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Formulation and Evaluation of Floating Bioadhesive Tablet of Candesartan cilexetil Using 3^2 Factorial Designs

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ABSTRACT

Objective: The objective of the work is to formulate candesartan cilexetil floating bioadhesive tablets which can considerably improve the bioavailability of medicine underneath the condition of redoubled continuance of drug in abdomen.
Methods: Floating bioadhesive tablet was ready by direct compression of chemical compound like HPMCE15 and Carbopol934p together.
Result: After analysis of different evaluation parameter and drug release, F4 batch was selected as promising formulation for delivery of candesartan cilexetil floating bioadhesive tablets with 91.22% drug release at 12^{th} h.
Conclusion: Among the further batches, the F4 batch was selected as an optimized batch as a result of the pre-compression and post-compression parameters results area unit satisfactory.

Keywords: Candesartan cilexetil, Floating bioadhesive tablets, Polymer, Total floating time.

INTRODUCTION

Among the assorted routes of administration oral intake has long been the foremost convenient and ordinarily utilized route. There are a unit some ways to intend changed unleash dose forms for oral administration and one amongst them is floating bioadhesive tablets.[1]In recent years, several tries are created give to supply to produce} dose kind which is able to provide longer transit time and additional economical absorption for specific medicine that have a window of absorption or stability issues.[2] Floating dose kinds are designed to possess decent buoyancy to float on the highest of abdomen contents and prolong viscus duration of the dose form. additionally, interest has been directed to the event or oral bioadhesive systems to find the oral dose kind on the tissue layer wall of the abdomen or internal organ to extend the residence of the drug within the gastrointestinal tract.[3] FBDS may be a gastro-retentive dose kind, which may prolong the viscus duration to provide a suitable drug bioavailability. Floating bioadhesive drug delivery system (FBDDS) is appropriate for medicine with associate degree absorption window within the abdomen or the higher gut, for medicine that acts domestically within the abdomen and for medicine that area unit poorly soluble or unstable within the viscus fluid FBDDS or hydro-dynamically balanced systems have a bulk density not up to viscus fluid and so stay buoyant within the abdomen while not poignant the viscus voidance rate for a protracted amount of your time, supported the mechanism of buoyancy, 2 clearly completely different technologies, i.e., non-effervescent and effervescent systems are employed in the event of FBDDS. The bubbling system uses matrices ready with swellable polymers and effervescent elements, for instance, saleratus and acid or saturated fatty acid. In non-effervescent FBDDS, the drug mixes with a gel-forming matter, that swells in reality with viscus

fluid once oral administration to keep up a comparatively stable form and a bulk density of but unity inside the outer gelatinlike barrier. The air at bay by the swollen chemical compound confers buoyancy on these dose forms. [4,5] Candesartan cilexetil, a prodrug, is hydrolysed to candesartan throughout absorption from the digestive tube and may be a Class-II drug low solubility, high permeableness, with anti-hypertensive properties. candesartan cilexetil by selection blocks the binding of angiotensin II to AT1 in several tissues. This inhibits the AT1-mediated vasoconstrictor associate degreed aldosterone-secreting effects of angiotensin II and ends up in an overall decrease in force per unit area.[6] The objective of this work was to develop a completely unique modified-release pill created by the direct compression method. The pill possesses an associate degree distinctive combination of bioadhesion and floatation to prolong the viscus duration of candesartan cilexetil.[7] In this study, a computer optimization method victimization factorial style was utilized to develop bioadhesive and floating pill formulations and verify the significances of formulation variables on the response properties of tablets. Finally, associate degree optimum pill formulation was selected victimization the technique of response surface methodology.[8]

MATERIALS AND METHODS

Materials

Candesartan cilexetil was procured from Yarrochem, Mumbai. HPMCE15 were obtained from Chemdyes Corporation, Gujarat. Carbopol 934p were obtained from Research Lab-Fine Chem. Industries, Mumbai. MCC, Sodium Bicarbonate, Magnesium stearate, Talc was obtained from Thomas Baker Pvt. Ltd, Mumbai. For analytical grade all reagents were used.

Method

Preliminary trials:

Preliminary experiments were conducted to investigate the influence of Hydroxypropyl methylcellulose (HPMC E15M), citric acid and sodium bicarbonate on the in vitro drug release and buoyancy, and to select an appropriate concentration of Hydroxypropyl methylcellulose (HPMC E15M) and sodium bicarbonate for further study. For each formulation (1-10, as listed in table 1), weigh accurately drug, polymer and other excipients. The active ingredient drug (Candesartan cilexetil), polymer and other excipients were sifted through sieve no. 100#. All the material were collected in mortar and pestle and triturated, to prepare a homogeneous mass. The blend was lubricated with magnesium stearate. After proper mixing with lubricant i.e., magnesium stearate, the prepared blend was compressed into tablets by using 6mm punch using 8-station tablet punching machine.

Table 1: Trials batches of formulation

INGREDIENTS	A1 (mg)	A2 (mg)	A3 (mg)	A4 (mg)	A5 (mg)	A6 (mg)	A7 (mg)	A8 (mg)	A9 (mg)	A10 (mg)
CANDESARTAN CILEXETIL	11	11	11	11	11	11	11	11	11	11
HPMC E15	30	30	25	35	20	35	20	30	25	30
CARBOPOL 934	10	10	15	10	5	15	10	15	7	10
SODIUM BICABONATE	15	20	20	20	20	20	20	20	20	25
CITRIC ACID	1	1	1	1	1	1	1	1	1	1
MAGNESIUM STEARATE	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
TALC	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MCC	32	27	27	22	42	17	37	22	35	22
TOTAL	100	100	100	100	100	100	100	100	100	100

Experimental Designing and Analysis:

Factorial Design of experiment (DOE) has been largely used in pharmaceutical field to study the effect of formulation variables and their interactions on response variables. Statistical

experimental design was accomplished using a software DESIGN EXPERT® version 11 (Stat-Ease Inc., Minneapolis, USA). Response surface graphics were used to show the factor interaction amongst the considered variables. A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels coded for low, medium and high (−1, 0 and 1, respectively), and experimental trials were carried out at all possible combinations. The amounts of HPMC E15 (X1) and sodium bicarbonate (X2) were selected as independent variables. The times required for % drug release (Y1), and floating lag time in second (Y2) were selected as dependent variables. A total of 9 experimental runs were essential for analyzing the interaction of each level on formulation characters and to optimize. [9,10]

Table 2: Variables in coded value

Formulation Code	X_1	X_2	HPMC (X1)	Sodium Bicarbonate (X2)
F1	-1	-1	25	15
F2	0	-1	30	15
F3	1	-1	35	15
F4	-1	0	25	20
F5	0	0	30	20
F6	1	0	35	20
F7	-1	1	25	25
F8	0	1	30	25
F9	1	1	35	25

Table 3: Factorial batches of formulation

INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
CANDESARTAN CILEXETIL	11	11	11	11	11	11	11	11	11
HPMC K15M	25	25	25	30	30	30	35	35	35
CARBOPOL 934	10	10	10	10	10	10	10	10	10
SODIUM BICABONATE	15	20	25	15	20	25	15	20	25
CITRIC ACID	1	1	1	1	1	1	1	1	1
TALC	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MAGNESIUM STEARATE	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MCC	37	32	27	32	27	22	27	22	17
TOTAL	100	100	100	100	100	100	100	100	100

1] PREFORMULATION STUDIES:

a) Ultraviolet (UV)-spectrum:

The Candesartan Cilexetil solution in 0.1N HCL screened in the range of 200–400 nm.[11]

b) Melting point:

The melting point of the drug was determined using packing a capillary method.

c) Construction of calibration curve:

Candesartan cilexetil of about 100mg was dissolved in appropriate amount of 0.1N Hydrochloric acid and makeup the volume to 100ml to make 1000ug/ml. The above solution was diluted appropriately to get concentration of 200ug/ml. From this solution, working standard solution of 20-100microgram/ml was prepared by dilution with0.1N Hydrochloric acid. The absorbance (also called optical density) of solution was measured at 255nm compared to reagent blank.[12]

d) Fourier transmission infrared (FT-IR) spectroscopy:

Fourier transform instruments determine the absorption spectrum for a compound in the common range 4000 to 400cm-^{1}. Preparation of samples: A base line modification was made using dried KBR. Weighed quantity of the drug was mixed carefully with potassium bromide (dried at 40-50°C) which was then compressed below 10-ton pressure in a hydraulic press to form a pellet which was then scanned from 4000-400cm-^{1}. [13,14]

2] Drug excipients compatibility studies:

Fourier-transform infrared (FTIR) spectrum matching approach was used for recognition of any possible chemical interaction between the Candesartan cilexetil and polymers. IR spectroscopy was conducted using a FTIR spectrophotometer (Jasco FT-IR 410), and the spectrum was recorded in the wavelength region of 4000–400/cm. [15]

3] Physical properties of drug powder:

The drug Candesartan cilexetil undergoes over various tests such as Bulk density, Tap density, Carr's compressibility, Hausner's ratio, Angle of repose to identify its physical properties. [16,17]

4] Evaluation of tablets:

Appearance: The general appearance of the tablets was checked.

Hardness: Hardness of the tablets measured by using a Monsanto hardness tester. The tablet hardness has been defined as the force required to break the tablet in diametric compression test.[18]

Weight variation:

To study the weight variation, 10 tablets of each formulation were weighed using an electronic digital balance. The average weight of each tablet was calculated and the percentage deviation in weight was calculated.[18]

Friability:

Friability testing was done by using Roche friability tester. A sample of 5 tablets was taken and was carefully dedusted prior to testing. The tablets were accurately weighed and placed in the drum of the Roche friabilator. The drum was rotated for 100 times at 25rpm and the tablets were removed, dedusted and accurately weighed.[19]

$$\text{friability(F)} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

Drug content:

Powder corresponding to 11 mg of Candesartan cilexetil was precisely weighed and moved into a 100 ml volumetric flask and dissolved in suitable quantity of 0.1N HCl by sonicating for 15-20 minutes. The prepared solution was filtered, diluted up to 100ml with 0.1N HCl and analyzed using a UV-visible spectrophotometer at 255nm. [19]

5] In vitro buoyancy studies:

The in vitro buoyancy study was categorized by determining floating lag time and total floating time. The time occupied for the tablet to appear on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and the interval of the time the dosage form continuously remains on the medium is called the total floating time (TFT). The test was performed by placing the tablet in the 100ml beaker containing 0.1N HCl. The time of duration of floatation was observed visually.[20]

6] Measurement of bioadhesive strength:

Bioadhesive force of the tablets was measured on a modified physical balance. The apparatus consisted of an improved double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been changed by a glass slide with plastic hang suspended by Teflon rings and copper wire. Another Teflon block of 3.8 cm diameter and 2 cm height was manufactured with an upward protuberance of 2 cm height and 1.5 cm diameter on one side. This was reserved in a beaker, which was then positioned below the left hand set of the balance. The goat gastric mucus membrane was used as the model membrane and pH 1.2 buffer solution was used as a moistening fluid. The goat stomach mucosa was saved in tyrode solution at 37^{O}C for 2 hrs. The mucus membrane was separated and washes away carefully with 1.2 pH buffer solution. It was then knotted to a Teflon-coated glass slide and this slide was secured over the protuberance in the Teflon block using a thread. The block was then reserved in a beaker containing pH 1.2 buffer solutions at a level that just be in contact with the membrane so as to moisten the membrane. By carrying a 5 g weight on the right pan, two sides were well-proportioned. The beaker with the Teflon block was reserved below the left-hand setup of the balance. The tablet was stuck to the lower side of the left-hand side pan. Five grams weight from the right pan was then removed. This let down the glass slide end to end with the tablet over the membrane through a weight of 5.0 g. This was reserved uninterrupted for 5 min. Then, the weights on the right-hand side were gradually added in increments of 0.5 g till the tablet just

divided from the membrane surface. The surplus weight on the right pan, i.e., total weight minus 5 g was taken as a quantity of the bio-adhesive strength. By using this weight analyze the bio-adhesive force using following formula:[21]

$$\text{force of adhesion (N)} = \frac{\text{bioadhesive strength}}{100} \times 9.81$$

7] Swelling index:

The swelling behavior of the dosage unit was measured by studying its weight gain. The swelling index of the tablets was determined by placing a tablet in petri dish containing 0.1N HCl and after 1,2,3,4,6,8 and 10 hours each, tablet in the petri plate was withdrawn, blotted with tissue paper to eliminate excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point. Swelling index was calculated using the following formula:[22]

$$\text{swelling index} = \frac{\text{wet weight of tablet} - \text{dry weight of tablet}}{\text{dry weight of tablet}} \times 100$$

8] In vitro dissolution studies:

Drug release studies were carried out in USP type II dissolution rate test apparatus using 0.1 N HCl (pH 1.2) as dissolution medium at 37 ± 0.5∘C.

Dissolution protocol:

- Dissolution apparatus - USP apparatus no. 2 (paddle)
- Temperature - 37 ± 0.5 ^{0}C
- RPM - 50
- Dissolution medium - 0.1N HCl (pH 1.2)
- Volume of dissolution medium - 900 Ml
- Volume of sample removed - 5 Ml
- Sampling intervals - 0,0.5,1,2,3,4,5,6,7,8,9,10,11,12,14,16 hrs.
- No. of replicates – 3

Every time the sample withdrawn was replaced by fresh dissolution medium maintained at the same temperature. The sample removed was filtered and analyzed at 255nm using UV-Vis spectrophotometer. [23,24]

9] Kinetics of Drug Release

An appropriate drug release test is required to characterize the drug product and ensure batch to batch reproducibility and consistent pharmacological/biological activity. The release of drug from a sustained release formulation is controlled by various factors through different mechanisms such as diffusion, erosion or osmosis. Several mathematical models are proposed by many researchers to describe the drug release profiles from various systems. The drug release kinetics are studied by plotting all the data obtained from the in vitro release in various kinetics models like zero order, first-order, Higuchi, Hixon-Crowell, Korsemeyer and Peppas models to ascertain the kinetic modelling of drug release. There are several linear and non-linear kinetic models widely used to describe release mechanisms and to compare test and reference dissolution profiles.[25]

RESULTS AND DISCUSSION

1] Preformulation studies:

a) Ultraviolet (UV) spectrum:

The solution of Candesartan cilexetil in 0.1 N HCL (pH 1.2) was found to exhibit maximum absorption (λ_{max}) at 255 nm after scanning in the range of 200-400 nm. (Figure.1)

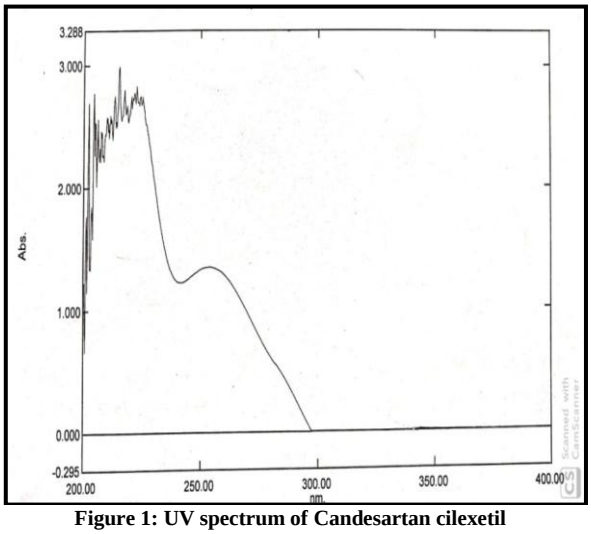

Figure 1: UV spectrum of Candesartan cilexetil

b) Melting point:

The melting point of drug by capillary method was found to be approximately 164±0.5°C.

c) Construction of calibration curve:

UV method: The calibration curve for CANDESARTAN CILEXETIL drug was determined in 0.1N HCL pH 1.2 (Figure.2)

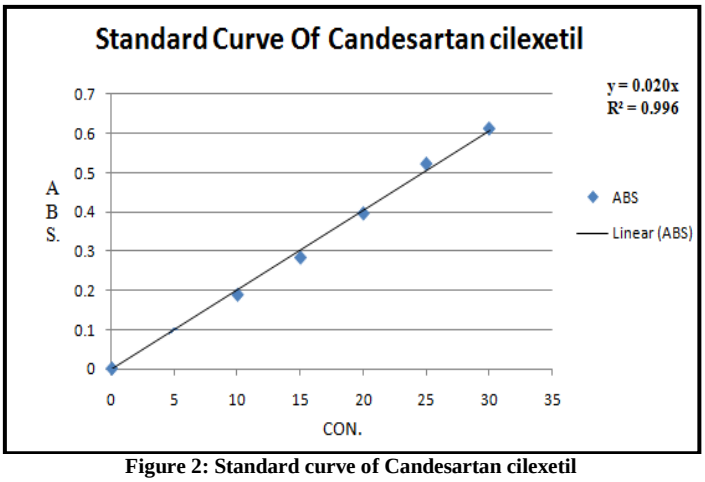

Figure 2: Standard curve of Candesartan cilexetil

d) Fourier transmission infrared (FT-IR) spectroscopy:

The identity of drug was confirmed by comparing IR spectrum of drug with reported spectrum of Candesartan cilexetil. (Figure.3)

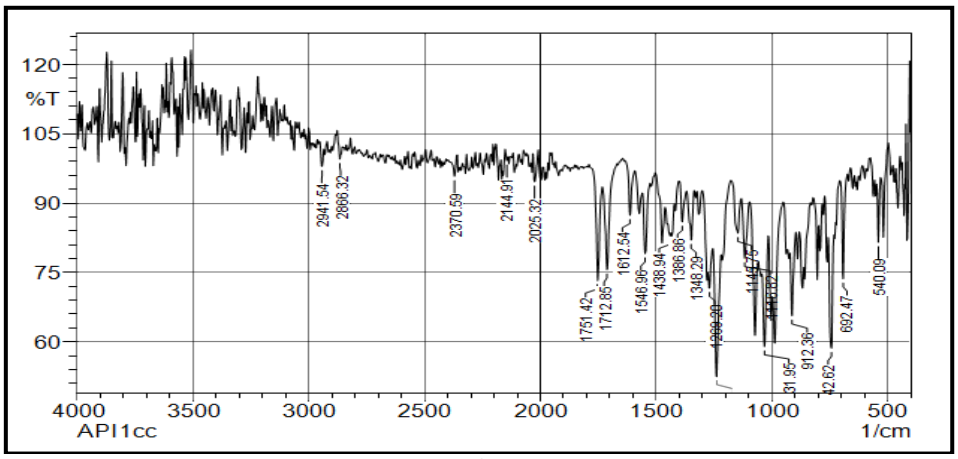

Figure 3: FTIR spectrum of drug Candesartan cilexetil

2] Drug excipients compatibility studies:

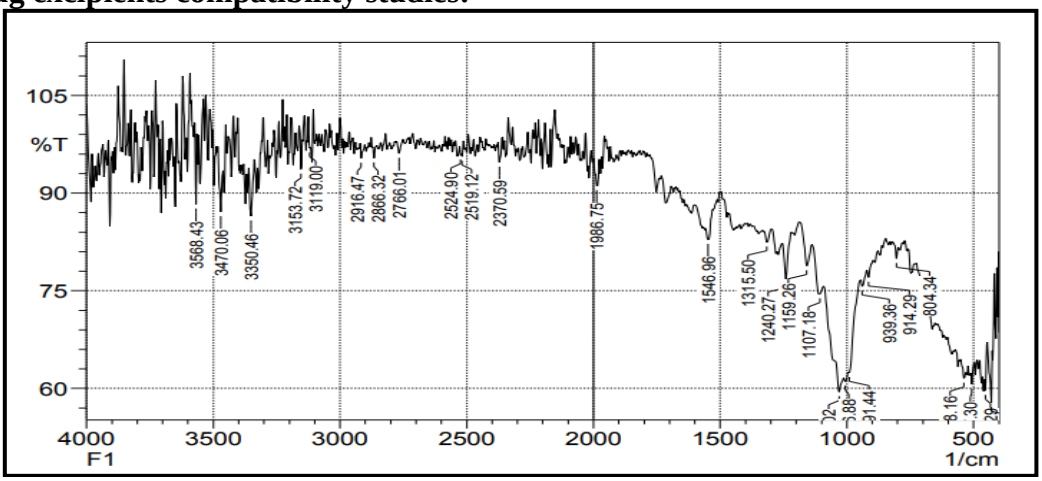

Figure 4: FTIR spectrum of Drug + Excipients

The FTIR spectra of the pure drug and drug excipients physical mixture indicated that characteristics bands of drug were not altered, without any change in their position, indicating no chemical interactions between the drug and excipients used.

3] Physical properties of drug powder

The prepared powders were characterized for angle of repose, bulk density, tapped density, Hausner's factor, Carr's index, and compressibility index and the values were reported in Table.(Table 4)

Table 4: Pre-compression parameter of blend

Batches	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (%)	Hausner's ratio	Angle of repose (Degree)
F1	0.76	0.83	8.43	1.09	23.66
F2	0.66	0.71	7.57	1.07	22.57
F3	0.65	0.71	8.45	1.09	23.74
F4	0.71	0.79	10.12	1.11	24.31
F5	0.70	0.76	7.89	1.08	22.04
F6	0.74	0.83	10.84	1.12	21.31
F7	0.72	0.81	11.11	1.12	24.55
F8	0.66	0.71	7.04	1.07	24.87
F9	0.70	0.76	7.89	1.08	22.30

4] Evaluation of bioadhesive floating tablet:

The results were represented in (Table 5).

Table 5: Post compression evaluation of tablet

Formulation code	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	% Weight variation	% drug content
F1	5.12	3.04	4.9	0.72	99	96.36
F2	5.11	3.10	5	0.74	100	92.97
F3	5.13	3.06	5.2	0.71	96	95.34
F4	5.11	3.04	5.1	0.75	98	97.49
F5	5.10	3.05	5.6	0.72	99	92.22
F6	5.11	3.05	5.4	0.70	97	96.86
F7	5.12	3.12	5	0.71	100	94.85
F8	5.11	3.11	5.6	0.75	99	96.96
F9	5.10	3.04	5.7	0.73	98	94.22

5] In vitro buoyancy studies:

Floating lag time of all nine batches shown in (Table 6) (Figure 5).

Table 6: Floating evaluation of tablets batches F1—F9

Batch No.	Floating Lag Time (Sec)	Total Floating Time (Hrs.)
F1	50	12
F2	45	14
F3	28	14
F4	52	>16
F5	44	16
F6	32	12
F7	58	12
F8	39	12
F9	35	12

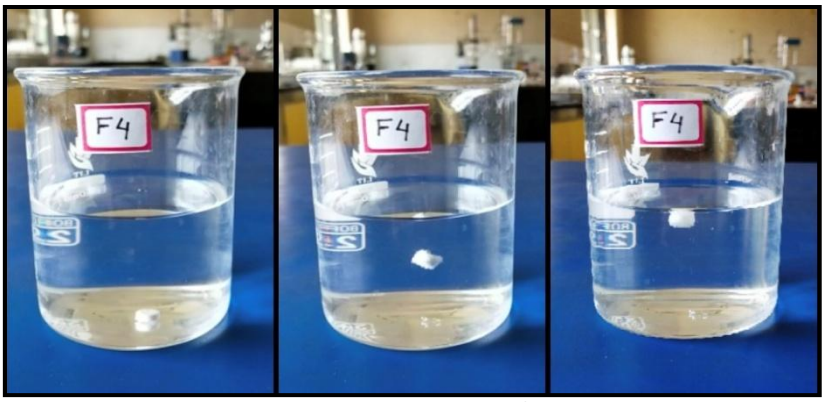

Figure 5: Floating behaviour of tablet

6] Measurement of bioadhesive strength:

The mucoadhesive strength of the tablet was dependent on the property of the bioadhesive polymers, which on hydration adhere to the mucosal surface and also on the concentration of polymer used. Bioadhesive force values ranged from 1.07 to 1.86. Results were represented in (Table 7) (Figure.6)

Table 7: Bio-adhesive evaluation of tablets batches F1—F9

Batch No.	Bio-adhesive Strength (Gm)	Bio-adhesion Force (N)
F1	11	1.07
F2	13	1.27
F3	14	1.37
F4	19	1.86
F5	11	1.07
F6	13	1.27
F7	18	1.76
F8	12	1.17
F9	14	1.37

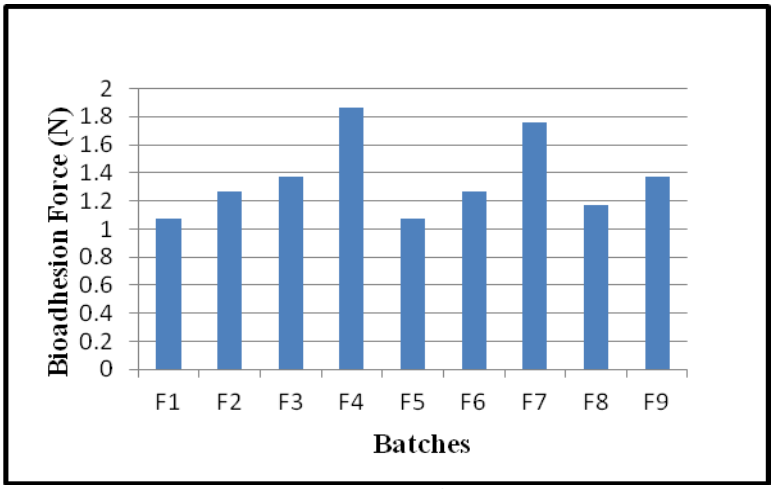

Figure 6: Bio-adhesive strength of tablet batches F1-F9

7] Swelling index:

Swelling index profile of all formulations is shown in (Figure.7).

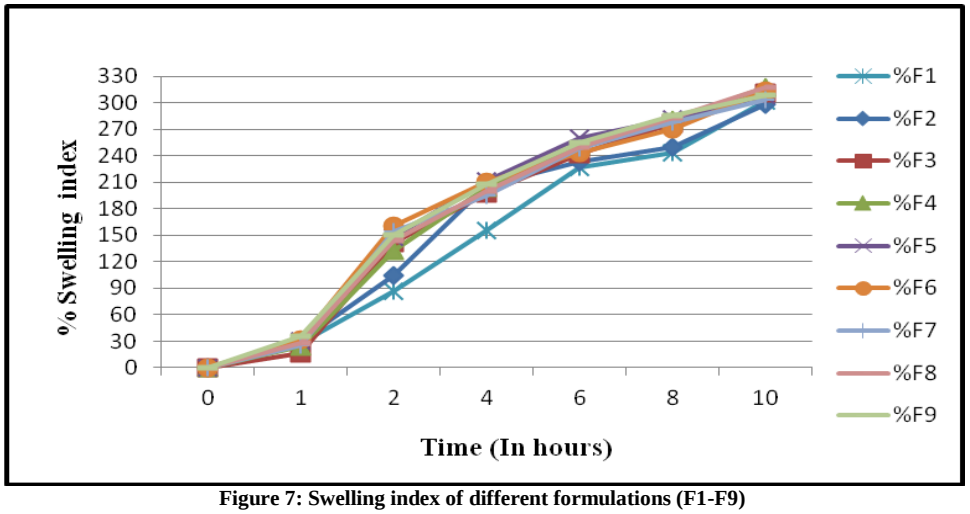

Figure 7: Swelling index of different formulations (F1-F9)

8] In vitro dissolution studies:

All the nine formulations were subjected to in vitro dissolution studies using a USP Type-II dissolution test apparatus. The in-vitro dissolution studies of the batches concluded that the batches F2 and F3 over 14 hrs and F1, F6, F7, F8, F9 released for 12 hrs, F5 released for 16 hrs & F4 for more than 16 hrs. The F4 Batch showed that the best result as the percent cumulative drug release of F9 is 91.22% at 16 h.

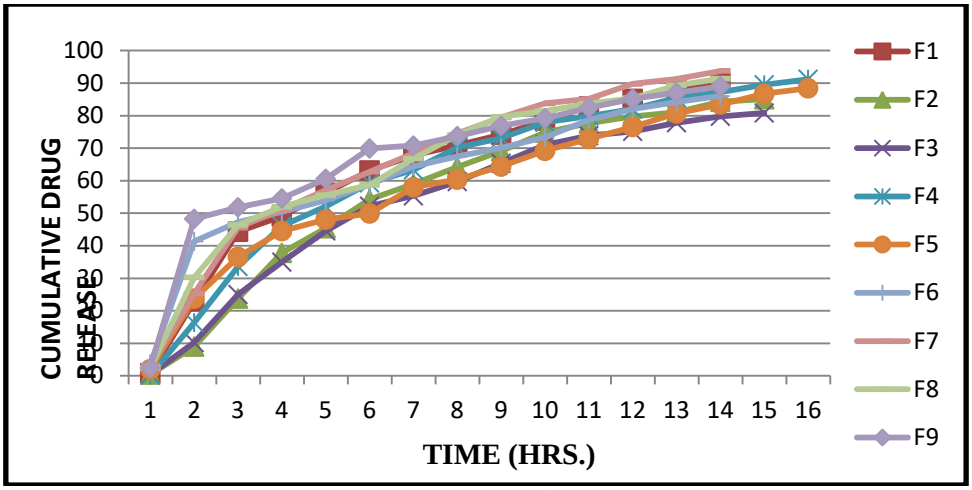

Figure 8: In vitro drug release profile of batches (F1-F9)

9] Kinetics of Drug Release:

The dissolution data of all batches F1 to F9 was fitted to zero order, first-order, Higuchi, Hixson Crowell, Korsemeyer and Peppas. The method was adopted for deciding the most appropriate model. The release profile of the best batch F4, fitted best to the Higuchi model (R^2=0.998). The priority should be given to the model with the highest R^2 value. Thus, it may be concluded that drug release from F4 batch tablet is best explained by the Higuchi model. (Table 8) (Figure.9)

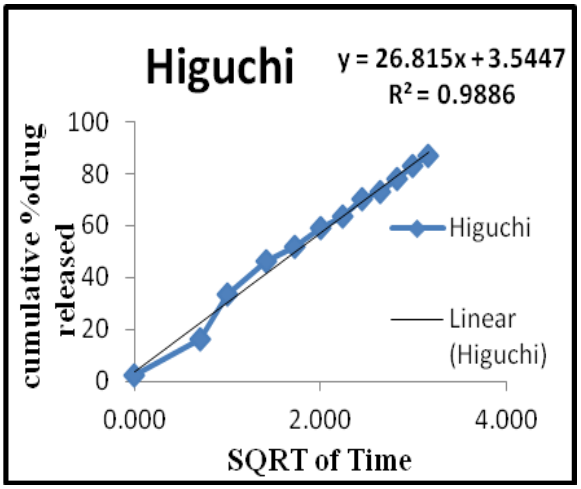

Figure 9: Higuchi model of optimized F4 formulation

Table 8: Kinetic release data of different model for optimized formulation F4

Release kinetic model	Regression coefficient (R^2)
Zero order	0.889
First order	0.984
Higuchi model	0.988
Korsmeyer- Peppas model	0.879
Hixson- Crowell model	0.968

Experimental Designing and Analysis:

A 3^2 full factorial design was used to investigate effect of two factors-Polymer viz HPMC K15M and effervescent agent sodium bicarbonate. The factorial design was carried out using the software DESIGN EXPERT® version 11 (Stat-Ease Inc., Minneapolis, USA). Analysis of variance (ANOVA) was applied for estimation of significance of the model. Using a 5% significance level, a model was considered significant if the $p < 0.05$. It was found that for responses Y1 and Y2, quadratic contribution and linear contribution model were significant ($p<0.001$), respectively.

Response 1: dissolution

The **Model F-value** of 210.37 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB is significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Coded Factors

Dissolution rate (Y_1) = +88.00 +3.00*A-3.17*B +1. 50*AB

Final Equation in Terms of Actual Factors

Y1 = +118.74359-0.600000*HPMC E15 - 2.43333*Na Bicarbonate+0.060000*HPMC E15*Na Bicarbonate

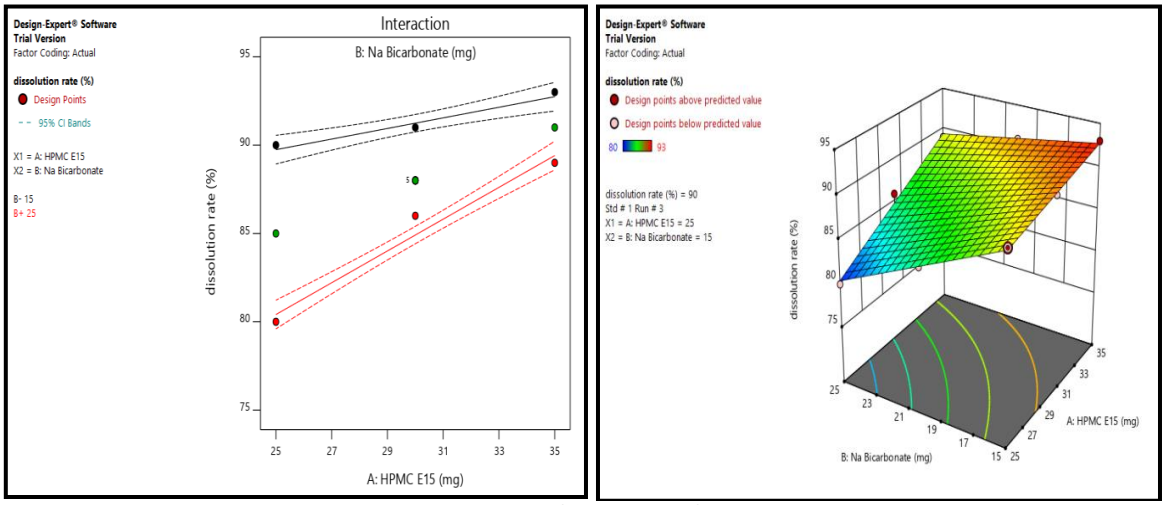

Figure 10: Interaction plot and 3D surface diagram of response 1(dissolution rate)

Response 2: Floating lag time (FLT):

The **Model F-value** of 49.61 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Coded Factors

Floating Lag Time [Y2] = +43.00 +1.50*A -10.83*B

Final Equation in Terms of Actual Factors

Y2 = +77.33333+0.300000*HPMC E15 - 2.16667*Na Bicarbonate

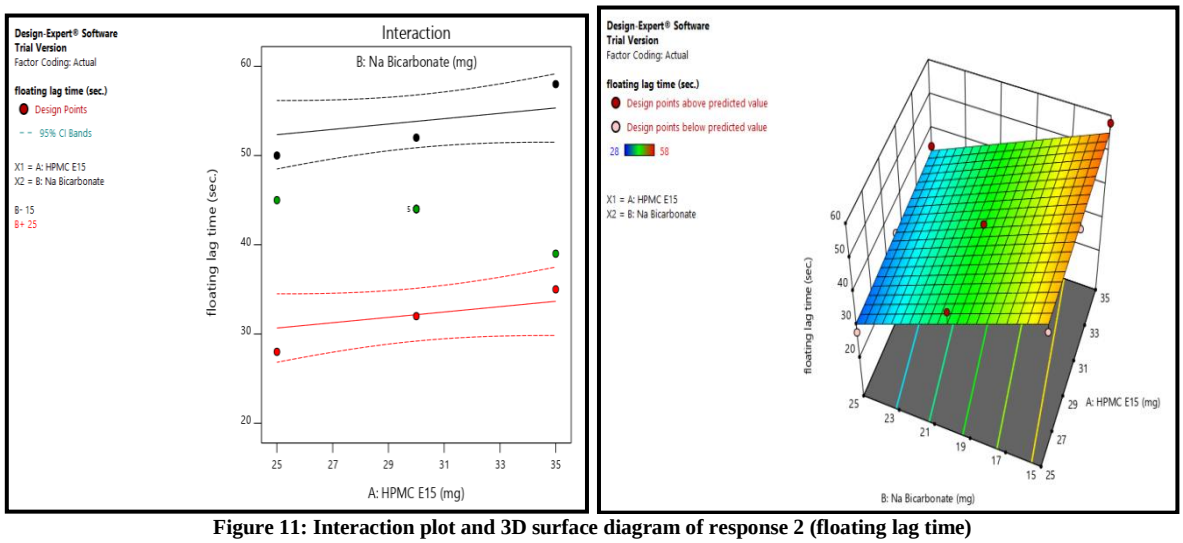

Figure 11: Interaction plot and 3D surface diagram of response 2 (floating lag time)

Figures (4) show the plot of the amount of HPMC E15 (X1) and amount of sodium bicarbonate (X2) versus drug release and floating lag time, respectively. The plot was drawn using a software DESIGN EXPERT® version 11 (Stat-Ease Inc., Minneapolis, USA). The data demonstrate that both X1 and X2 affect the drug release and floating lag time.

CONCLUSION

Floating- Bioadhesive tablets of Candesartan cilexetil was prepared by using HPMC E15 and Carbopol 934P polymers, sodium bicarbonate as an effervescent base to achieve optimum buoyancy and magnesium stearate as lubricants.

Using 3^2 full factorial design, the effect of interaction of two independent variables - Polymer X1 (HPMC), gas generating agent X2 (Sodium bicarbonate) - on drug release and floating lag time was studied and optimized. Further, the study showed that all two dependent variables had significant effect on the selected responses.

The in-vitro dissolution studies of the batches concluded that the batches F2 and F3 over 14 hrs and F1, F6, F7, F8, F9 released for 12 hrs, F5 released for 16 hrs & F4 for more than 16 hrs. Out of which, F4 was found to be the best formulation.

Studies revealed that the F4 batch follows Higuchi model release kinetics and coefficient of regression is highest for this model which is R^2= 0.998.

From this, it was concluded that the combinations of polymers affect the release of the drug. Increasing the concentrations of polymers decreases the release of the drug over the period of time, thereby giving a sustained release of the drug.

Also, the floating- bioadhesive drug delivery system might be a better combinational option over using only either Floating or bioadhesive systems for better gastroretention and sustained release of the drug.

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