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Formulation, Optimization and Evaluation of Sustained Release Matrix Tablets of Tiaprofenic Acid using Design of Experiments

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Abstract

The main aim of the study was to formulate, optimize and evaluate Sustained Release Matrix tablets of Tiaprofenic acid Using Design of Experiments. Tiaprofenic acid is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of Rheumatoid Arthritis. Total 15 formulations were formulated by using various hydrophilic swell able polymers like HPMC K100, HPMC K15, Almond gum and guar gum in combination at various concentrations. Direct compression method is used for formulation as the drug is moisture sensitive. Design Expert software was used to determine the optimized formulations, which showed desired effects. Tablets were evaluated for pre- compression parameters like angle of repose, Hausner's ratio and Compressibility index. All the formulations were evaluated for post compression parameters like hardness, friability, weight variation, drug content, swelling index and in-vitro dissolution studies. The optimized formulations F8 and F13 were within the limits of the official compendia. Formulation F8 showed drug release of 94.6% at 12 hours. Formulation F13 showed Drug release of 93.6% at 12hrs. It was found that the combination of polymers showed combined effect on release rate of drug. Thus, the formulations were suitable to be formulated as sustained release tablets. The optimized formulations were found to follow zero order kinetics with non-Fickian diffusion.

Keywords: Tiaprofenic acid, HPMC K100, HPMC K15, Almond gum, guar gum, Design Expert.

Full-length article **Corresponding Author*, e-mail:*ratnakolapalli@gmail.com*

1. Introduction

Drug Delivery is defined as the process of administering a pharmaceutical compound to achieve a therapeutic benefit in humans/ animals. Oral drug delivery method is the most widely utilized routes for administration for systemic delivery of drug via various pharmaceutical products of different dosage forms. Owing to its potential advantages including well-established delivery system, patient friendly, convenient, cost effective, and noninvasiveness, it has been the most favored drug delivery system in pharmaceutical field.

1.1. Matrix System

A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

Advantages

1. Easier to produce than reservoir or encapsulated devices.
2. Versatile, effective and low cost.
3. Possible to formulate high molecular weight compounds.
4. Increased stability by protecting the drug from hydrolysis or other changes in gastrointestinal tract.

Disadvantages

1. Cannot provide zero order release.
2. Removal of remaining matrix is necessary for implanted system.

1.2. Experimental Design

- The "design of experiments" (DOE) is a set of statistical techniques that allows the formulator to select the most influential factors on an experimental response and to obtain their optimum values.
- The DOE will provide the appropriate set of runs to perform in the laboratory to obtain the maximum information with the minimum number of runs.
- It permits the researcher to identify cause and effect relationship between variables[1].

1.3. Full Factorial Design

- Itis the most commonly used design.
- Factorial Design is an experimental design consists of two or more factors each with different possible "values" or "levels".

- Factorial design enable the investigator to study the joint effect of each factor on a response as well as effect of interaction between the factors on the response.
- The total number of experiments for studying k factors at two levels is 2^k[2].
- The levels are termed as high and low or +1 and -1 respectively.

2. Materials and Methods

2.1. Materials

Tiaprofenic acid was obtained as a gift sample

2.2. Methods

2.2.1. Standard Plot of Tiaprofenic Acid

10mg of Tiaprofenic acid was weighed and transferred into a 10ml volumetric flask, dissolved in methanol and volume was made up to the mark with buffer.1ml of above stock solution was taken in a 10ml volumetric flask and make up the volume up to the mark with the buffer.From the above working standard solution, 1ml was transferred into 10ml volumetric flask and the volume was made up with buffer to get 10µg/ml. Similarly, from the working standard 0.2, 0.4 0.6 and 0.8ml were taken in a volumetric flask and the volume was made with pH 7.4-phosphate buffer to give 2µg/ml, 4µg/ml, 6µg/ml and 8µg/ml respectively.The absorbencies of the above solutions were measured at 315nm using UV spectrophotometer.A graph was plotted with concentration on x-axis and absorbance on y- axis[3].

2.2.2. Optimization Using Experimental Designs

- The optimization of the prepared formulations was done by using 2 -factor 2-level full fractional statistical design using Design Expert 13 (32-bit) software (Stat-Ease Inc., Minneapolis, USA). The design of the experiment is a technique developed to evaluate potential factors simultaneously, systematically, and speedily.
- The amount of polymer HPMC K100M (X1), and the amount polymer HPMC K15M (X2) were selected as independent variables. The time required for 100% drug release was selected as dependent variable.
- Similarly, in another run the amount of polymer Almond gum (X1), and the amount polymer Guar gum(X2) were selected as independent variables and the time required for 100% drug release was selected as dependent variable.
- With a 2 level 2 factorial design (full factorial design) using replicates 8 runs were obtained. Further additional runs were obtained by augmentation. The following set of possible runs were obtained[4].

2.2.3. Pre- Compression Studies

All the ingredients weighed according to above formulation table and tested for angle of repose, bulk density, tapped density and compressibility index[5-7].

2.2.4. Preparation of Tablets

Matrix tablets of Tiaprofenic acid with other excipients were prepared by direct compression. Different grades polymeric matrix materials were chosen[8]. A diluent for increasing the compressibility and flowability of the ingredients as well as to maintain the tablets at constant weight used. Suitable lubricant and glidant were chosen[9-10].The drug, polymer and diluent were thoroughly mixed by means of pestle and mortar. This powder mixture then lubricated then compressed into tablets in rotary tablet punching machine[11].

2.2.5. Post Compression parameters

Tablets were tested for general appearance, hardness, friability, weight variation, drug content, swelling index and in-vitro dissolution[12-14].

2.2.6. Stability Studies

Stability studies were conducted for the optimized formulations F8 and F13 as per ICH guidelines at 37.5ºtemperature and 75% RH for a period of 30, 60 and 90 days. The formulations were evaluated for hardness, friability drug content and percent drug release at 12hrs after 3 months[15]**.**

3. Results and discussion

3.1. Results

3.1.1. Standard Plot

Standard graph for Tiaprofenic acid was constructed by plotting a graph with concentration on x-axis and absorbance on y-axis. The standard graph followed Beer-Lambert's law i.e. as concentration increases absorbance also increases.

3.1.2. Pre- compression studies

Based on angle of repose, carr's index and hausners ratio values all the formulations (F1- F15) are said to have very poor flow characteristics.Thus to improve their flow properties Mg. stearate and Talc are incorporated in the formulations.Flow properties for the formulations were observed to improve after addition of lubricant and glidant.Angle of repose for the formulations F1- F8 fall in the range of 40.1^0 –47.2^0 while the Compressibility index and Hausners ratio fall in the ranges of 21.8 – 26.8% and 1.32 – 1.36 respectively. Similarly angle of repose for the formulations F9- F15 fall in the range of 40.1- 47.2^0 while the Compressibility index and Hausners ratio fall in the ranges of 21.9 – 26.3% and 1.28 – 1.36 respectively.

3.1.3. Post compression parameters

- ***Swelling Index (%)***

The ability of the tablet to swell upon hydration is an indication of the rate-limiting step in release of the drug from the tablet. As the polymer swells, the drug is released through polymer gel layer slowly. Thus, it is important for the tablet to swell for a period of more than 6 hours. All the formulations (F1- F15) were observed to swell for 6hrs or more thus indicating they can be formulated as sustained release tablets. Among all the formulations, Formulation F8 showed swelling index of 206% for up to 7hrs while Formulation F13 showed swelling index of 182% for up to 7hrs. All the formulations were tested for swelling index. F8 and F13 showed better swelling properties.

- ***In-vitro Dissolution studies***

The obtained in-vitro dissolution values were given as responses in the Design expert Software. These responses were evaluated using Analysis of variance (ANOVA) and linear regression by comparing the actual value with the

predicted value[16]. The software generates 3-D Response surface graphs and contour graphs. The software generates an optimized solution, which is correlated with the expected values and Percent Relative error is calculated[17].The in-vitro dissolution study values were then given as responses and Analysis of Variance (ANOVA) was performed.Contours plots and Response surface graphs were generated which explain the effect of factors on responses. The plots show that as the polymer concentration the percent drug release decreases[18].It also shows effect of interaction between factors on the responses.In a contour plot, the region where the specifications not met is shaded out. Flag planted is a representation of optimum. The yellow regions refers to the space where factors can be set to satisfy requirements for both responses[19].The predicted R2 is in reasonable agreement with adjusted R2 for all the responses, i.e., the difference is less than 0.2.Predicted values are the values predicted by the design for the formulations based on the responses and the actual values are the values that are obtained practically[20].

3.1.4. Fit statistics

The predicted R2 is in reasonable agreement with adjusted R2 for all the responses, i.e., the difference is less than 0.2. Predicted values are the values predicted by the design for the formulations based on the responses and the actual values are the values that are obtained practically.

- ***Kinetic Drug Release Profile of OptimizedFormulations***

Kinetic studies were performed for the optimized formulations[11]. It observed that the formulations followed zero order release rate as the regression coefficient (R=0.997) for zero order graph was found to be greater than first order graph (R= 0.971)and the diffusion of drug from the system was observed to be Non- Fickian diffusion as n value from peppas plot was found to be between 0.5 and 1[12].

3.1.5. Stability Studies

Stability studies were performed for optimized formulation F8 and F13.

3.2. Discussion

Tiaprofenic acid is a Non-Steroidal Anti-Inflammatory Drug (NSAID), which belongs to BCS class II with half-life of 1.5 to 2.5hrs. Oral dose of Tiaprofenic acid is 300mg taken twice daily. To improve patient compliance, it is required to decrease the dose and dosing frequency of the drug. Sustained Release delivery systems is one novel technique, which helps to prolong the therapeutic effect of drug. Design of Experiments, a mathematical tool is used for generating optimized formulations, which decreases the number of trials. Standard graph for Tiaprofenic acid was constructed by plotting a graph with concentration on x-axis and absorbance on y-axis. The standard graph followed Beer-Lambert's law i.e., as concentration increases absorbance also increases. The FTIR spectroscopy was used for investigating intermolecular interactions in the developed formulation. The characteristic FTIR vibration bands were observed in both formulae. Moreover, in the FTIR profile of Tiaprofenic acid SR tablet, the specific peaks corresponding to the drug could be detected. Also, there were no new peaks or shifts detected in this spectrum when compared to standard pure drug confirming the absence of any chemical interactions of Tiaprofenic acid with other excipients. Flow properties for the formulations were observed to improve after addition of lubricant and glidant. Angle of repose for the formulations F1- F8 fall in the range of 40.10 –47.20.While the Compressibility index and Hausner's ratio fall in the ranges of 21.8 – 26.8% and 1.32 – 1.36 respectively. Similarly angle of repose for the formulations F9- F15 fall in the range of 40.1- 47.20 while the Compressibility index and Hausner's ratio fall in the ranges of 21.9 – 26.3% and 1.28 – 1.36 respectively.

All the formulations (F1- F15) showed optimum hardness values between 4 – 5 kg/cm. Friability for all the formulations were within the accepted limits i.e., less than 1%. Drug content for each formulation showed drug content greater than 90%. Weight variation for 20 tablets was under the accepted limits off official compendia i.e., not more than 2 tablets showed variation greater than 5%. The ability of the tablet to swell upon hydration is an indication of the rate-limiting step in release of the drug from the tablet. As the polymer swells, the drug is released through polymer gel layer slowly. Thus, it is important for the tablet to swell for a period of more than 6 hours. All the formulations (F1-F15) were observed to swell for 6hrs thus indicating they can be formulated as sustained release tablets.All the formulations (F1- F15) were observed to swell for 6hrs or more thus indicating they can be formulated as sustained release tablets.Among all the formulations, Formulation F8 showed swelling index of 206% for up to 7hrs while Formulation F13 showed swelling index of 182% for up to 7hrs. All the formulations (F1- F15) showed drug release up to 12hrs. It observed that with increase in concentration of the polymers HPMC K100, HPMC K15, Almond gum and guar gum: the release rate decreased. The combination of polymers showed combined effect on the drug release rate. Formulation F8 consisting of polymers HPMC K100 and HPMC K15 showed Percent Drug release of 94.6 at 12hrs. Formulation F13 consisting of polymers Almond gum and Guar gum showed Percent Drug release 0f 93.6 at 12hrs.

With the purpose of gaining a better perception of how sustained release tablet critical properties influenced by variations in tablet composition and concentrations, the full factorial experimental design was applied in the present study.Besides understanding the individual effect of the investigated factors, this design of experiments technique also allows to elucidate, with the reduced number of experiments, various interactions between independent variables, which could not detected with a traditional one-factor-at-a-time method.The responses were calculated, and then statistical analysis (ANOVA) performed. he results of the statistical analysis (analysis of variance, ANOVA) showed that generated models for Percent drug release at 6hrs and Percent drug release at 12hrs were significant ($p < 0.05$), indicating that the listed responses are well described by the proposed models. Experimental design results revealed that the release rate of drug was significantly affected by the concentration of polymers used. Based on responses, a solution with maximum desirability is generated by the software.This graphically represented in overlay plot. Overlay plot highlights the point where the response criteria can be met. Percent relative error was

calculated between the predicted mean and the observed mean. The percent relative error of HPMC optimized formulation was found to be 0.7% and 0.1% for Response 1 and Response 2 respectively. While percent relative error for optimized natural gum formulation was Formulation, Optimization and Evaluation of Sustained Release Matrix Tablets of Tiaprofenic Acid using Design of Experiments 104 found to be 0.8% and 1% for Response 1 and Response 2 respectively.

Std	Run	Factor 1 A:HPMC K15 g	Factor 2 B:HPMC K100 g	Response 1 %drug release a... %	Response 2 %drug release a... %
3	1	0.06	0.09		
7	2	0.06	0.09		
4	3	0.135	0.09		
1	4	0.135	0.09		
5	5	0.06	0.18		
6	6	0.06	0.18		
8	7	0.135	0.18		
2	8	0.135	0.18		
9	9	0.18	0.06		
11	10	0.18	0.135		
13	11	0.09675	0.135		
10	12	0.09	0.06		
12	13	0.18	0.06		

Std	Run	Factor 1 A:Almond gum g	Factor 2 B:Guar gum g	Response 1 %drug release a... %	Response 2 %drug release a... %
1	1	0.135	0.09		
2	2	0.135	0.09		
3	3	0.18	0.09		
4	4	0.18	0.09		
5	5	0.135	0.18		
6	6	0.135	0.18		
7	7	0.18	0.18		
8	8	0.18	0.18		
9	9	0.18	0.09		
10	13	0.09	0.135		
11	12	0.135	0.135		
12	11	0.09	0.18		
13	10	0.09	0.18		

Figure 1. Input of dependent and independent variables in Design Expert software.

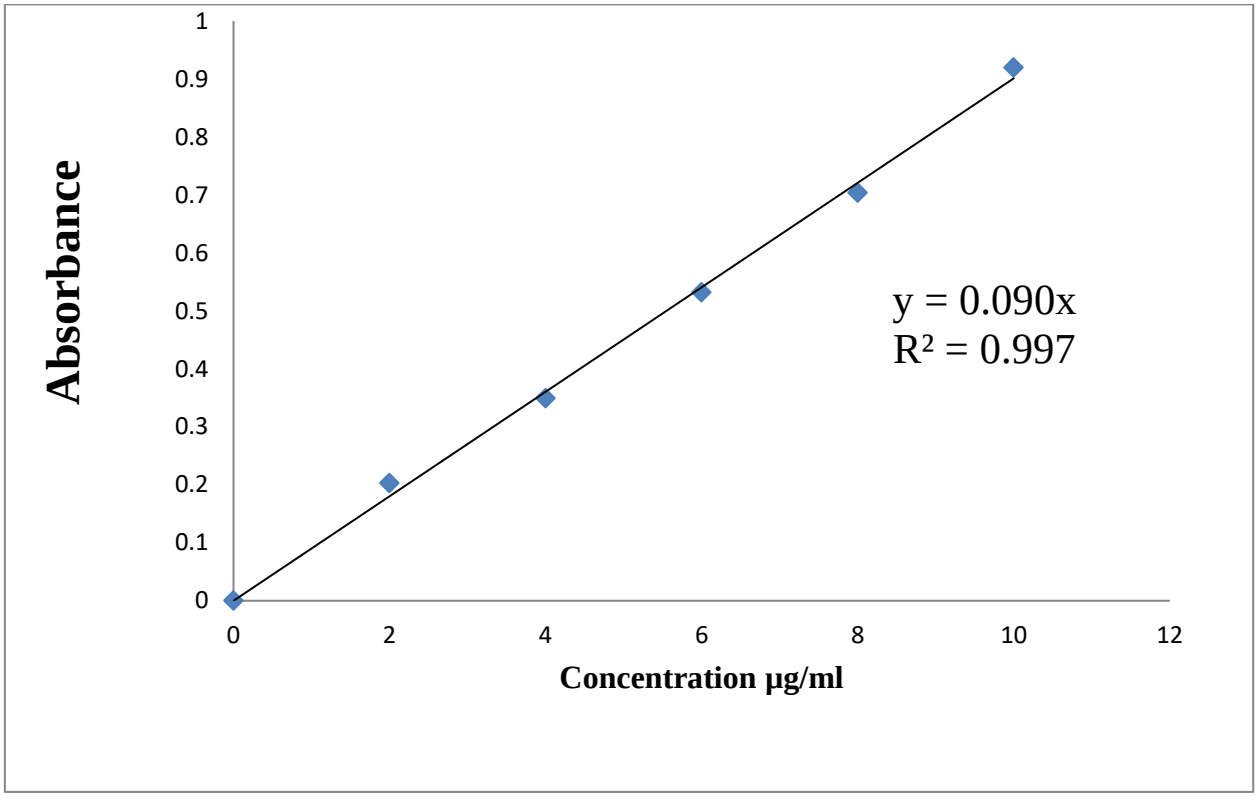


Figure 2. Standard graph for Tiaprofenic acid

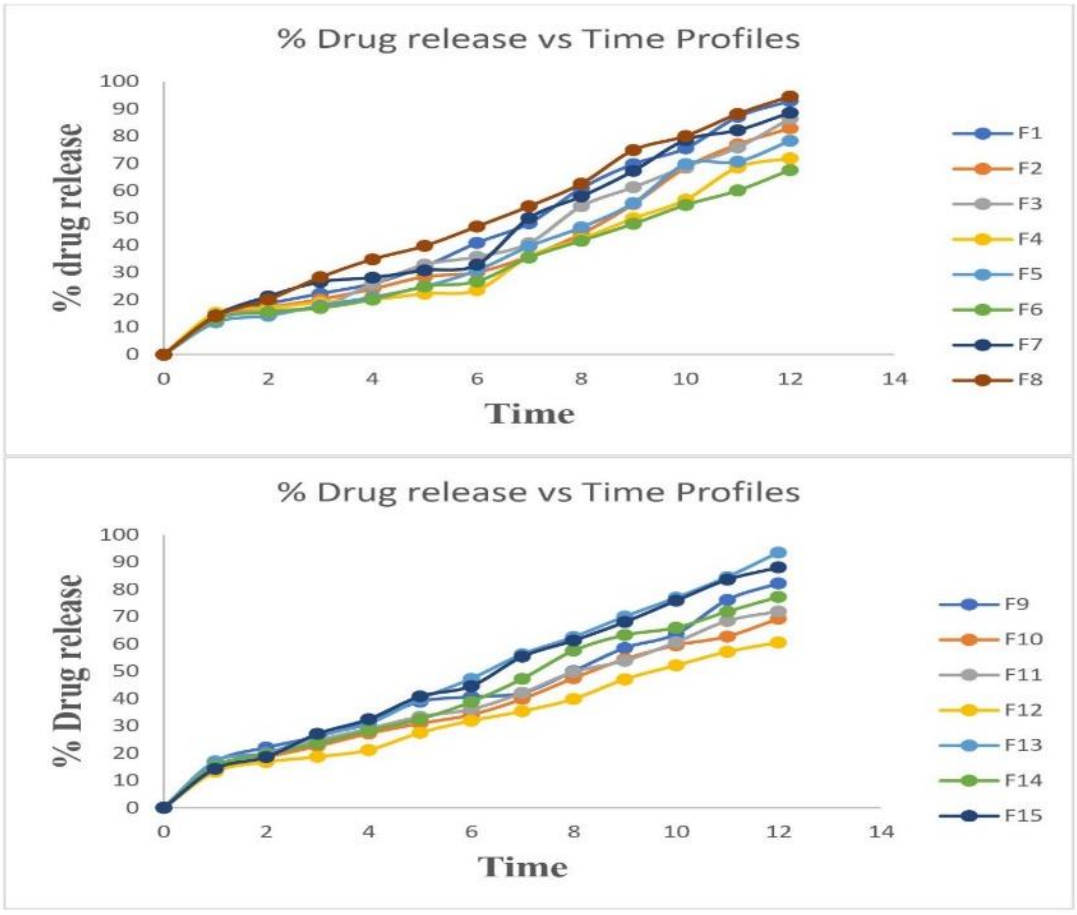


Figure 3. Percent Drug Release vs. Time profile

Std	Run	Factor 1 A:Hpmc K15 g	Factor 2 B:Hpmc K100 g	Response 1 %dr at 6hr %	Response 2 %dr at 12hr %
1	1	0.06	0.09	40.9	93.8
2	2	0.06	0.09	41.1	92.9
3	3	0.135	0.09	30.9	82.9
4	4	0.135	0.09	31	82.4
5	5	0.06	0.18	35.8	86.3
6	6	0.06	0.18	35.3	86.8
7	7	0.135	0.18	23.5	71.9
8	8	0.135	0.18	23.8	71
9	9	0.18	0.06	30.9	77.7
12	10	0.18	0.135	26.8	67.6
11	11	0.09675	0.135	32.1	88.6
13	12	0.09	0.06	46.9	94.6
10	13	0.18	0.06	30	78.3

Figure 4(a). Responses input in the statistical design for HPMC formulations

Std	Run	Factor 1 A:Almond gum g	Factor 2 B:Guar gum g	Response 1 %dr at 6hr %	Response 2 %dr at 12hr %
1	1	0.135	0.09	40.7	87.6
2	2	0.135	0.09	40	86.3
3	3	0.18	0.09	34.1	72.8
4	4	0.18	0.09	34.8	72
5	5	0.135	0.18	36	67.9
6	6	0.135	0.18	36.2	67
7	7	0.18	0.18	30.1	60.4
8	8	0.18	0.18	31.9	60.6
9	9	0.18	0.09	34	72.6
10	10	0.09	0.135	47.3	94.3
11	11	0.135	0.135	38.8	77.3
12	12	0.09	0.18	44.6	81.8
13	13	0.09	0.18	44.9	81.2

Figure 4(b). Responses input in the statistical design for Natural gums formulations

ANOVA for selected factorial model

Response 1: %dr at 6hr

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	506.04	3	168.68	23.62	0.0001	significant
A-Hpmc K15	363.92	1	363.92	50.96	< 0.0001	
B-Hpmc K100	206.71	1	206.71	28.94	0.0004	
AB	0.1656	1	0.1656	0.0232	0.8823	
Residual	64.28	9	7.14			
Lack of Fit	63.68	4	15.92	132.66	< 0.0001	significant
Pure Error	0.6000	5	0.1200			
Cor Total	570.32	12				

ANOVA for selected factorial model

Response 2: %dr at 12hr

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	927.43	3	309.14	86.85	< 0.0001	significant
A-Hpmc K15	717.18	1	717.18	201.48	< 0.0001	
B-Hpmc K100	304.70	1	304.70	85.60	< 0.0001	
AB	7.13	1	7.13	2.00	0.1906	
Residual	32.04	9	3.56			
Lack of Fit	30.80	4	7.70	31.04	0.0010	significant
Pure Error	1.24	5	0.2480			
Cor Total	959.46	12				

Figure 5(a). ANOVA performed by software for HPMC formulations

ANOVA for selected factorial model

Response 1: %dr at 6hr

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	328.82	3	109.61	108.99	< 0.0001	significant
A-Almond gum	319.54	1	319.54	317.75	< 0.0001	
B-Guar gum	10.35	1	10.35	10.29	0.0107	
AB	0.0584	1	0.0584	0.0580	0.8150	
Residual	9.05	9	1.01			
Lack of Fit	6.74	3	2.25	5.84	0.0327	significant
Pure Error	2.31	6	0.3850			
Cor Total	337.87	12				

ANOVA for selected factorial model

Response 2: %dr at 12hr

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1320.79	3	440.26	475.16	< 0.0001	significant
A-Almond gum	1275.39	1	1275.39	1376.48	< 0.0001	
B-Guar gum	77.07	1	77.07	83.18	< 0.0001	
AB	0.0075	1	0.0075	0.0081	0.9304	
Residual	8.34	9	0.9266			
Lack of Fit	7.49	3	2.50	17.62	0.0022	significant
Pure Error	0.8500	6	0.1417			
Cor Total	1329.13	12				

Figure 5(b). ANOVA performed by software for natural gum formulations

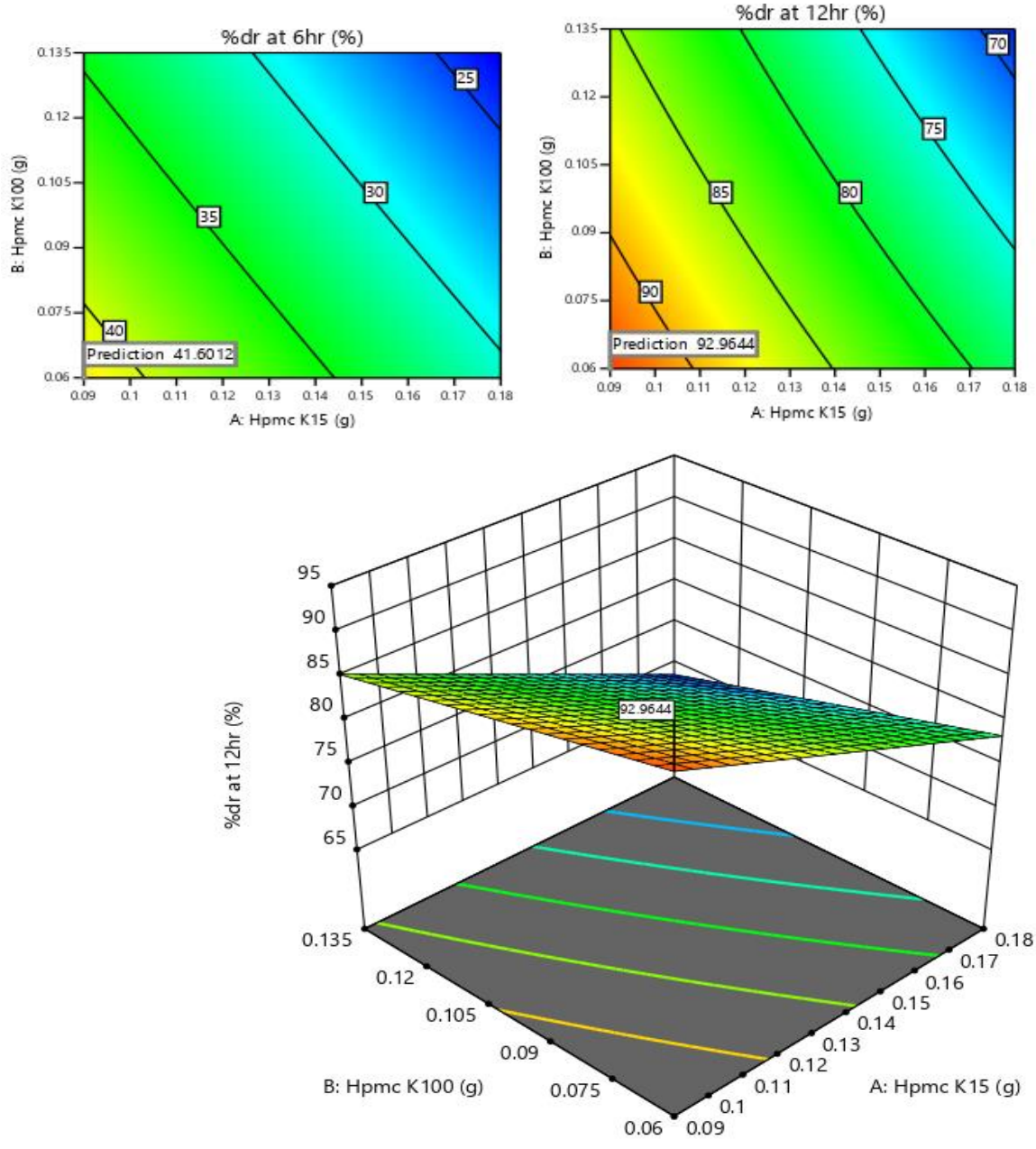


Figure 6(a). Contour and response surface graphs for HPMC Polymers

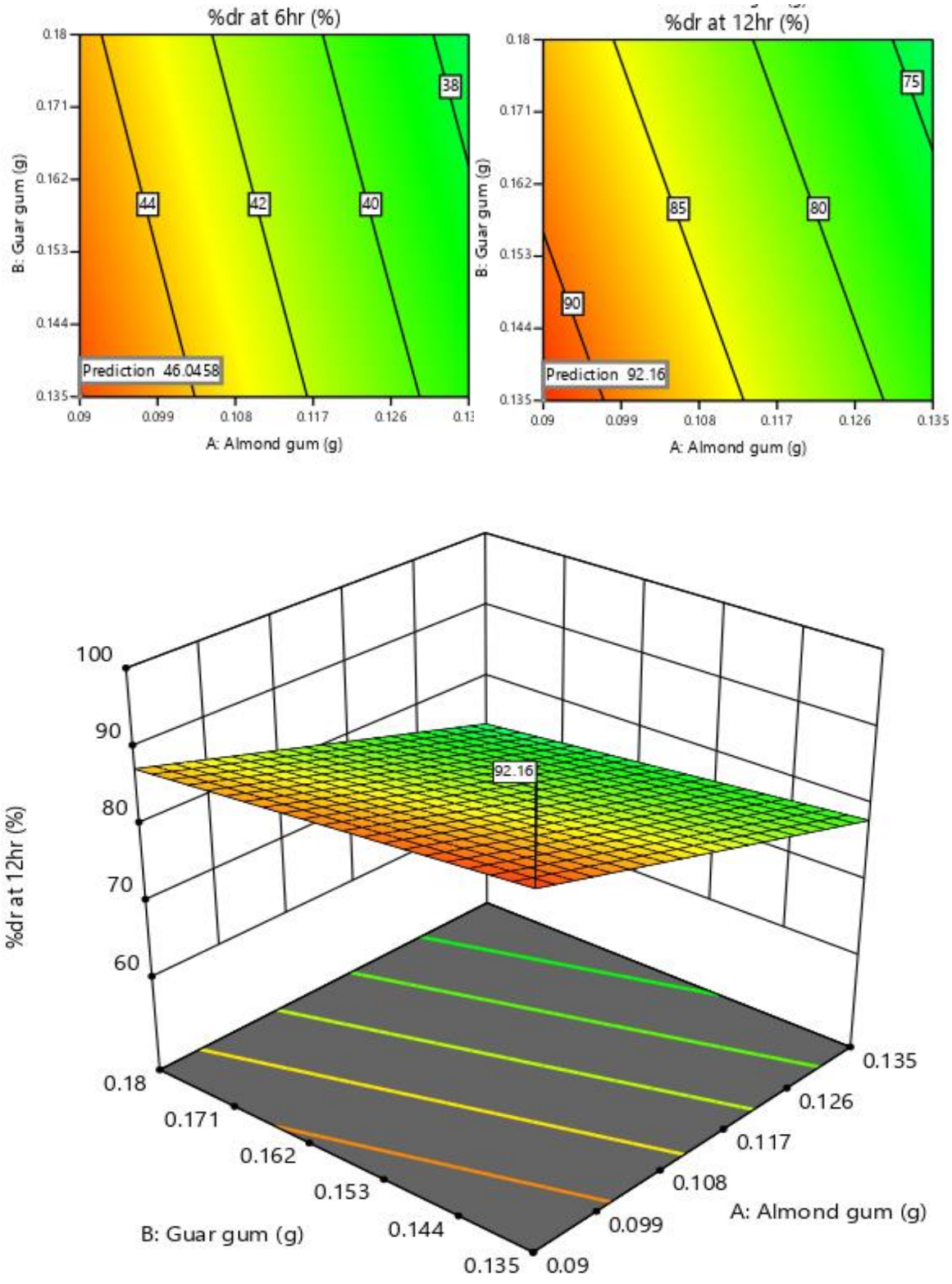


Figure 6(b). Contour and response surface graphs for natural gum

Std. Dev.	2.57		R^2	0.8496
Mean	32.43		Adjusted R^2	0.7995
C.V. %	7.92		Predicted R^2	0.6726
			Adeq Precision	10.8841

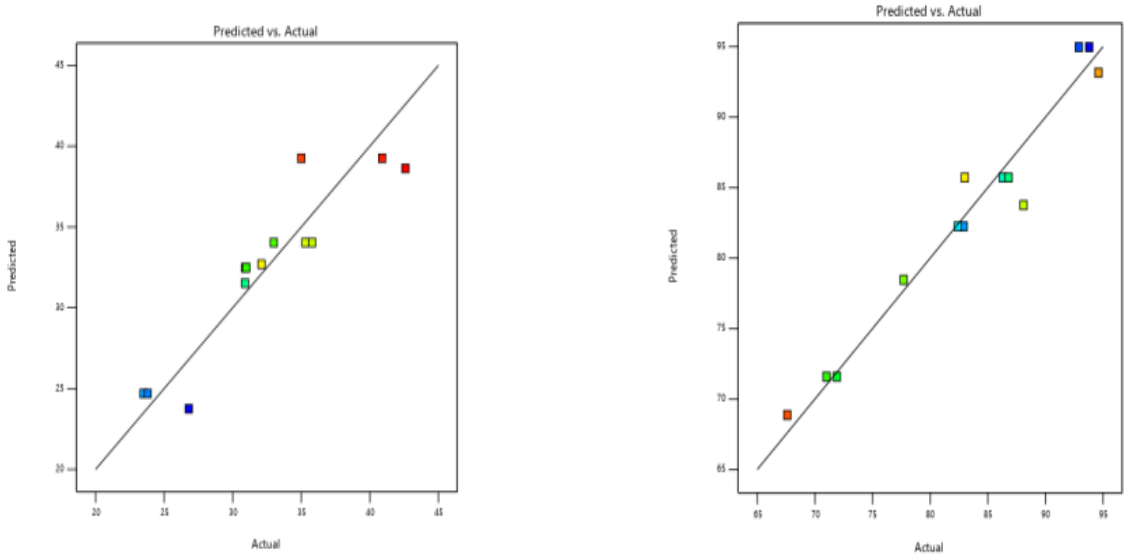
Std. Dev.	2.07		R^2	0.9588
Mean	83.00		Adjusted R^2	0.9450
C.V. %	2.49		Predicted R^2	0.9252
			Adeq Precision	22.7643

Fit statistics for Response 1and 2 for HPMC formulations

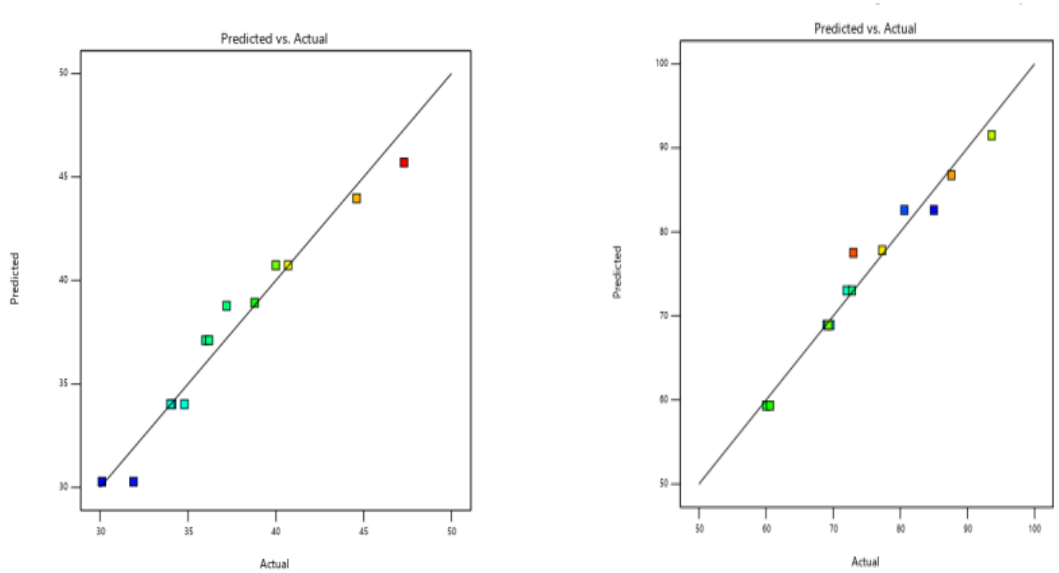
Std. Dev.	1.12		R^2	0.9603
Mean	37.36		Adjusted R^2	0.9470
C.V. %	3.01		Predicted R^2	0.9089
			Adeq Precision	24.7614

Std. Dev.	2.09		R^2	0.9670
Mean	74.65		Adjusted R^2	0.9560
C.V. %	2.80		Predicted R^2	0.9399
			Adeq Precision	27.7799

Fit statistics for Response 1and 2 for formulations containing natural gums



Predicted vs. Actual values for responses HPMC formulation



Predicted vs Actual values for responses of formulations containing natural gums

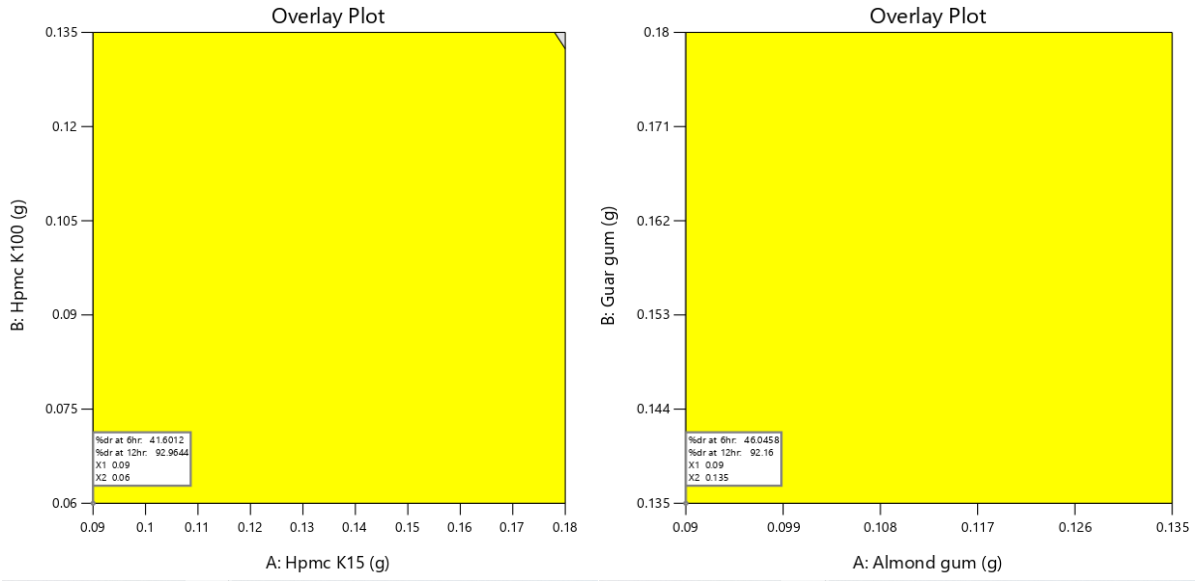


Figure 7. Overlay plot for optimized formulations

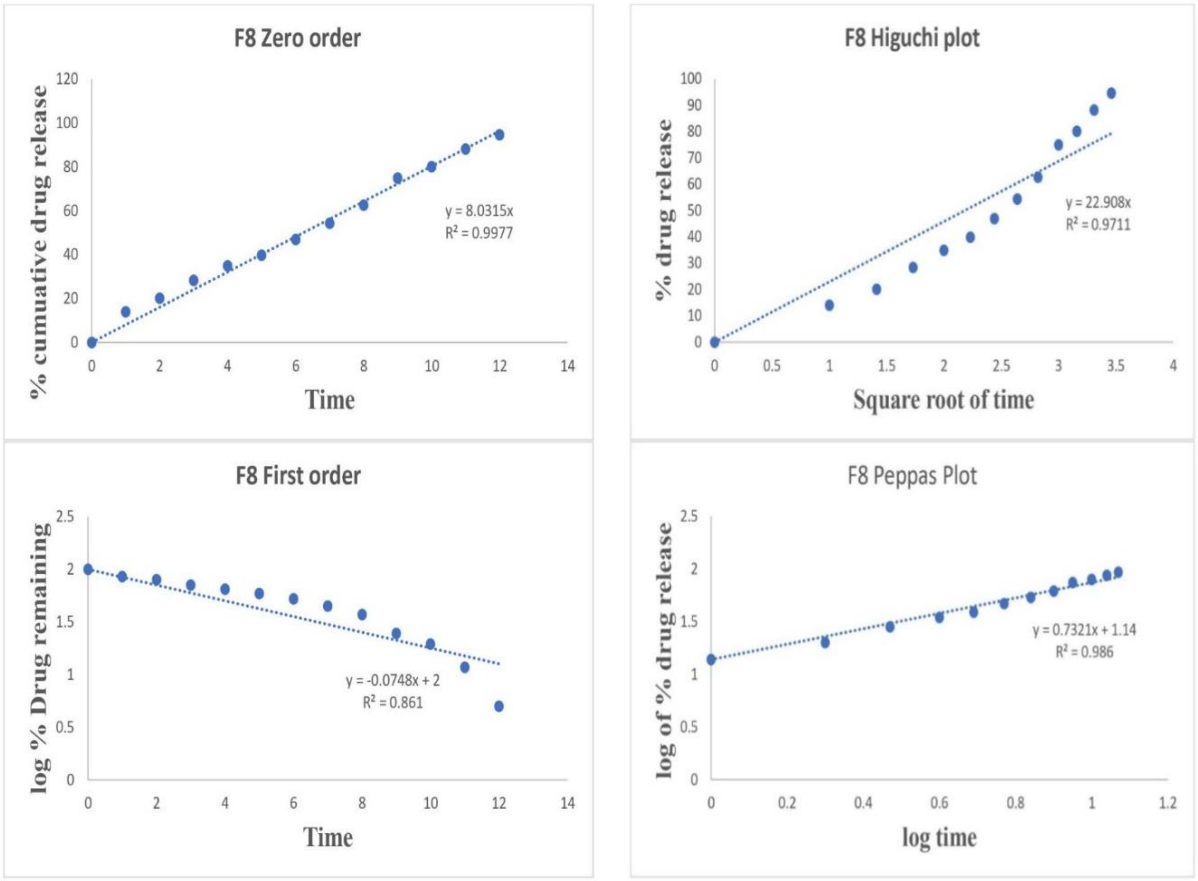


Figure 8(a). Kinetic profiles for Formulation F8

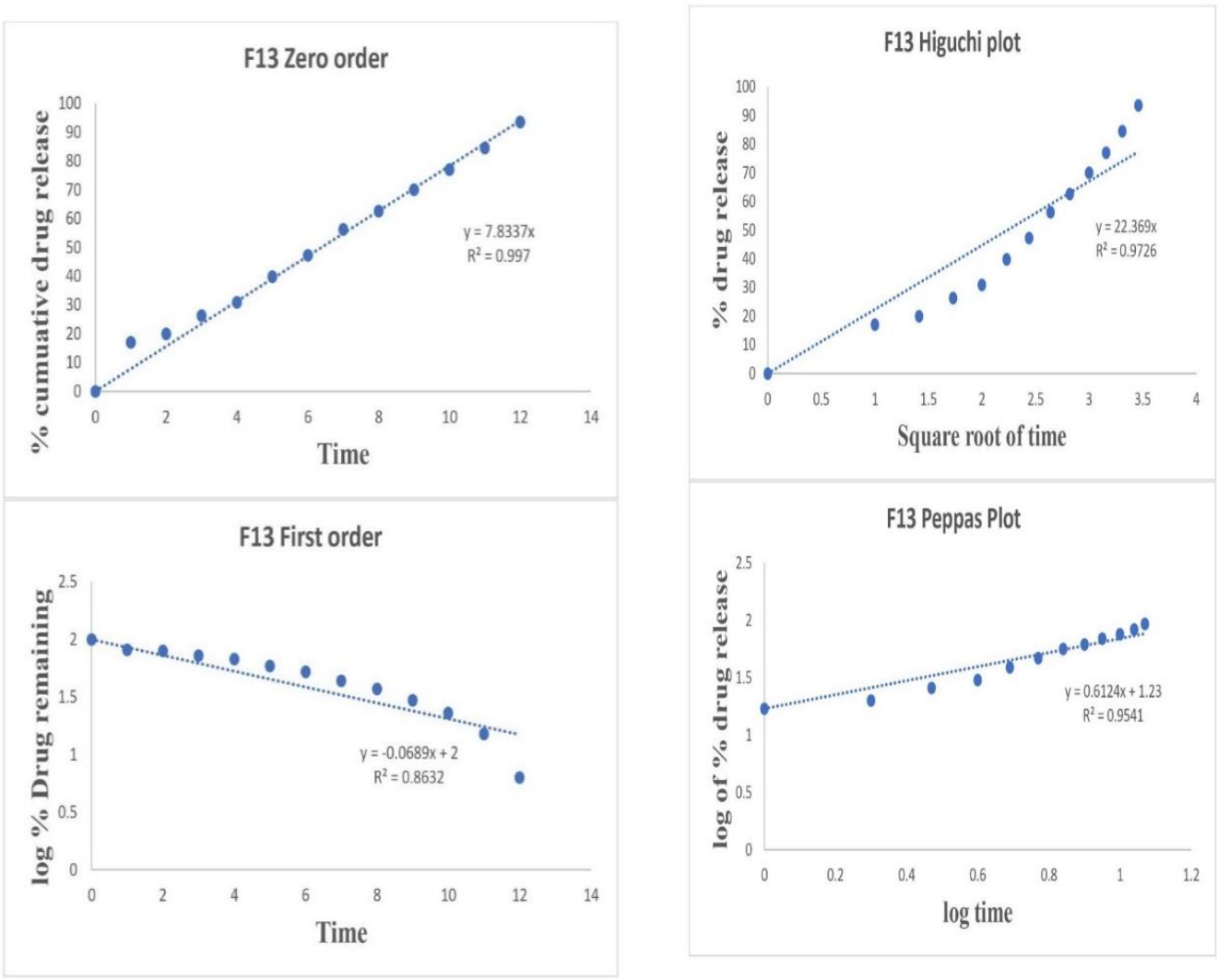


Figure 8(b). Kinetic profiles for Formulation F13

Test	Initial	Storage at $40^0 \pm 2^0$C and 75± 5% RH		
		1 month	2 months	3 months
Drug content	96.6	96.3	96.3	96.1
Percent drug release at 12hrs	94.6	94.6	94.5	94.3
Hardness	4.5± 0.26	4.5± 0.26	4.5± 0.23	4.5± 0.23

Stability studies for formulation F8

Test	Initial	Storage at 40^0± 2^{0}C and 75± 5% RH		
		1 month	2 months	3 months
Drug content	96.3	96.3	96.12	96.1
Percent drug release at 12hrs	93.6	93.5	93.5	93.3
Hardness	4.5± 0.26	4.5± 0.26	4.5± 0.23	4.5± 0.2

Stability studies for formulation F13

Table 1. Formulation Table for Tiaprofenic acid using HPMC Polymers

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
Tiaprofenic acid	300	300	300	300	300	300	300	300
HPMC K15	60	135	60	135	180	180	90	90
HPMC K100	90	90	180	180	60	135	135	60
MCC	80	80	80	80	80	80	80	80
PVP	50	50	50	50	50	50	50	50
Talc	10	10	10	10	10	10	10	10
Mg. Stearate	10	10	10	10	10	10	10	10
Total weight	600	675	690	765	690	765	675	600

Table 2. Formulation Table for Tiaprofenic acid using Natural gums

Ingredients	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)
Tiaprofenic acid	300	300	300	300	300	300	300
Almond gum	135	180	135	180	90	135	90
Guar gum	90	90	180	180	135	135	180
MCC	80	80	80	80	80	80	80
PVP	50	50	50	50	50	50	50
Talc	10	10	10	10	10	10	10
Mg. Stearate	10	10	10	10	10	10	10
Total weight	675	720	765	810	675	720	720

Table 3(a). Pre- compression Parameters of Formulations before addition of diluent and lubricant

Formulation	Angle of repose[a] (^{0})	Bulk Density[b] (g/ cc)	Tapped density[c] (g/cc)	Compressibility Index[d] (%)	Hausnersratio[e]
F1	59.5± 0.02	0.34± 0.02	0.55± 0.02	38.2± 1	1.6± 0.01
F2	50.1± 0.2	0.33± 0.01	0.5± 0.02	34± 0.02	1.51± 0.01
F3	52± 0.01	0.33± 0.005	0.5± 0.2	34± 1	1.51± 0.03
F4	47.2± 0.03	0.38± 0.01	0.55± 0.1	30.9± 0.01	1.44± 0.02
F5	50.1± 0.1	0.35± 0.01	0.55± 0.1	36.3± 0.2	1.57± 0.03
F6	51.5± 0.03	0.35± 0.02	0.55± 0.02	36.3± 1	1.57± 0.03
F7	50.4± 0.03	0.35± 0.005	0.55± 0.2	36.3± 0.01	1.57± 0.1
F8	45.3± 0.2	0.38± .02	0.55± 0.01	30.9± 0.02	1.44± 0.01
F9	45± 0.01	0.33± 0.005	0.5± 0.2	34± 1	1.51± 0.03
F10	47.2± 0.03	0.38± 0.01	0.55± 0.1	30.9± 0.01	1.44± 0.02
F11	50.1± 0.1	0.35± 0.01	0.55± 0.1	36.3± 0.2	1.57± 0.03
F12	51.5± 0.03	0.35± 0.02	0.55± 0.02	36.3± 1	1.57± 0.03
F13	47.4± 0.03	0.35± 0.005	0.55± 0.2	36.3± 0.01	1.57± 0.1
F14	53.3± 0.02	0.34± 0.02	0.55+ 0.02	38.2± 1	1.6± 0.01
F15	53.3± 0.2	0.38± .02	0.55± 0.01	30.9± 0.02	1.44± 0.01

a: equivalent weight to 2g, mean± s.d, n=3; b: equivalent weight to 5g, mean± s.d, n=3;
c: equivalent weight to 5g, mean± s.d, n=3; d: mean± s.d, n=3; e: mean± s.d, n=3

Table 3(b). Pre- compression Parameters of Formulations before addition of diluent and lubricant

Formulation	Angle of repose[a] (^{0})	Bulk Density[b] (g/ cc)	Tapped density[c] (g/cc)	Compressibility Index [d] (%)	Hausners ratio
F1	41.5± 0.02	0.38± 0.02	0.5± 0.02	24± 1	1.32± 0.01
F2	40.1± 0.2	0.33± 0.01	0.45± 0.02	26± 0.02	1.34± 0.01
F3	42± 0.01	0.33± 0.005	0.44± 0.2	25± 1	1.33± 0.03
F4	45.2± 0.03	0.38± 0.01	0.48± 0.1	21.8± 0.01	1.26± 0.02
F5	45.1± 0.1	0.35± 0.01	0.45± 0.1	22.2± 0.2	1.29± 0.03
F6	41.5± 0.03	0.30± 0.02	0.40± 0.02	25± 1	1.33± 0.03
F7	43.4± 0.03	0.30± 0.005	0.41± 0.2	26.8± 0.01	1.36± 0.1
F8	43.3± 0.2	0.31± .02	0.42± 0.01	26.1 ± 0.02	1.32± 0.01
F9	45± 0.01	0.30± 0.005	0.40± 0.2	25± 1	1.33± 0.03
F10	47.2± 0.03	0.35± 0.01	0.47± 0.1	25.5± 0.01	1.34± 0.02
F11	40.1± 0.1	0.32± 0.01	0.41± 0.1	21.9± 0.2	1.28± 0.03
F12	41.5± 0.03	0.30± 0.02	0.41± 0.02	26.3± 1	1.36± 0.03
F13	44.4± 0.03	0.30± 0.005	0.40± 0.2	25± 0.01	1.33± 0.1
F14	43.3± 0.02	0.34± 0.02	0.45+ 0.02	24.4± 1	1.32± 0.01
F15	43.3± 0.2	0.30± .02	0.40± 0.01	25± 0.02	1.33± 0.01

Table 4. Post- Compression parameters of Tiaprofenic acid SR Formulation

FORMULATION	HARDNESS[a] (kg/cm)	FRIABILITY[b] (%)	DRUG CONTENT[c] (%)	WEIGHT VARIATION[d] (g)
F1	5± 0.38	0.2± 0.02	95.4± 0.3	604± 4.32
F2	4.5± 0.23	0.44± 0.07	96.3± 0.28	688± 4.32
F3	4.5± 0.23	0.16± 0.01	94.7± 0.2	675 ± 3.76
F4	4± 0.23	0.69± 0.02	94.8± 0.23	763 ± 2.28
F5	5± 0.28	0.8± 0.06	96.8± 0.4	695 ± 2.42
F6	4.5± 0.28	0.44± 0.01	93± 0.45	756 ± 2.46
F7	5± 0.28	0.8± 0.06	91± 0.58	678 ± 1.56
F8	4.5± 0.23	0.4± 0.03	96.3± 0.28	606 ± 1.27
F9	5± 0.28	0.69± 0.02	94.7± 0.2	607± 1.27
F10	5± 0.28	0.2± 0.01	94.8± 0.23	710± 3.76
F11	4.5± 0.23	0.69± 0.04	95.4± 0.3	775± 3.68
F12	5± 0.38	0.44± 0.06	94.3± 0.28	793± 4.32
F13	4.5± 0.23	0.44± 0.03	96.7± 0.4	680± 1.27
F14	4.5± 0.23	0.2± 0.01	91± 0.45	715± 3.86
F15	5± 0.28	0.8± 0.04	93.7± 0.2	704± 1.56

a: mean, n=3; b:mean, n=10; c: mean±s.d, n=3; d: mean±s.d, n=20

Since the percent relative error is within the limits i.e.,<1%, the software generated data is found to be in close agreement with the practical data.Then an optimized formulation was determined by correlating the actual values with the solution generated by the software. F8 found to be the optimized formulation with HPMC K100 and HPMC K15 polymers. F13 found to be the optimized formulation with polymers Almond gum and Guar gum.In order to determine the mechanism of drug release from the formulation, the in-vitro dissolution data fitted to Zero order, First order, Higuchi plot and Korsemeyer- Peppas plot. Interpretation of release exponent value (n) was calculated. It observed that the formulation F8followed zero order release rate as the regression coefficient (R=0.997) for zero order graph was found to be greater than first order graph (R= 0.861) and the diffusion of drug from the system was observed to be Non- Fickian diffusion as n value from Peppas plot was found to be between 0.5 and 1. While, the formulation F13 was observed to follow zero order release rate as the regression coefficient (R=0.997) for zero order graph was found to be greater than first order graph (R= 0.862).In addition, the diffusion of drug from the system observed to be Non- Fickian diffusion as n value from Peppas plot was found to be between 0.5 and 1. Stability studies were conducted for the optimized formulations as per ICH guidelines at 37.5 °C temperature and 75% RH for a period of 30, 60 and 90 days. The tablets remained intact and there was no change in drug content and Percent drug release at 12hrs after 3 months.

4. Conclusion

The purpose-based study was successfully done and the sustained release matrix tablets of Tiaprofenic acid were prepared with water-soluble polymers (Almond gum, Guar gum, HPMC K100 and HPMC K15). Concentrations of the polymers showed great impact on the release of the drug as concentrations of the polymers increased, the release of the drug was found to be decreased. An increase in the polymer proportion resulted in the increased viscosity of the tablet matrix gel layer as well as the formation of a gel layer with a longer diffusional path. This phenomenon resulted in the decreased effective diffusion of the drug and therefore reduction in the drug release rate. The viscous gel layer of hydrophilic polymer expands considerably on exposure to aqueous media and acts as effective barrier for drug diffusion; hence provides greater sustained effect of dosage form by releasing the drug for prolonged period. Design experiments gives optimum number of runs to be performed to obtain desirable responses. Two level 2 factorial design used in the present study. The percent relative error found low thus proving the actual value corroborates with the predicted value. Present investigation shows that various grades of HPMC at suitable concentration combinedly can be used effectively to modify the release rates in hydrophilic matrix tablets prepared by dry granulation technique. Similarly, a combination of Almond gum and Guar gum at suitable concentration can be used effectively to modify the release rates in hydrophilic matrix tablets prepared by dry granulation technique. Hence, it can be concluded that the combined effect of hydrophilic polymers, i.e., HPMC K100 and HPMC K15M; Almond gum and Guar gum at suitable concentrations produced significant effect on drug release.

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