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Formulation, development and optimization of gastroretentive floating drug delivery system of Olmesartan Medxomil

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ABSTRACT

Objective: The objective of the present study was to develop an optimized gastroretentive floating drug delivery system of Olmesartan Medoxomil and investigate the effect of hydrophilic retardant on invitro release by using 3^2 full factorial design. **Methods:** Floating tablets of olmesartan medoxomil were prepared by direct compression method using effervescent technique by employing two different grades of HPMC. (HPMC K4M and HPMC K100M). Sodium bicarbonate was incorporated as gas generating agent. The concentration of HPMC K4M (X_1) and concentration of HPMC K100M (X_2) were selected as independent variables. The floating lag time, total floating time and time taken to 80% drug release were selected as dependent variables. Targets were defined for each response so as to select the optimim formula using numerical optimization. All the floating matrix tablets formulations were subjected to pre-compression and post-compression parameter evaluation. **Result:** The results indicated that the concentration of X_1 and X_2 significantly affected the floating lag time, total floating time and T_{80}. Drug release properties were affected by concentration of HPMC K4M and HPMC K100M. Optimized formulation F9 with increased equal concentrations of X1 and X2 and sodium bicarbonate showed good physical propreties with short lag time of 55sec and T_{80} of 18 hrs. **Conclusion:** The drug release from the tablet was sustained and non fickian transport of drug from the tablet was confirmed. The optimized formulation was stable when kept for short term stability study for one month.

Keywords: Olmesartan Medoxomil, Effervescent technique, Direct Compression Method, 3^2 Full Factorial Design, Short Term Stability Study.

Introduction

Controlled release drug administration means not only the prolongation of the duration of drug delivery, similar to the objective in sustained release and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. Oral controlled release drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a pre-determined period throughout the course of GI transit. Gastroretentive dosage forms are the systems that can stay in the gastric region for several hours and thus, prolong the gastric residence time of the drugs. After oral administration, such a dosage form is retained in the stomach and releases the drug in a controlled and sustained manner so that the drug can be supplied continuously in the upper GIT. This prolonged gastric retention improves bioavailability, decreases drug wastage, and improves solubility of drugs that are less soluble in a high pH environment[1]. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. One of the most feasible approaches for achieving and predictable drug delivery profile in GIT is to control the GRT so that gastric emptying process can be extended from few minutes to 12 hr using GRDF's that offers new and better option for

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drug therapy[2].Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist**.** Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis. Olmesartan medoxomilis indicated for the treatment of mild to moderate essential hypertension. **[3]..**The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (Cmax) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.Olmesartan medoxomil inhibits the pressor effect of an angiotensin II infusion in a dose- dependent manner at doses of 2.5 to 40 mg. The inhibition was 90% at doses of olmesartan medoxomil >40 mg 24 hours post dose.

Materials and methods

Olmesartan medoxomil was obtained as a gift sample from Akums Pharma Ltd. Haridwar. HPMC K4M, HPMC K100M were obtained from Aglomed pharma, Roorkee. All other reagents used were of analytical grade.

Drug excipients compatibility study

Fourier Transform Infrared (FTIR)

Drug excipients interactions play vital role in the release of drug from the formulation. Fourier Transform Infrared spectroscopy has been used to study the physical and chemical interaction between the excipients used. FTIR technique has been used to study the physical and chemical interaction between drurg and excipients used**. [4]**

Powder flow property

The flow properties of powder were determined included the following: bulk density, tapped density , carr's index, Hausner's ratio and angle of repose. All the above properties were measured according to USP XXXI**. [5]**

Preparation of standard curve of olmesartan medxomil in methanol

Accurately weighed olmesartan medoxomil (10 mg) was placed in 100 ml volumetric flask, 10 ml of methanol was added to it and sonicate for 1 minute and then made up the volume to 100 ml with methanol. From the above solution, 1 ml of solution was pipette out and diluted to 10 ml with methanol. The resultant solution obtained was 10 µg/ml and was scanned in UV range of 200 to 400 nm. Olmesartan medoxomil showed maximum absorbance at 257 nm. Thus, 257 nm was taken as λmax**.**

Preparation of floating tablets of olmesartan medoxomil

The composition of different formulations of Olmesartan Medoxomil floating tablets is shown in table 1. Direct compression method had been employed to prepare floating tablets of Olmesartan Medoxomil with HPMC K4M and HPMC K100M . All ingradients were weighed accurately and passed through mesh #60. In order to mix thoroughly polymer and drug blended geometrically in mortar pestle for 15 mins and then sodium bicarbonate, citric acid, magnesium sterate, talc and lactose were mixed one by one. After thorough mixing these ingradients the powder blend was passed through mess #44. The tablets were compressed on rotary tablet press. **[6].**

Experimental Design

A 3^2 full factorial design was used for the optimization.

Optimization of floating tablets of Olmesartan Medoxomil by 3^2 full factorial design

In the present study three levels two factors, full factorial design was employed for the optimization of floating tablets of olmesartan medoxomil. The concentration of HPMC K4M and HPMC K100M were selected as independent variable and floating lag time, total floating time and T_{80} were selected as dependent variables

Table no 1: Full factorial design layout

Batch code	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

X_1 code for amount of HPMC K4M and X_2 code for amount of HPMCK100M.

Table no 2: Coded values X_1 code for amount of HPMC K4M and X_2 Code for amount of HPMCK100M

Coded value	Amount of HPMC K4M in mg (X_1)	Amount of HPMCK100M in mg (X_2)
-1	0	0
0	40	40
1	80	80

Formulation of factorial batches and Statistical modeling for optimization

A three level, two factor experimental design as shown below described the proportion in which independent variables- concentration of HPMC K4M and HPMC K100M was used in the formulation. The concentration of polymer was varied at three level 0, 40 mg and 80 mg. floating lag time, total floating time and T_{80} of 9 formulations were analysed.

Table no 3: statistical model for optimization

Factor	Level			
Independent variables	**High(1)**	**Medium(0)**	**Low (-1)**	**Dependent variable**
HPMC K4M	**80**	**40**	**0**	**Floating lag time**
HPMC K100M	**80**	**40**	**0**	**Total floating time & T_{80}**

Table no 4: Composition Of Floating Tablet Of Olmesartan Medoxomil

Ingradients	Formulations code (All the quantities are in mg.)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Olmesartan medoxomil	50	50	50	50	50	50	50	50	50
HPMC K4M	0	0	0	40	40	40	80	80	80
HPMC K100M	0	40	80	0	40	80	0	40	80
Sodium bicarbonate	70	70	70	70	70	70	70	70	70
Magnesium stearate	8	8	8	8	8	8	8	8	8
Talc	7	7	7	7	7	7	7	7	7
Lactose	230	190	150	190	150	110	150	110	70
Citric acid	35	35	35	35	35	35	35	35	35

The run or formulation which are designed based on factorial design are evaluated for the response. The response values are subjected to multiple regression analysis to find out the relationship between the factor used and the response value obtained. The response values subjected for this analysis is floating lag time, total floating time and T_{80}. The multiple regression analysis was done using DESIGN EXPERT 9.0.3.1 D-optimal type. Which is specially meant for this optimization. Analysis of data was carried out using ANOVA and the individual parameter was evaluated with F test , using the regression coefficient of factor , the polynomial equation for each response is generated.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms(X_1^2 and X_2^2) are included to investigate nonlinearity.On the basis of preliminary trials a 3^2 full factorial design was employed to study the effect of independent variables ie concentration of HPMC K4M and HPMC K100M on dependent variable ie floating lag time, total floating time and T_{80}.Analysis of variance, contour and RSM plots represent the effect of the independent variables graphically

Regression Analysis Equation for LT

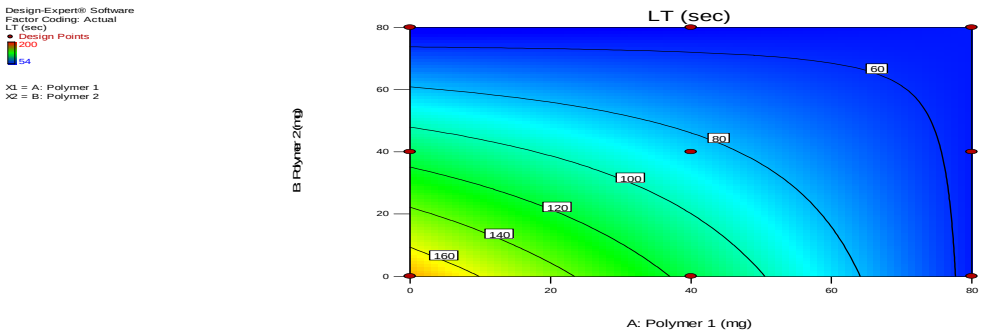


Fig1:Contour plot to study the effect of two HPMC grade polymer concentrations on floating lag time

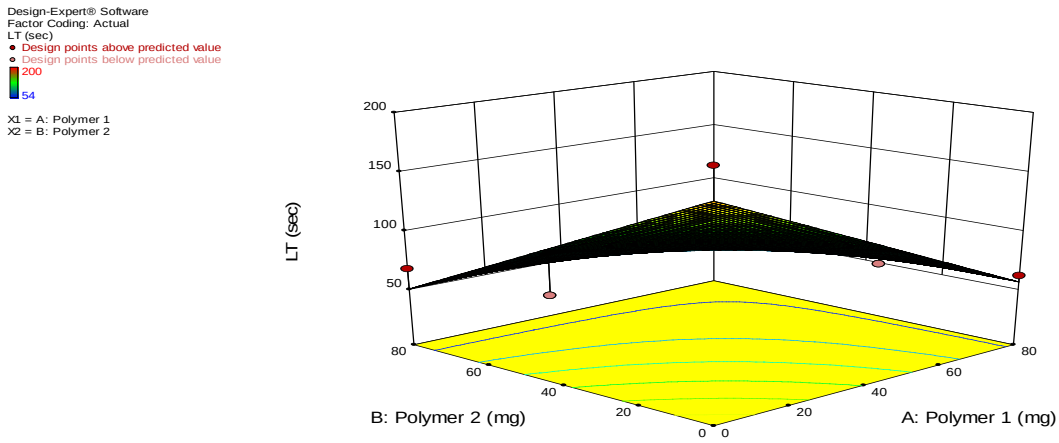


Fig 2: RSM plot to study the effect of two HPMC grade polymer concentrations on floating lag time
LT= 174.4166-1.4729X1-1.55208X2+0.0195X1X2

Regression Analysis for total floating time

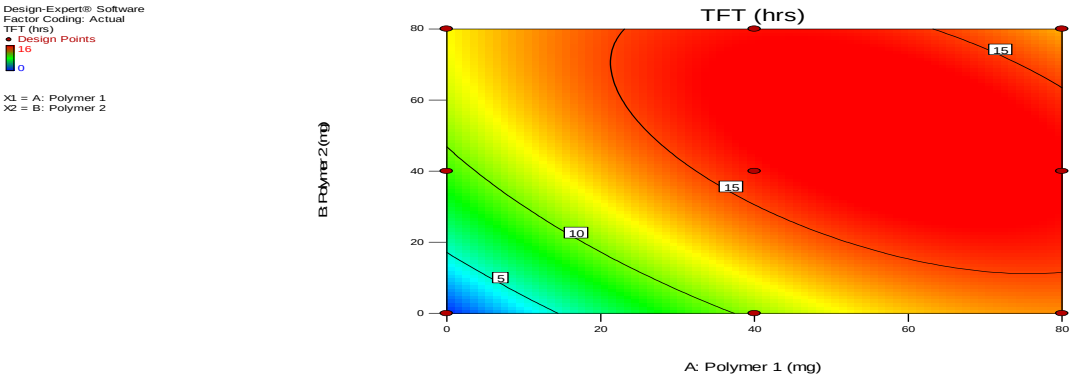


Fig 3: Contour plot to study the effect of two HPMC grade polymer concentrations on total floating time

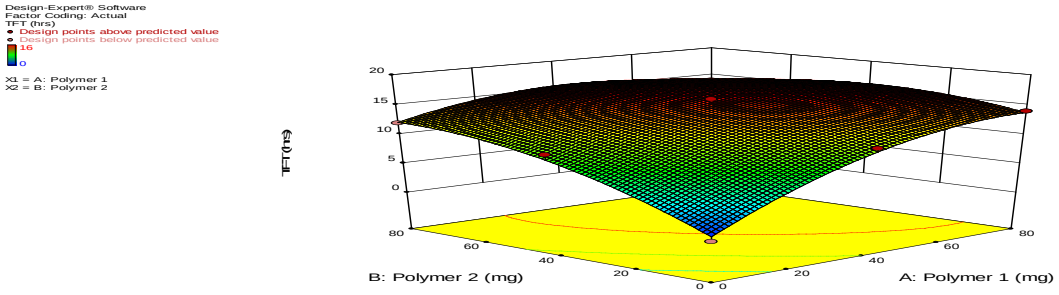


Fig 4: RSM plot to study the effect of two HPMC grade polymer concentrations on total floating time

$TFT = 0.7778+0.32083X1+0.27500X2-1.87500X1X2-1.97917X1^2-1.6667X2^2$

Total floating time gives correlation co-efficient 0.7778. The P value for variable X1 and X2 were 0.0127 and 0.0059 respectively ($P<0.05$), it indicate that X1 and X2 variable shown significant effect on drug release Combination co-efficient was positive and the P value less than 0.05, which indicates that combination of independent variable showed significant effect on floating lag time.The co-efficient of X1 and X2 were positive indicate that when concentration of both the variable increase than total floating time was increased.

Regression Analysis for T_{80}

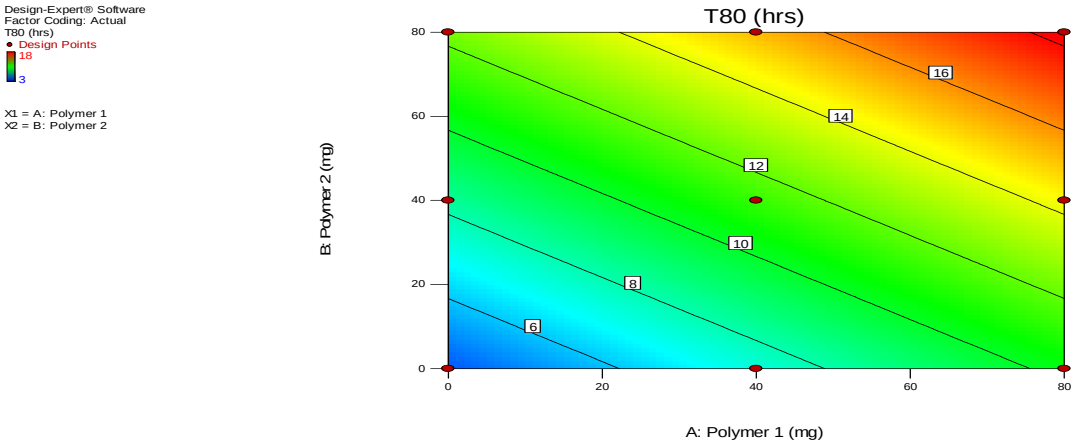


Fig 5: Contour plot to study the effect of two HPMC grade polymer concentrations on T_{80}.

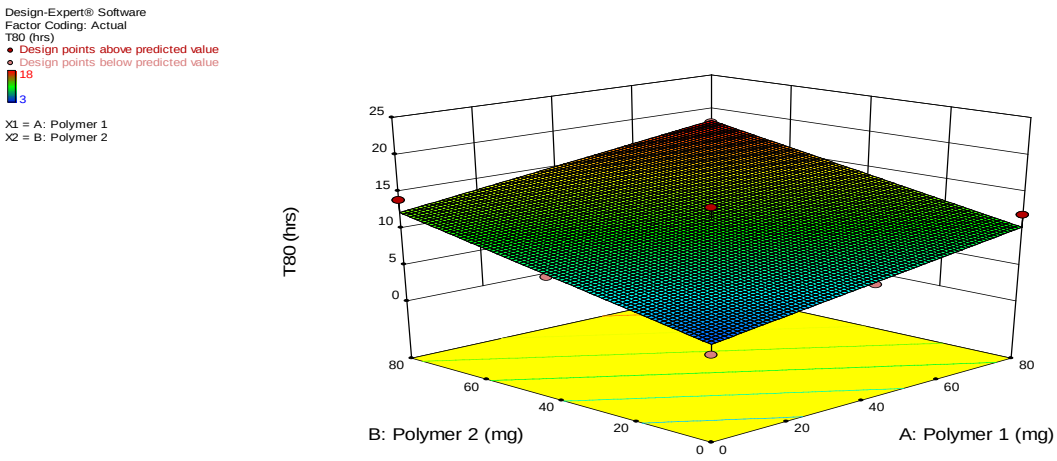


Fig 6: RSM plot to study the effect of two HPMC grade polymer concentrations on T_{80}.

$$T_{80} = 4.3333 + 0.07500X1 + 0.10000X2$$

T_{80} gives correlation co-efficient 4.3333. The P value for variable X1 and X2 were 0.0030 and 0.0007 respectively ($P<0.05$), it indicate that X1 and X2 variable shown significant effect on drug release. Combination co-efficient was positive and the P value less than 0.05, which indicates that combination of independent variable showed significant effect on T_{80}.

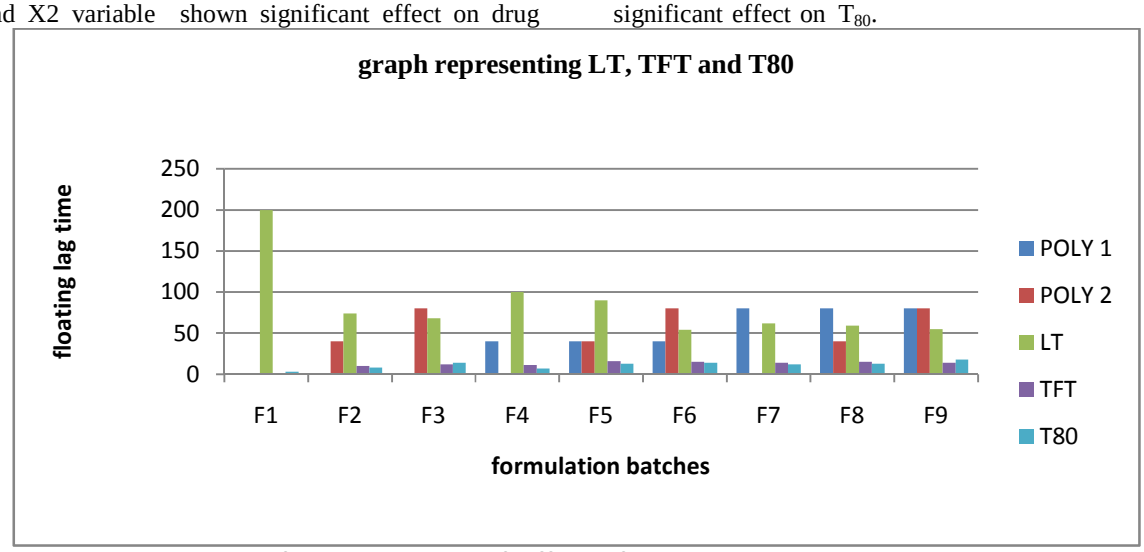


Fig 7: Comparision of TFT, LT and T_{80} of different formulation batches with respect to polymer concentration.

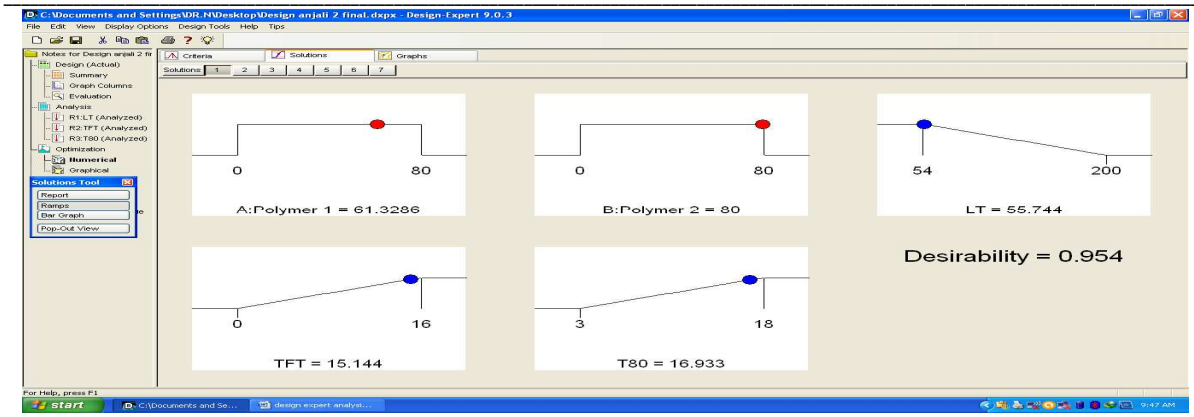


Fig 8: Plot depicting target solutions after optimization

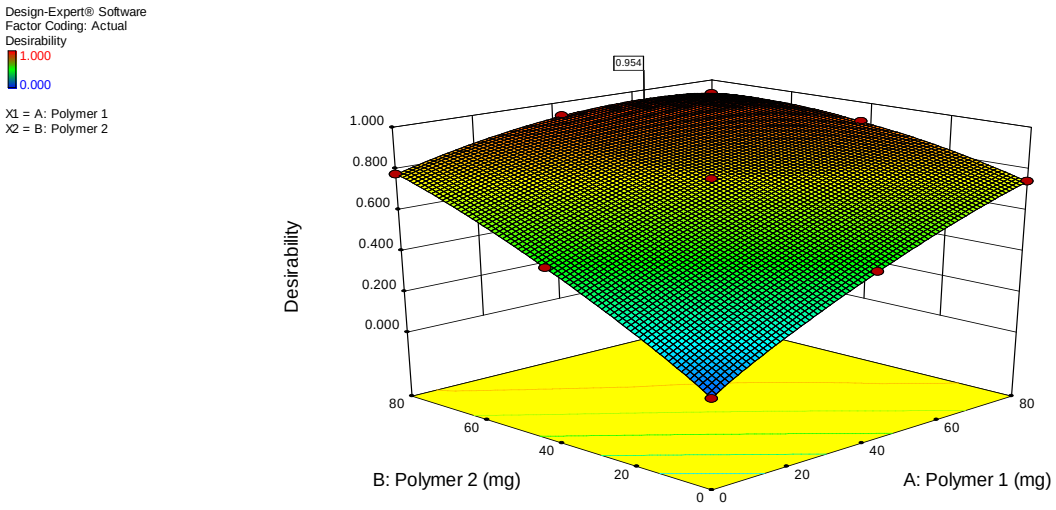


Fig 9: RSM plot depicting the predicted desirability value after optimization

Evaluation of floating tablet: The prepared tablets were evaluated for the following parameters:

Thickness of Tablets

The thickness of six tablets was measured using Vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined**. [7]**

Hardness

The hardness of the tablet was determined by Monsento hardness tester. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded**.[8]**

Friability

The Friability of tablets was performed in a Roche Friabilator. It consists of a plastic chamber that revolves at 25 rpm. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed. The friability (F) is given by the formula**. [9]**

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} * 100$$

Weight Variation

Twenty tablets were individually weighed and average weight was calculated.The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the

percentage limit and if no tablet differs by more than two times the percentage the percentage limit.

In-vitro buoyancy studies

The in vitro buoyancy was determined by floating lag time method. The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to float was determined as floating lag time. Total floating time was also determined**. [10]**

In-vitro Dissolution Studies

In vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) at 100 rpm. Dissolution test was performed using 0.1N HCL as dissolution medium and the temperature was maintained at 37 ± 0.5ºC. Aliquot of dissolution medium was withdrawn at specific time intervals 2,4,6,8,10,12,14,16,18,20,22,24.

The samples were filtered through a 0.45 □ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 257 nm UV spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve. **[11]**

Result and discusssion

Standard curve of Olmesartan Medoxomil

Standard curve of olmesartan was prepared in methanol. Standard curve data ere subjected to linear regression analysis. R^2 value were found to be 0.970 which indicate linearity

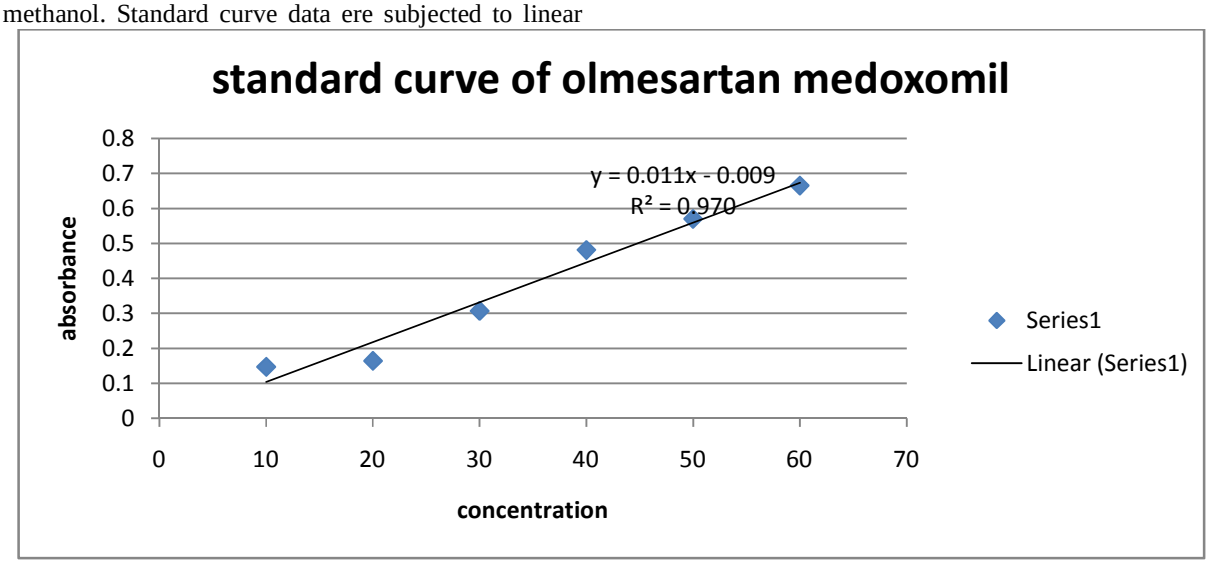


Fig 10: Standard curve of olmesartan Medoxomil

Indentification of pure drug

Swelling index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\textbf{Swelling index} = (W_t - W_0/W_0)*100$$

Where, W_0 is the initial weight of tablet, and W_t is the weight of the tablet at time t.[12]

Kinetic modeling and mechanism of drug release

To know the mechanism of drug release from these formulations, The data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), Korsmeyer (log cumulative percentage of drug released vs log time), equations along with zero order (cumulative amount of drug released vs time) pattern**. [13-15]**

Accelerated stability study

The tablets of best batch were packed in aluminum pouch and charged for accelerated stability studies at 40 °C and 75% RH for 1 month in a humidity jar.[16]

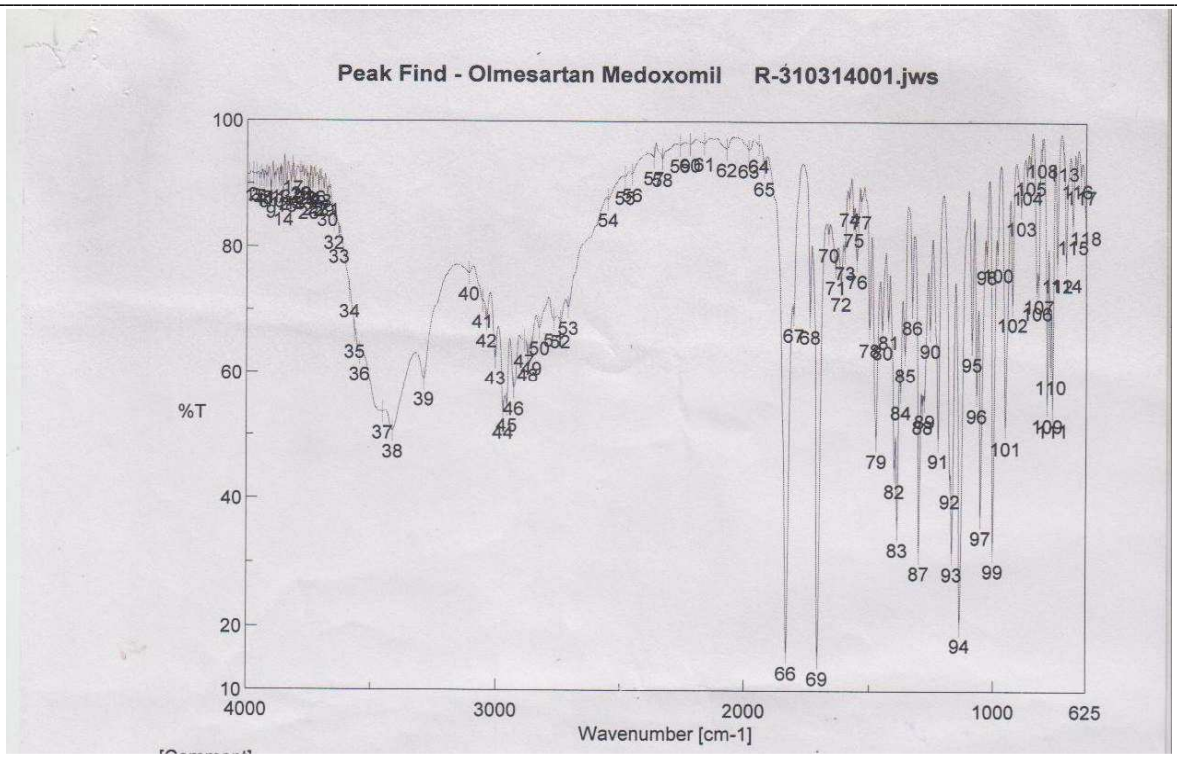


Fig 11: FTIR of Olmesartan Medoxomil

Drug Polymer interaction Studies

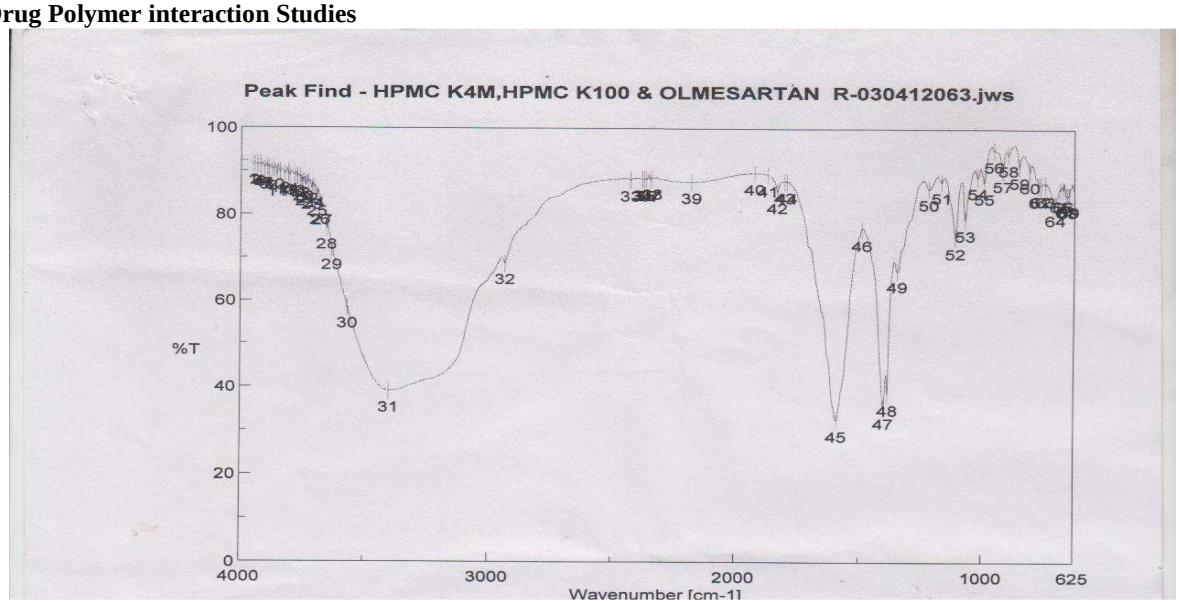


Fig 12: FTIR of the formulation

Olmesartan showed characterstic peak at 2974cm^{-1} (aliphatic C-H Streching),3039 cm^{-1} (aromatic C-H Streching), 3271cm^{-1} (broad peak intermolecular Hydrogen bond), 3720 cm^{-1} (C=O of carboxylic group), 1483 cm^{-1} (C-N Streching). The formulation containing polymer showed all the peaks of Olmesartan Medoxomil with no change in intensity.

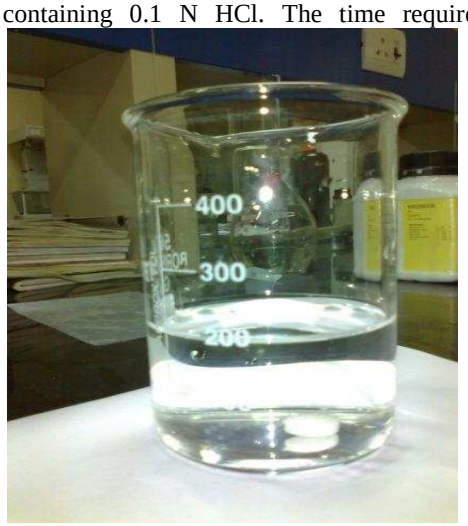
Table no 5: Evaluation parameter of tablets of different batches

Tablets Batch	Weight variation test (mg.)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	398.47±2.31	4.25±0.31	5.0±0.40	0.45±0.020
F2	398.77±2.13	3.94±.02	4.5±0.20	0.36±0.015
F3	399.21±4.2	3.96±0.04	4.5±0.30	0.38±0.020
F4	398.37±1.01	4.03±0.05	5.0±0.40	0.28±0.030
F5	399.43±2.31	3.81±0.06	5.0±0.35	0.27±0.060
F6	400.20±0.41	4.34±0.23	5.5±0.50	0.32±0.035
F7	400.12±1.32	4.08±0.07	5.0±0.20	0.22±0.040
F8	401.53±0.86	3.93±0.06	4.0±0.30	0.28±0.015
F9	401.74±1.39	4.12±0.07	5.0±0.20	0.23±0.020

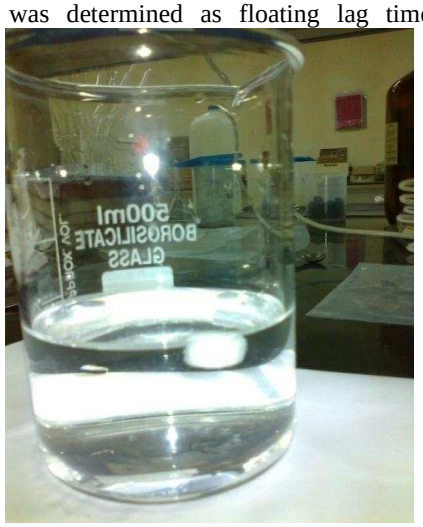
Table no 6: In vitro buoyancy studies

Batch	Floating lag time(sec)	Floating time
F1	200	0 hrs
F2	74	10hrs
F3	68	12hrs.
F4	100	11hrs.
F5	90	16hrs.
F6	54	15hrs.
F7	62	14hrs.
F8	59	15hrs
F9	55	14hrs

The in-vitro buoyancy was determined by floating lag time method. The tablets were placed in 100 ml beaker containing 0.1 N HCl. The time required for the tablets to float was determined as floating lag time.



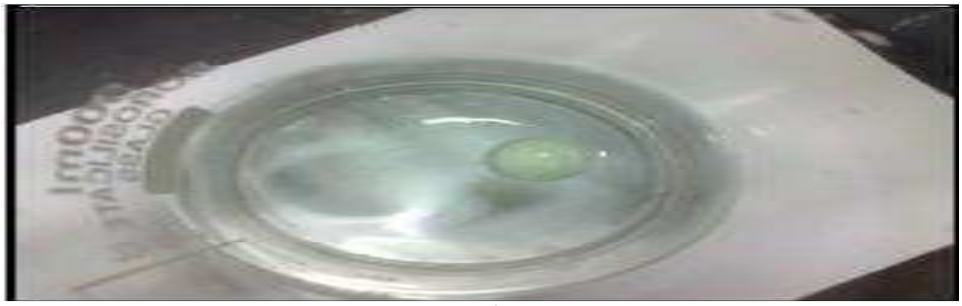
At 0 sec



after 40 secs

In vitro buoyancy study showed that all the batches from F1 to F9 have floating lag time less than 4 minutes because of evolution and entrapment of carbondioxide inside the hydrated polymer matrices, resulting from the interaction between gas generating agent and dissolution medium which led to lowering the density of matrices enabling the tablets to float. On the other hand, as a solvent front penetrated the polymer layer, swelling of HPMC K4M and HPMC K100M caused to increase in volume of tablet resulted in net

reduction in density of the tablet, which prolonged the duration of floatation up to 18 hrs.



After 16 hrs

Fig 13: Buoyancy studies of tablet at different time interval

Table no 7: Dissolution studies of different batches

TIME (in hrs)	CUMMULATIVE PERCENT RELEASE								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
2	38.39	18.34	17.32	22.43	19.21	17.32	19.43	20.11	11.92
3	79.54	42.12	30.21	41.56	38.42	34.42	40.24	36.75	16.93
5	98.22	65.86	39.42	66.76	46.34	47.59	48.25	41.44	21.84
7		74.41	48.64	80	59.52	53.54	56.11	53.33	32.06
8		80.64	56.42	88.53	63.54	58.67	64.66	60.51	39.46
10		92.45	61.36	94.36	68.98	64.77	73.22	68.67	48.47
12		98.55	67.48	97.87	72.32	70.52	78.98	75.34	55.12
13			72.49		79.87	75.33	85.33	81.43	59.49
14			78.87		87.41	80.32	89.89	89.54	62.11
15			85.64		91	85.66	94.31	93.77	68.42
16			92.48		96.73	91.29	97.75	98.24	71.45
17			98.56			98.43			78.74
18									81.72
19									88.89
20									93.21
21									97.54

Invitro buoyancy study showed that all the batches from F1 to F9 have floating lag time less than 4 minutes because of evolution and entrapment of carbondi oxide inside the hydrated polymer matrices, resulting from the interaction between gas generating agent and dissolution medium which led to lowering the density of matrices enabling the tablets to float.[16-18] On the other hand, as a solvent front penetrated the polymer layer, swelling of HPMC K4M and HPMC.K100M caused to increase in volume of tablet resulted in net reduction in density of the tablet, which prolonged the duration of floatation up to 18 hrs. Among these formulations F9 give the desired release and retarded the 80% drug release for 18 hrs.

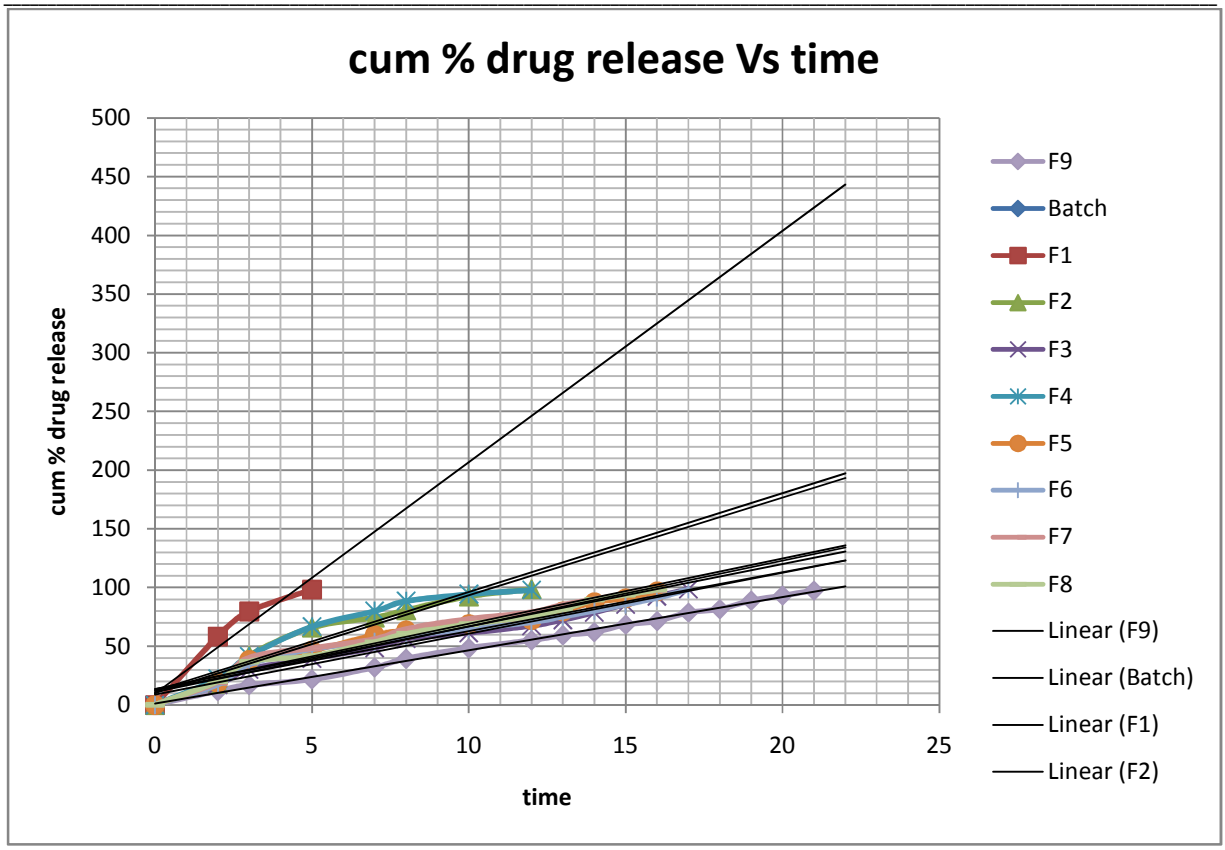


Fig 14: In vitro dissolution studies of different formulation batches

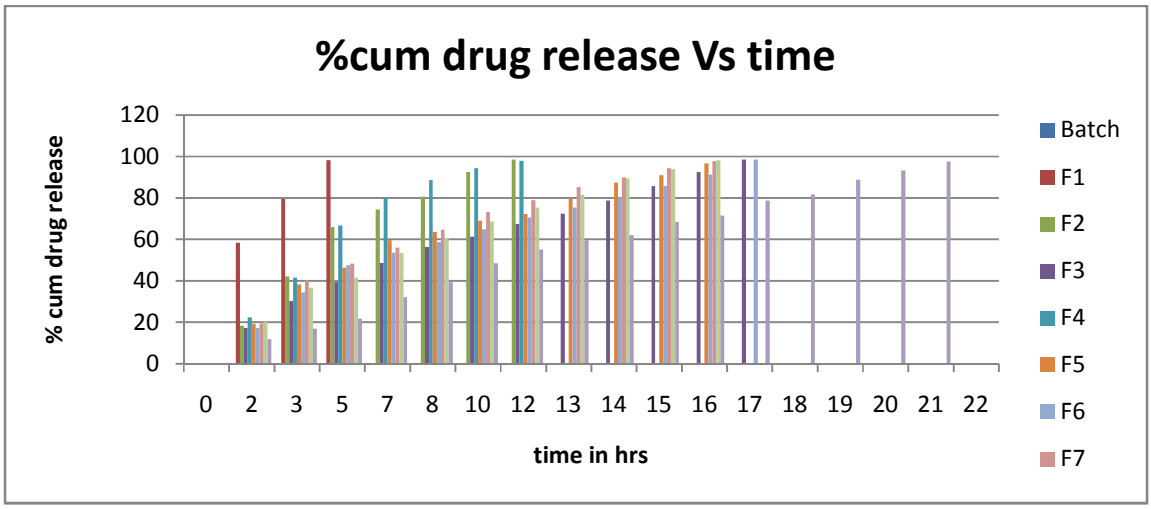


Fig 15: Dissolution profile of formulations F1 to F9

Table no 8: Invitro drug release kinetics study

Model	Zero order	First order	Higuchi plot	Korsmeyer peppas
R^2	0.997	0.728	0.922	0.992
Slope	4.527	11.51	23.47	0.908
Intercept	1.284	-6.627	-21.02	0.769

The data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), Korsmeyer (log cumulative percentage of drug released vs log time), equations along with zero order (cumulative amount of drug released vs time) .The dissolution profile of the best batch was fitted to zero-order, first-order, Higuchi and korsmeyer models to ascertain the kinetic modeling of drug release. It may be concluded that the drug release from gastro retentive olmesartan medoxomil tablet is explained by zero model because R^2 value of zero order model has 0.997. The values n in korsmeyer peppas equation is 0.769 which is greater than 0.50, thus we can conclude that dissolution follows non fickain diffusion.

Swelling index

Swelling index of the tablet include the absorption of liquid medium then increases the weight of the tablet. This is very important characteristics of the polymer which control the drug release from the formulation via diffusion from the studies it was found that increase the concentration of HPMC K4M increases the swelling property.F9 showed maximum swelling among all HPMC containing formulations. HPMC K4M and HPMC K100M tablet when in contact with dissolution medium swell due to breakage of hydrogen bond between the polymer chain and form a thick gel layer and eroded simultaneously. This result indicated that the swelling index of all the formulations changed after different time interval.

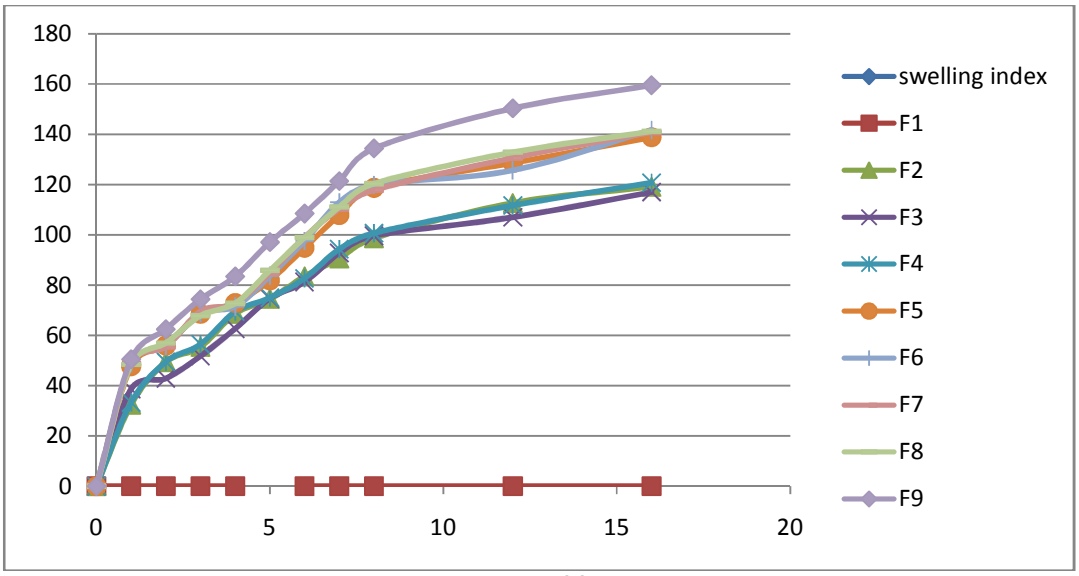


Fig 16: Swelling studies of formulation batches

Accelerated stability studies

Gastro retentive tablets of olmesartan medoxomil formulated in the present study were subjected to accelerated stability studies in Aluminum / Aluminum pouch pack as aluminum strip is considered the best protecting packaging material but in the present study simulation was made using aluminum foil pouch. As the dosage form is formulated for site-specific drug delivery to stomach, no change should occur in its floating lag time and drug dissolution profile. Dose dumping and failure of buoyancy are probable effects anticipated during the stability study of such dosage forms. The tablets of best batch F9 were packed in aluminum pouch and charged for accelerated stability studies at 40 °C and 75% RH for 1 months in a humidity jar.

[19-22]

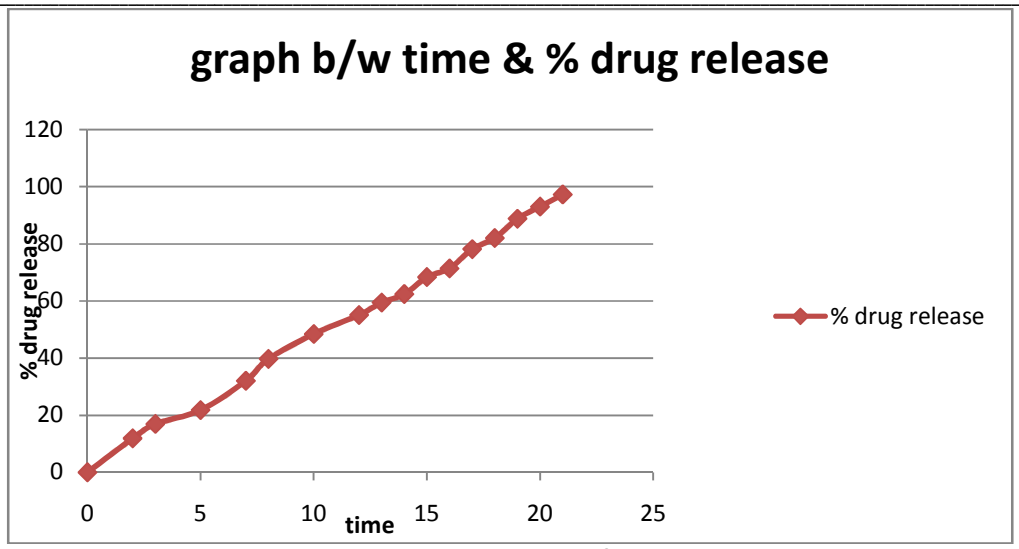


Fig 17: Accelerated stability studies of the optimized batch

Conclusion

In the present work floating tablets of Olmesartan Medoxomil were prepared by direct compression. All the tablets were subjected to weight variation, hardness, friability,diisolution, swelling index, drug excipient interaction studies. The tablets were found to be good in their integritywithout any chipping, capping and sticking. Formulation F9 showed good result than rest of the formulations according to targets obtained. Formulation F9 showed best result with required floating lag time of 55 secs, total floating time of 14 hrs and T_{80} of18 hrs. drug release was decreased with increased concentration of polymers. IR spectroscopic studies indicated that there was no drug excipient interactions. Kinetic studies for optimized formulation F9 follows zero order and Higuchi model release systems. Zero order release describes the system where the drug release rateis independent of its concentration of dissolved substance.

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