the sum of these two points. A scattering angle of 173°C, a temperature of 24.9°C for the holder, and a viscosity of 0.897 mPa.s. were used to figure out the width of at least 100 microbeads in each batch. The micro sponges' average size was given in (d) nm.[10]

Zeta potential (Figure 7)

Almost all small or large particles or objects that come into contact with a liquid get an electric charge on their surfaces. Zeta potential is a good way to guess how stable a mixture will be. It is recorded with the holding cell at 25°C, the dispersion medium's viscosity at 0.895 mPa.s, the conductivity at 0.358 mS/cm, and an electrode voltage of 3.3V.[11]

Surface morphology and shape (Figure 8)

A scanning electron microscope (SEM) LEO 435 VP was used to look at the form and surface properties of the microbeads that were made. The samples for the SEM were made by

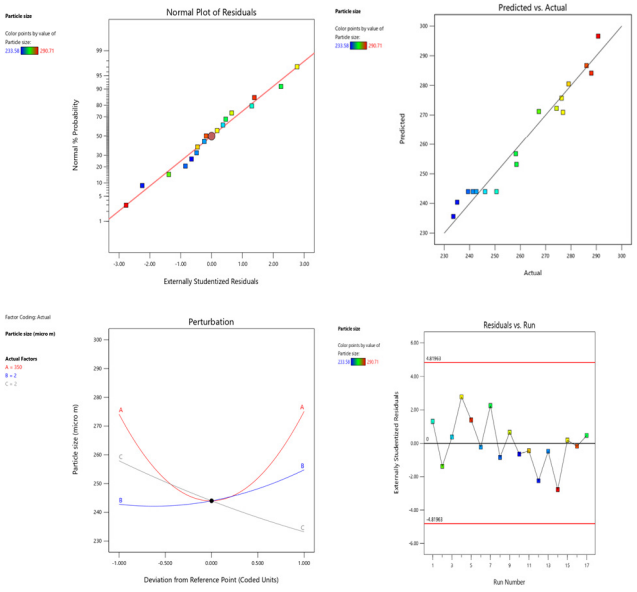

Figure 1: Model graphs of Y1 response

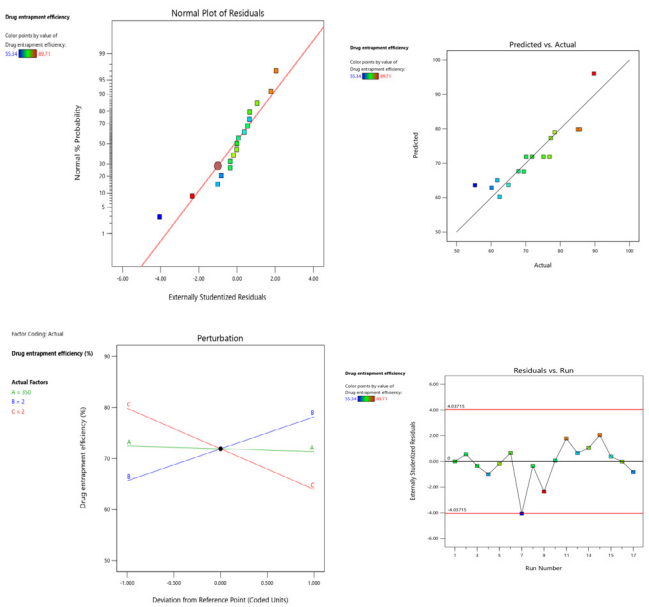

Figure 3: Model graphs of Y2 response

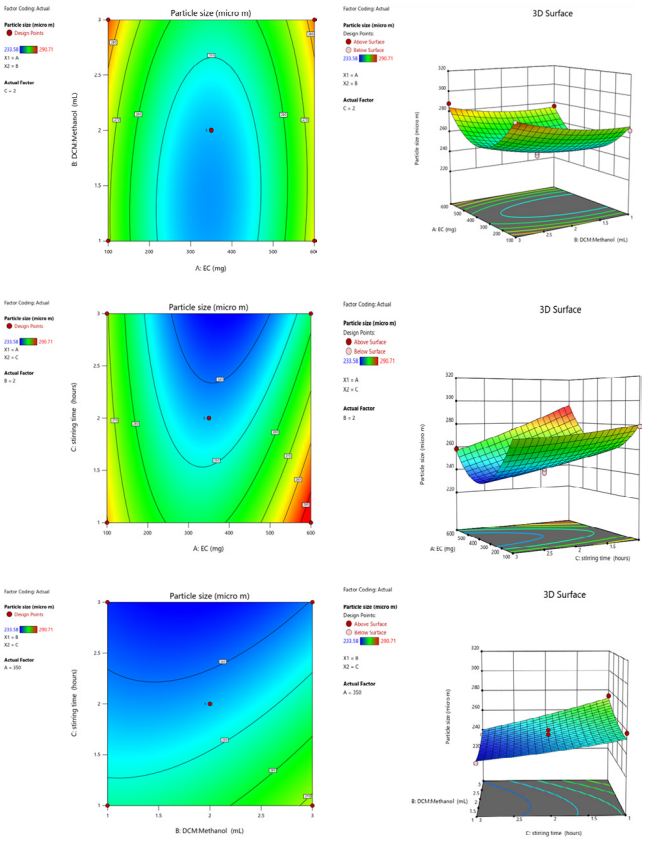

Figure 2: Response surface three-dimensional and counter plots Y1

carefully spreading the floating microbeads out on a piece of double-sticky tape that was attached to a short piece of metal. After that, a 30 mm thick film of gold coater was put on the stubs while they were under high voltage and pressure. The items were then thought of employing a 20KV electron beam.[11]

Differential scanning calorimetry

Differential scanning calorimetry (DSCs) examine pure drug thermal behavior. Based on detecting heat flow in and out of the sample and reference for the controlled temperature cycle, 2 to 5 mg sample was encapsulated in an aluminum pan and heated at 10°C/min over 20 to 300°C under 50 mL/min liquid nitrogen. The degree curve peak, onset, end set, heat, and height formed the thermogram[11].

X-ray diffractometer (Table 7)

To study the physicochemical characteristics of initial raw material and optimized micro sponges formulations, the X-ray diffractometer (XRD) method was applied. XRD (Shimadzu, Model 7000), with Cu Kα radiation and the voltage 40.0 kV, current 30.0 mA was applied to the instrument. The diffraction pattern was carried out at a scan range of 10-80 deg with continuous mode, and a scanning speed of 2 deg/min[12].

Compatibility study

FTIR spectroscopy was used to study how eplerenone, a physical mix of drugs, interacts with other medicines. The spectra were taken 10 times over a wave number range of 4000 to 500 cm^{-1} at a 2 $I/cm1^3$ precision.

In-vitro drug release

In-vitro studies of drug release were done with a six-basket dissolving device of the USP XXIII paddle type. In 900 mL of artificial stomach fluid PB with a pH of 7.4 and a speed of 37 ± 0.5ºC at 100 rpm was used as the breakdown medium. At certain times, 5 mL samples were taken out and examined by a UV spectrophotometer at the λ_{max} value 244 nm after being diluted properly and compared to a blank. The amount that was taken out was refilled with the same amount of new PB pH 7.4 buffer.[14]

Kinetics of Release Studies

The formulations' *in-vitro* release characteristics were fitted into four data treatment models.[15,16]

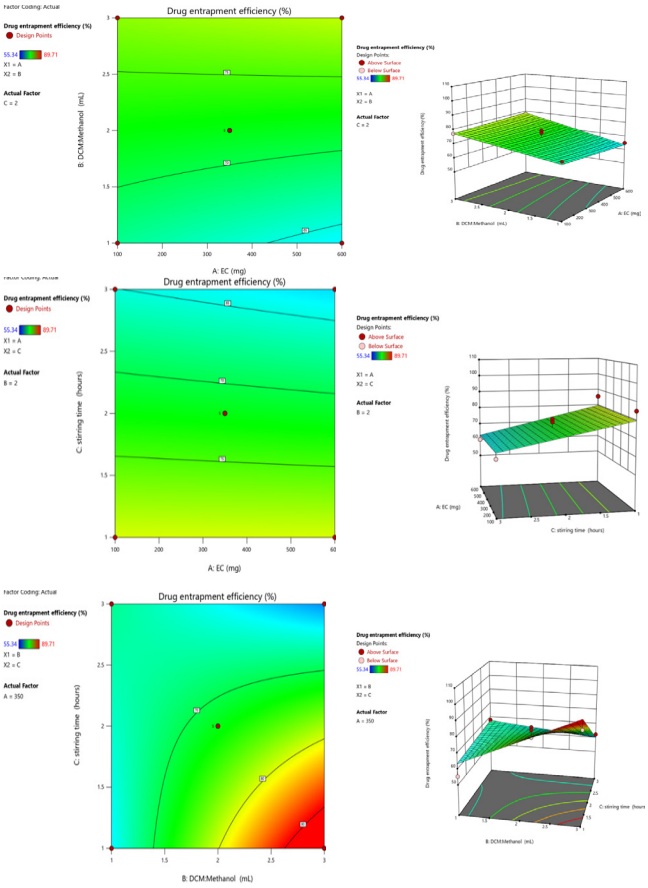

Figure 4: Response surface three-dimensional and counterplots of Y2

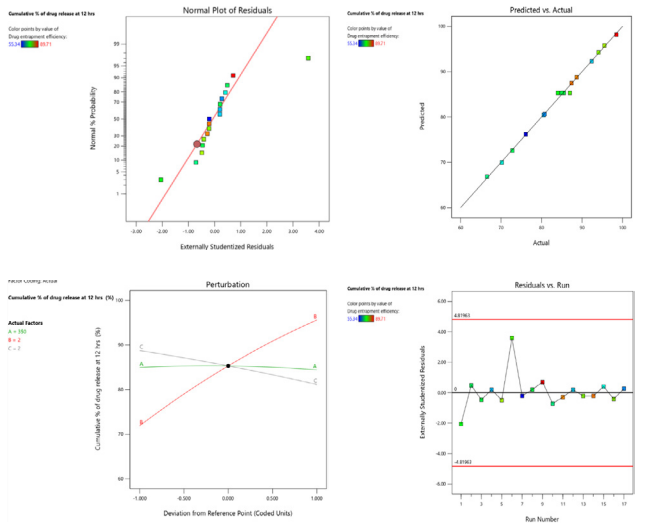

Figure 5: Model graphs of Y3 response

Zero-order equation

$Q=Q_0 - K_0 t$

Q is the amount of drug released at a time, K_0 is the zero-order release rate constant

A proportion of drug release plotted *versus* time will be linear if it follows zero-order release kinetics. This release

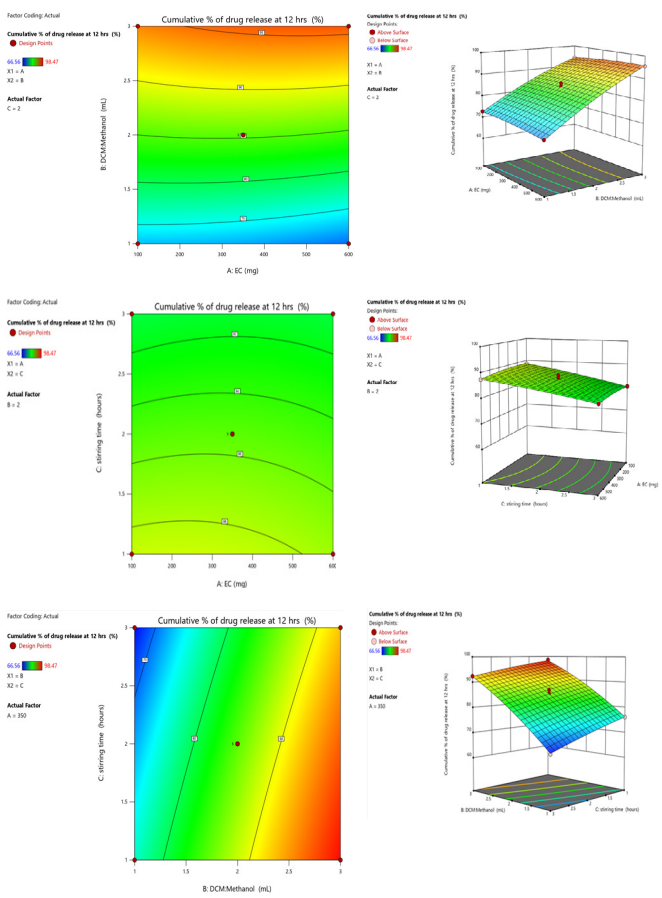

Figure 6: Response surface three-dimensional and counterplots of Y3

Table 6: Floating time, percentage yield, and drug content of various formulation

Formulation code	*Total Floating time*	*Percentage yield*	*Buoyancy percentage*
F1	12	83.21 ± 0.02	91.10 ± 0.51
F2	12	80.00 ± 0.12	99.16 ± 0.83
F3	12	84.15 ± 0.24	89.84 ± 0.21
F4	12	81.62 ± 0.82	90.51 ± 0.60
F5	12	89.56 ± 0.74	91.90 ± 0.02
F6	12	84.31 ± 0.68	93.48 ± 0.00
F7	12	86.92 ± 0.82	92.27 ± 0.93
F8	12	88.27 ± 0.31	94.11 ± 0.72
F9	12	84.3 ± 0.44	90.88 ± 0.92
F10	12	88.22 ± 0.65	92.04 ± 0.64
F11	12	79.62 ± 0.48	96.67 ± 0.77
F12	12	82.65 ± 0.38	90.82 ± 0.12
F13	12	88.38 ± 0.29	92.38 ± 0.51
F14	12	88.14 ± 0.81	90.12 ± 0.89
F15	12	85.21 ± 0.74	91.02 ± 0.99
F16	12	80.28 ± 0.69	92.73 ± 0.01
F17	12	85.49 ± 0.66	94.88 ± 0.24

*n=3, Avg ± S.D

strategy is good for sustained pharmacological effect. This includes transdermal, coated, osmotic, and matrix tablets with low-soluble medicine.

First-order equations

$InQ=InQ_0 - K_1t$

Q is the medication discharged at time t, and Q0 is the formulation's leftover drug. If first-order release kinetics are followed, the logarithm of the proportion of drug left *versus* time will be linear. Hydrolysis kinetics and pharmacological dose forms with water-soluble medicines in porous matrices may be studied using the model.

Higuchi equation

It shows that the surface root of time linearly affects the active fraction discharged per unit of surface (Q).

$Q=K_2t^{1/2}$

Higuchi square root of time release rate constants; K2.

If the Higuchi equation is followed, the percentage of medication released vs time will be linear. Based on flick's law, this equation depicts drug release as diffusion. Time-dependent square root.

Korsmeyer-peppas model

$Q/Q_0=Kt^n$

Q/Q_0 is a fraction of the drug released at time t k is a constant and n is diffusion exponent indicating the mechanism of drug release.

Studying stability

Stability experiments lasted 6 months at 25°C ± 60% RH. The final amber-colored glass containers were filled with the chosen composition and sealed. They were kept at 25°C ± 2%/60°C ± 2% RH for 180 days. After 1, 3, and 6 months, percentage drug entrapment and *in-vitro* drug release were assessed.

RESULTS AND DISCUSSION

Evaluation of Floating Microbeads

Percentage yield

Product yield marginally increased as the formulation's polymer ratio (EC) and ethyl cellulose amount rose. High solution viscosity may cause this. The percentage yield was found to be in the range of 89.56 ± 0.74 to 79.62 ± 0.48 for microbeads of eplerenone. However, microbeads of eplerenone using EC with PVA were found to show percentage yield.

Efficiency of drug entrapment

Eplerenone entrapment efficiency using EC with PVA was 55.34 to 89.71%. Within the crease, the produced microbeads' drug entrapment effectiveness rose with the polymer (EC) and PVA, Which established the carrier system, entrapping increased medication content in microbeads.

Buoyance percentage

Results of buoyancy percentage indicate that the polymer carrier has a better-floating tendency with ethylcellulose due to the low density of polymer and has less contact angle. The results were found to be in the range of 99.16 ± 0.83 to 89.84 ± 0.21.

Particle size and zeta potential

Microbeads of eplerenone floating on EC with PVA vary in size from 290.71 to 233.58 µm. With increasing polymer content, microbead particle size and drug entrapment increased. Floating microbeads with less polymer had lower particle sizes than those with more polymer, perhaps because particle walls grow with polymer concentration. The zeta potential was found to be at -21.5 mV with an electrophoretic mobility mean of -0.000166 cm^2/Vs. As the standard values of -25 to +25 mV are said to be stable particles from the above results, it was found to be stable.

Shape and surface morphology by SEM

Microbead morphology was examined with LEO 435VP scanning electron microscopy. SEM showed that EC-alone microbeads had distinct, rough exterior surfaces, perhaps owing to PVA cross-linking. Smooth, crack-free spherical ethyl cellulose microbeads have a smooth texture.

DSC

As the DSC thermogram is shown in Figure 9, a piercing endothermic peak at 236.95°C was observed in the finalized formulation, corresponding to the melting point observed in DSC of pure drug was 236.95°C as shown in Figure 9.

XRD

For identification of crystal assembly modification throughout the raw material treatment, which is exposed to thermal and mechanical stress during the formulation development. XRD pattern of EP and final formulation were carried out. The pure drug DDEA obtained sharp peaks of diffraction at an angle of 2 theta value of 19.56°. The value of the relative degrees of crystallinity is 1.0. So XRD analysis reveals that there is no change in the crystals Figure 10.

FTIR spectroscopy (Table 8)

Using FTIR, eplerenone was tested for compatibility with the formulation's polymeric excipient. On the 15th day, the formulations' FTIR spectra were compared to the pure drug's at RT (25°C). The findings showed that pure eplerenone's distinctive absorption peaks emerged in the samples without changing locations, suggesting no chemical interaction with polymers.

Compatibility studies

The pure drug samples' FTIR spectrums were recorded (Figure 11) and interpretation was done. The original characteristic, IR absorption peak responses of the pure drug (Eplerenone) observed at 2996.37 cm^{-1} (Aliphatic C-H stretching), 3010.17 cm^{-1} (Ole finic C-H stretching), 1691.33 cm^{-1} (R2 C=O (Keto), 1653.76 cm^{-1} (Ole finic C=C stretching), 1270.02 cm^{-1} (C-O stretching), these peaks were also observed in formulation spectra with slight deviation of Aliphatic C-H stretching at 2975.30 cm^{-1}, olefinic C-H stretching at 3087.17 cm^{-1}, R2 C=O (Keto) at 1690.00 cm^{-1}, olefinic C=C stretching at 1638.58 and C-O stretching at 1233.52 cm^{-1}, which reveals that eplerenone was not interacted with polymers as showed in Figure 11.

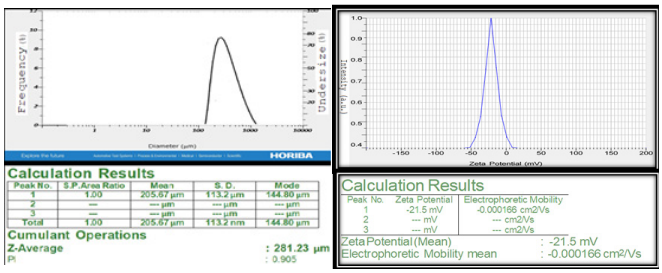

Figure 7: Particle size and zeta potential of formulated drug

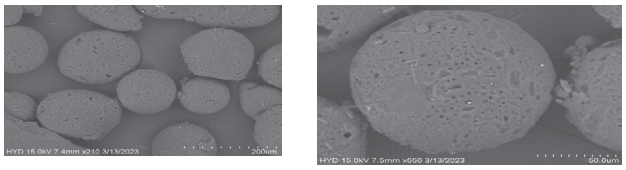

Figure 8: Floating microbeads of formulated drug

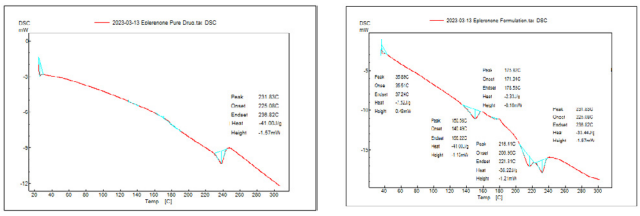

Figure 9: DSC thermogram of pure drug and formulated drug

In-vitro drug release (Figure 12)

The dissolution studies were conducted by using dissolution media PB 7.4 pH. The formulations F1-F18 containing ethyl cellulose and polyvinyl alcohol showed a release between 98.47 ± 0.66% to 66.56 ± 0.07% after 24 hours. This shows that sustained release was observed with the increase in polymer ratio for corresponding polymer levels from -1 to +1. The formulation F9 showed a maximum release of 98.47% of the drug up to 24 hours. The floating microspheres showed the release of the drug up to 12 hours and were found to behave in a sustained manner. This is due to the polymer used was, ethyl cellulose being a low-permeable and water-insoluble polymer. Among all formulations, formulation F9 has a maximum entrapment ratio with a higher amount of drug release up to 98.47%. The release was optimized with the software and formulation F18 release was found to be 95.80%. The observed response and predicted response was 96.62 and 95.80%, the %predicted error was found to be +0.84. The difference between the predicted and observed responses was less than 5%, which is within the limits.

Release kinetics (Figure 13, Table 9)

The *in-vitro* drug diffusion data was fitted to zero order, first order, Higuchi matrix, and Korsmeyer-peppas models to explain drug release and release rate dynamics from dosage forms. The Figure 13 linear drug release following matrix diffusion kinetics. Thus, drug release from floating alginate microbeads occurred mostly by diffusion.

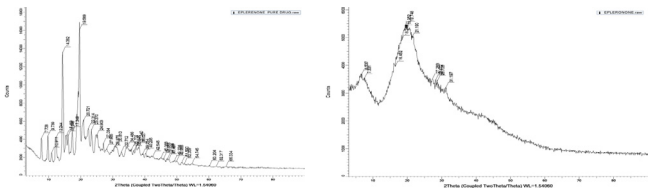

Figure 10: XRD of pure drug and formulated drug

Table 7: Relative intensity of pure drug and formulated drug

Code	*Angle*	*d-value*	*Relative intensity*
Eplerenone pure drug	19.56	4.53	I
Eplerenone formulation	19.74	4.49	1

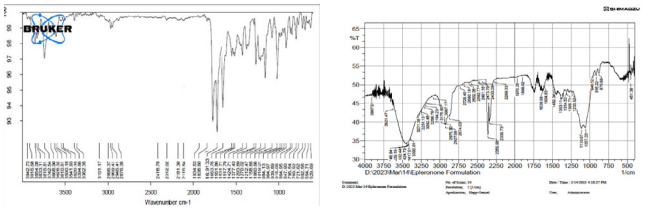

Figure 11: FTIR of pure drug and formulated drug

Table 8: FTIR spectra data of EP and physical mixtures

Functional group	*Range (cm^{-1})*	*Drug (Eplerenone) (cm^{-1})*	*Physical mixture (cm^{-1})*
Olefinic =C-H stretching	3000–3100	3010.17	3087.17
Aliphatic C-H stretching	2850–3000	2996.37	2975.30
C-O stretching	1245	1270.02	1233.52
R_2 C=O (Keto)	1695	1691.33	1690.00
Olefinic C=C stretching	1642	1653.76	1638.58

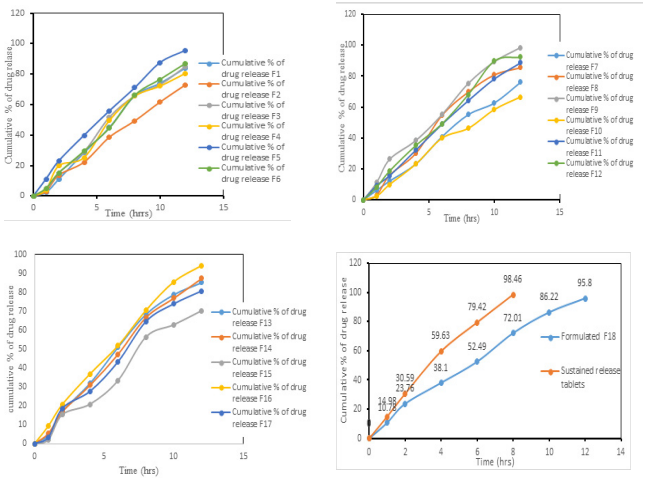

Figure 12: *In-vitro* dissolution profile of F1-F17 and comparative graph sustained release tablet and F18

Stability study (Table 10)

A stability study was conducted for formulation F18 at 25°C ± 2°C/60 ± 2%RH for 6 months as shown in Figure 14.

Table 9: Kinetic model parameters

F. code	*Zero-order R^2 values*	*First-order R^2 value*	*Higuchi R^2 value*	*Kors Meyer Peppas's plot*	
				R^2 value	*"n" values*
F18	0.9924	0.9059	0.9870	0.6810	0.81

Table 10: Stability study data for drug content and *in-vitro* drug release

Formulation code	*Final Formulation F18*	
	Initial	*After 6 months*
Drug entrapment efficiency (%)	89.01 ± 0.27	88.35 ± 0.48
In-vitro drug release (%)	95.82 ± 0.832	95.82 ± 0.10

*n=3, Avg ± S.D

Table 11: Suggested optimum formula

EC (mg)	*DCM: Methanol (mL)*	*stirring time (hours)*
343.944	2.94548	1.45931
Predicted particle size (µm)	Predicted drug entrapment efficiency (%)	Predicted cumulative % of drug release at 12 hours
270.61	88.46	95.07
271.55	88.04	95.99
271.54	87.55	96.34
Avg = 271.234 ± 0.539	Avg = 88.00167 ± 0.456	Avg = 95.80 ± 0.656

*n=3, Avg ± S.D

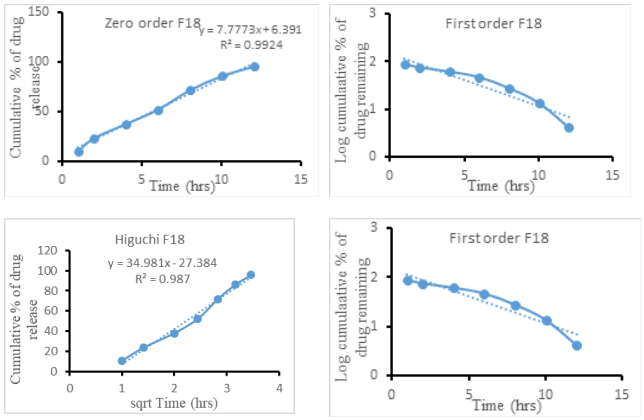

Figure 13: *In-vitro* drug release kinetic

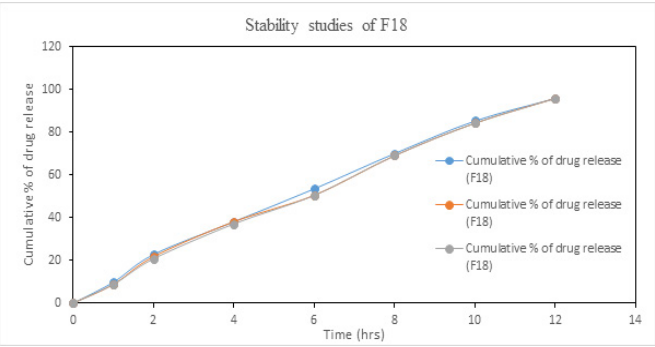

Figure 14: Stability studies graph of F18

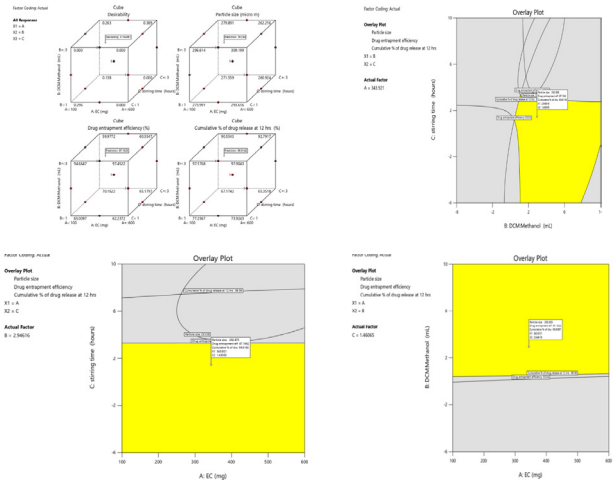

Figure 15: Overlay plot of response

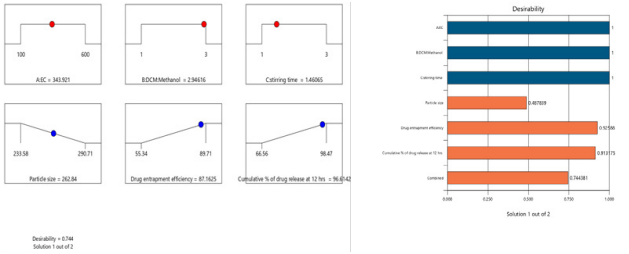

Figure 16: RAMPS and desirability

Table 12: Predicted and observed response of final formulation

Dependent variable Y	*Observed response*	*Predicted response*	*Predicted error%*	*C.V.%*
Particle size (µm) (Y_1)	262.86	271.23	- 3.18	2.28
Drug entrapment efficiency (%) (Y_2)	87.18	88.00	- 0.94	6.82
In-vitro drug release study at 12th hours (%) (Y_3)	96.62	95.80	+ 0.84	1.02

Formulation F18 was selected for stability tests based on design expert software output for %drug entrapment and in vitro drug release. At room temperature, the formulations did not alter appearance, suggesting stability. After 6 months, formulations held at the conditions described showed no significant change in drug content or *in-vitro* drug release. The formulation is stable and has an estimated 180-day shelf life under normal circumstances. The overlay of responses and desirability are shown in figures 15 and 16. The optimized formula details and predicted and observed response of final formulation are presented in table 11 and 12.

CONCLUSION

The study showed that fluid evaporation can be used to make floating microbeads that contain eplerenone. This method can be used to successfully make Eplerenone-loaded floating microbeads. The study showed that making floating Eplerenone microbeads with controlled release is a good way to cut down on how often you have to take your medicine.

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