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Design, Optimization and In-Vitro Characterization of Metformin Hydrochloride Oral *In-Situ* Gel.

Keerthi Boggarapu*[1], Prakash Rao B[1], Gunturu Abhilash[2], Reshmi Mathews[2], Beny Baby and Rajarajan S

[1]Department of Pharmaceutical Technology, Karnataka College of Pharmacy, Bangalore, Karnataka, India.
[2]Department of Pharmaceutics, Karnataka College of Pharmacy, Bangalore, Karnataka, India.

Research Article

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***For Correspondence**

Department of Pharmaceutical Technology, Karnataka College of Pharmacy, Bangalore, Karnataka, India.

Keywords: Oral in-situ gel, Metformin Hydrochloride, Xyloglucan, Pluronic F127.

ABSTRACT

The two level 2^3 Factorial design was used to develop the control release *in-situ* oral gels of Metformin Hydrochloride based on the concept of temperature triggering system by incorporation of various polymers. Metformin Hydrochloride is an anti-diabetic drug. The formulations were designed with an objective to retain in stomach for an extended time period. The effect of different polymer concentrations of Xyloglucan and Pluronic F127on *in-vitro* drug release were used to characterize and optimize the formulation. gelation temperature, gel strength, in-vitro drug release studies of 1 hour,8 hour and 12 hour were taken as a responses. The FT-IR and DSC studies revealed that no interaction between drug and polymers. Optimized formulation showed release of drug up to 94.17% in 12 hours. The predicted values of gelation temperature, gel strength, drug release at 1hr, 8hr and 12hr are 25.9^{o}C, 48.67min, 16.49%, 70..89%, 94.34% and actual values are found to be 25.9^{o}C, 48.4min, 17.83%, 72.08%, and 94.17%. The drug release from optimized formulation was found to be zero order. Thus the release of the drug from the dosage form was found to be time independent. It also showed almost linear regression in Higuchi's plot which conforms that diffusion is one of the mechanism for drug release and n value of Korsmeyer - Peppas plot was found to be 0.6 to 1 so, it indicates the drug release followed non-fickian diffusion controlled mechanism.

INTRODUCTION

The pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. The development of *in situ* gel systems has received considerable attention over the past few years. *In situ* gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. Compared to conventional controlled release formulations, *in situ* gel systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort [1, 2, 3]. *In situ* gel forming drug delivery is a type of mucoadhesive drug delivery system. In contrast to very strong gels, they can be easily applied in liquid form to the site of drug absorption. At the site of drug absorption they swell to form a strong gel that is capable of prolonging the residence time of the active substance. Both natural and synthetic polymers can be used for the production of *in situ* gels. *In situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and ionic cross- linking [4, 5, 6]. So, i*n situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes [7].

In situ is a Latin phrase meaning *in the place* [8]. In situ gelling systems are especially useful for geriatric and pediatric patients where patient is not able to take oral dosage form like tablets.

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Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycaemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization [9, 10, 11].

MATERIALS AND METHODS

Materials Used

Metformin HCl was a gift sample from Medrich laboratories, Hyderabad. Xyloglucan was a gift sample Leo chem. products Bangalore. Pluronic F 127 was a gift sample from Yarrow chem. products Mumbai.

Methodology

Preformulation Studies

Preparation of in-situ gel

Weighed required quantity of drug dissolve completely in 5mL of cold water and add polymers (Xyloglucan, Pluronic F-127) to the resulting solution. Add the required quantity of sorbitol and mixed it well, till the bubbles have gone and then keep it in the refrigerator to maintain solution state.

Drug-excipient compatibility studies by FT-IR: (Alpha e ATR-module, Bruker)

FT-IR studies were carried out for the - pure drug Metformin HCL, Metformin HCL + Xyloglucan, and Metformin HCL + Pluronic F-127 to investigate any possible interaction between the drug and the polymers.

Differential Scanning Calorimetry: (Shimadzu DSC 60)

DSC experiments were carried out in order to characterize the physical state of the drug and polymers.

Evaluation Studies

Gel temperature

Gelation temperature is the temperature where the conversion of sol to gel happens. It is carried out by visual inspection technique. The gelation temperature is measured by placing the formulation in a 10 mL vial containing magnetic bar which was further placed on a water bath. The vial gets heated with constant stirring of magnetic bar. The gelation temperature is noted when magnetic bar stopped due to formation of gelation. Similarly all the formulations repeated thrice and average is considered [12].

Gel-Strength

A sample of 50 g of gel was placed in a 50 ml beaker. Weight of 50g was allowed to penetrate in to the gel. The gel strength, which means the viscosity of the gel was determined by the time (minutes), the weight took to sink 5cm down through the prepared gel [13].

Drug content

100 mg of formulation is taken dissolved in 10 mL of 0.1NHCl from that 1mL is taken diluted to 100 mL with 0.1NHCl and analyzed in UV-spectrophotometer at 233 nm.

In-Vitro Drug Dissolution Studies

In vitro dissolution studies were performed by using a USP paddle type dissolution apparatus. The vials were placed in jar containing Phosphate buffer (pH-6.8) and the temperature was maintained at 37 ± 0.5°C and rpm 50. The samples were withdrawn at different time intervals and analyzed for drug content spectrosphotometrically at 233nm.

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OBSERVATIONS AND RESULTS

Preparation of in-situ gel

Formulation of Metformin HCl oral *in-situ* gel is done by simple mixing method. In this method, Xyloglucan was used to improve the gel transperancy and viscosity, Pluronic F-127 was used as a controlled delivery component, and sorbitol used as a stabilizing agent and sweetener. The formulation chart shown in the Table no.1.

Table No 1: Formulation Chart of Metformin Hcl In-Situ Gel By Using Factorial Design (Design Expert)

Formulation Code	Amount of Drug (gm)	Amount of Xyloglucan (gm)	Amount of Plurinic F-127 (gm)	Amount of sorbitol (mg)	Amount of Solvent (mL)
F1	1	0.1	1.5	25	5
F2	1	0.1	1.5	0	5
F3	1	0.066	2.0	0	5
F4	1	0.066	1.5	25	5
F5	1	0.066	2.0	25	5
F6	1	0.1	2.0	25	5
F7	1	0.066	1.5	0	5
F8	1	0.1	2.0	0	5

Drug-excipient compatibility studies by FT-IR

The peaks of drug, binary mixture of drug and xyloglucan, drug and pluronic F127 in the drug-excipient interaction study, was found that Metformin HCl was compatible with all the excipients used in the formulation shown in Table-2.

Table No 2: FT-IR Peaks of Metformin Hcl And Mixture of Xyloglucan and Pluronic F127 Energy (wave numbers) cm^{-1}

S.No	Peak range	Pure drug (Metformin HCl)	Drug+ Pluronic F-127	Drug+ Xyloglucan	Assignment
1.	3000 - 3100	3002.16	2928.71	3100.01	C-H stretching
2.	1615-1690	1640.02	1673.13	1662.57	C=N stretching
3.	1540-1590	1591.00	1589.96	1552.54	N-H Bending
4.	1150-1180	1168.78	1160.72	1157.11	C-N bending
5.	3200-3400	3309.41	3328.29	3367.00	N-H Stretching

From these results, it can be confirmed that there is no interaction between Metformin HCl and polymers (Xyloglucan and Pluronic F-127) in the physical mixture.

Differential Scanning Calorimetry (DSC)

The optimized formulation was subjected to DSC the melting peak appeared at 226.62 ^{0}C shown in the Fig.1 From the DSC Study it can be confirmed that there was no considerable Drug- Excipient interaction was observed.

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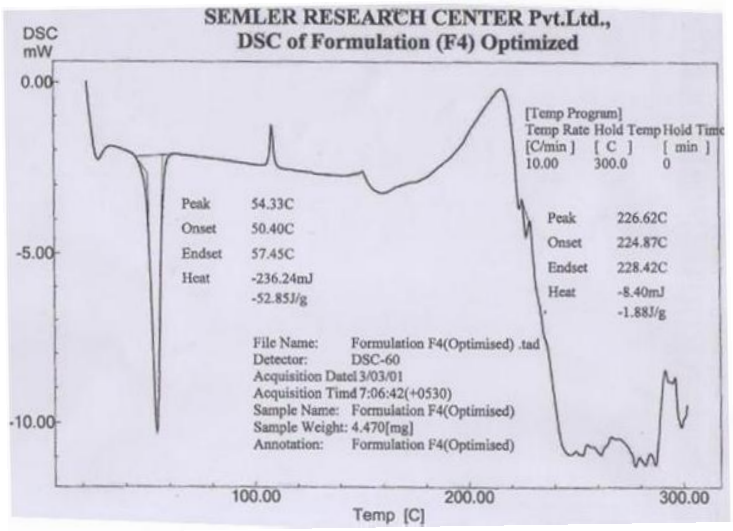


Figure 1: DSC of Optimized Fomulation

Gelation Temperature

Gelation temperature of the developed formulations varied from 21 ± 0.29 to 28 ± 0.95^{0}C.shown in the table-3.

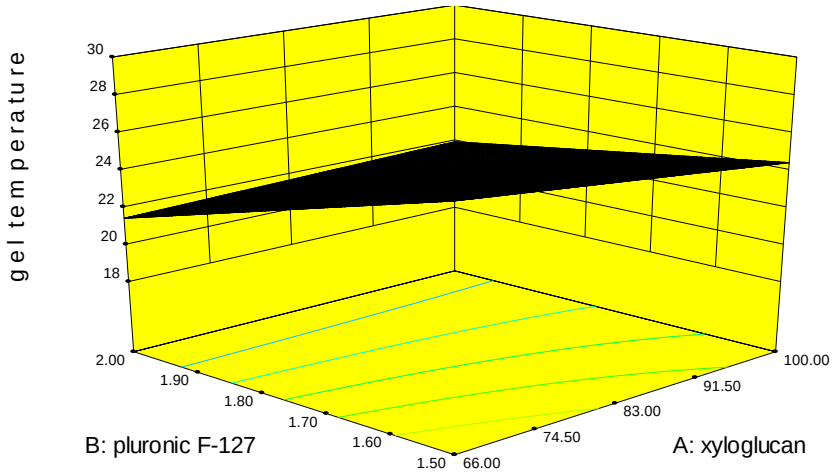
Table No 3: Response Variables of Prepared Formulations F1-F8

F. C.	Gelation temperature(^{0}c)	Gel strength (min)	Drug content (%)
F1	24±0.92	48±0.15	98.13 ± 0.94
F2	25±0.52	45±0.73	97.03 ± 0.57
F3	22±0.73	63±0.58	99.02 ± 0.29
F4	28±0.57	47±0.29	98.76 ± 0.48
F5	21±0.58	62±0.94	97.39 ± 0.73
F6	22±0.95	63±0.78	97.98 ± 0.52
F7	25±0.29	47±0.29	96.99 ± 0.73
F8	22±0.53	62±0.52	98.91 ± 0.91

The constant and regression coefficient for R_1 are as follows:

$$\text{Gelation temp} = 23.625 - 0.375 * A - 1.875 * B$$

The Model F-value of 7.85 and value of p is less than 0.0500 indicate the model is significant. Both the factors A and B showing negative effect which indicates that as the factors(A,B) increases the gelation temperature decreased, shown in the Fig.2.



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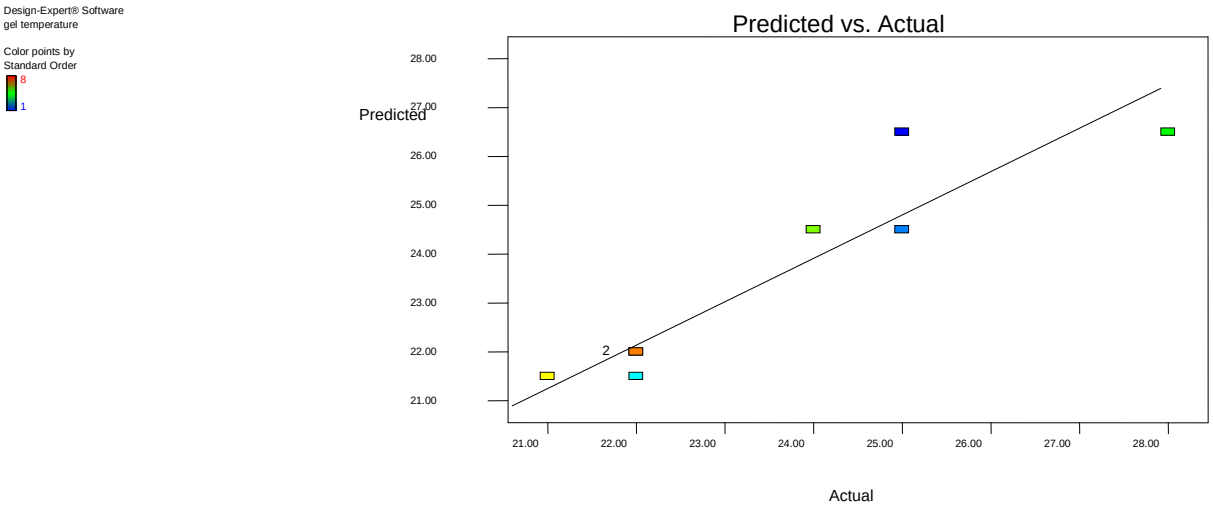


Figure 2: 3D Graph Showing Effect Of Xyloglucan And Pluronic F127 And Actual And Predicted Values For Gelation Temperature (R_1)

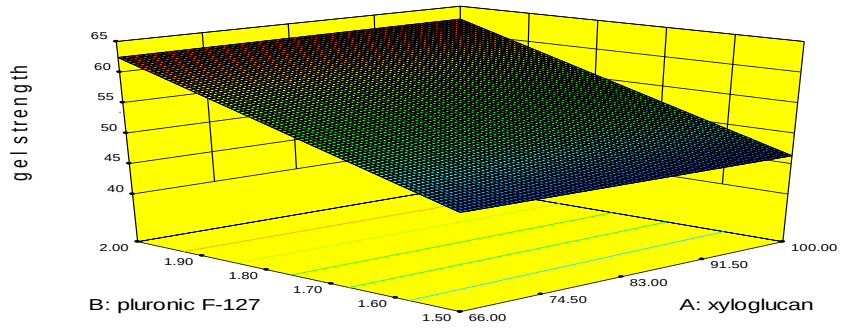
Gel Strength

Gel strength of the all developed formulations varied from 45±0.73 to 63±0.78min shown in the table-3.

The constant and regression coefficient for R_2 are as follows:

Gel strength = 54.687 -0.0625 *A 7.9375 *B

The Model F-value of 19.32 and value of p is 0.0014 indicate the model is significant. As the factor A increases the gel strength found to be decreased, as the factor B increases the gel strength found to be increased. shown in the Fig.3



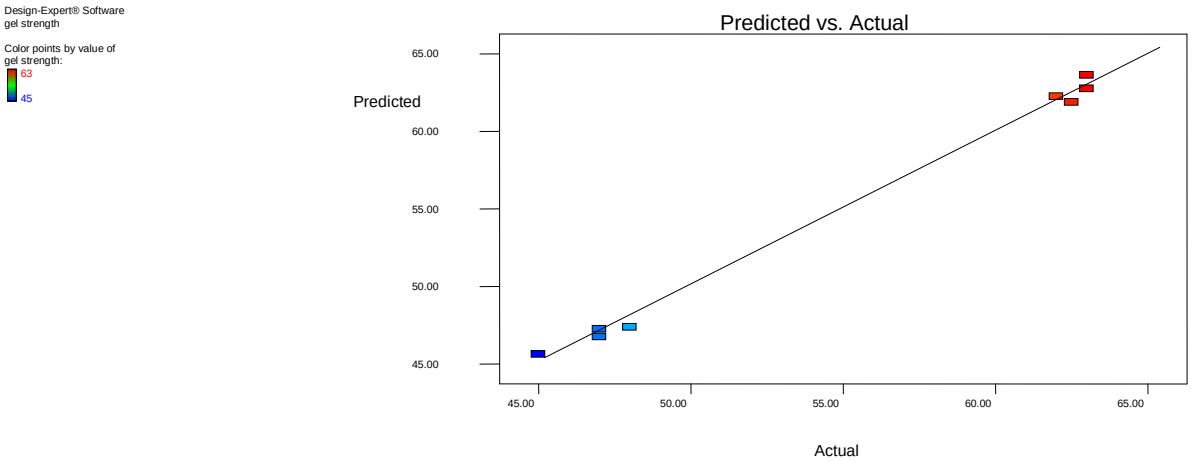


Figure 3: 3D Graph Showing Effect Of Xyloglucan And Pluronic F127 And Actual And Predicted Values For Gel Strength (R_2)

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Drug content: The results of drug content have been shown in the table-3.

Table 4: Summary of ANOVA Table for Dependable Variables

Source	d.f.	Sum of squares	Mean square	F value	Probability
Gelation Temperature					
A	1	1.13	1.13	0.85	0.4169*
B	1	28.12	28.12	20.45	0.0106*
Gelation Strength					
A					
B	1	0.031	0.031	0.034	0.8698*
C	1	504.03	504.03	556.17	0.0018*
	1	0.7812	0.7812	2.777	0.3440*
Drug release at 1 hour					
A	1	13.77	13.77	5.04	0.0882*
B	1	27.10	27.10	9.91	0.0346*
Drug release at 8 hour					
A	1	61.19	61.19	3.509	0.0476*
B	1	35.34	35.34	4.61	0.0983*
C	1	10.294	10.294	-	-
Drug release at 12 hour					
A	1	26.03	26.03	2.62	0.1663*
B	1	9.92	9.92	1.00	0.3632*
C	1	21.98	21.98	3.18	0.1491*

In vitro drug dissolution studies: The comparative studies of all formulations (F1-F8) are shown in Fig.4

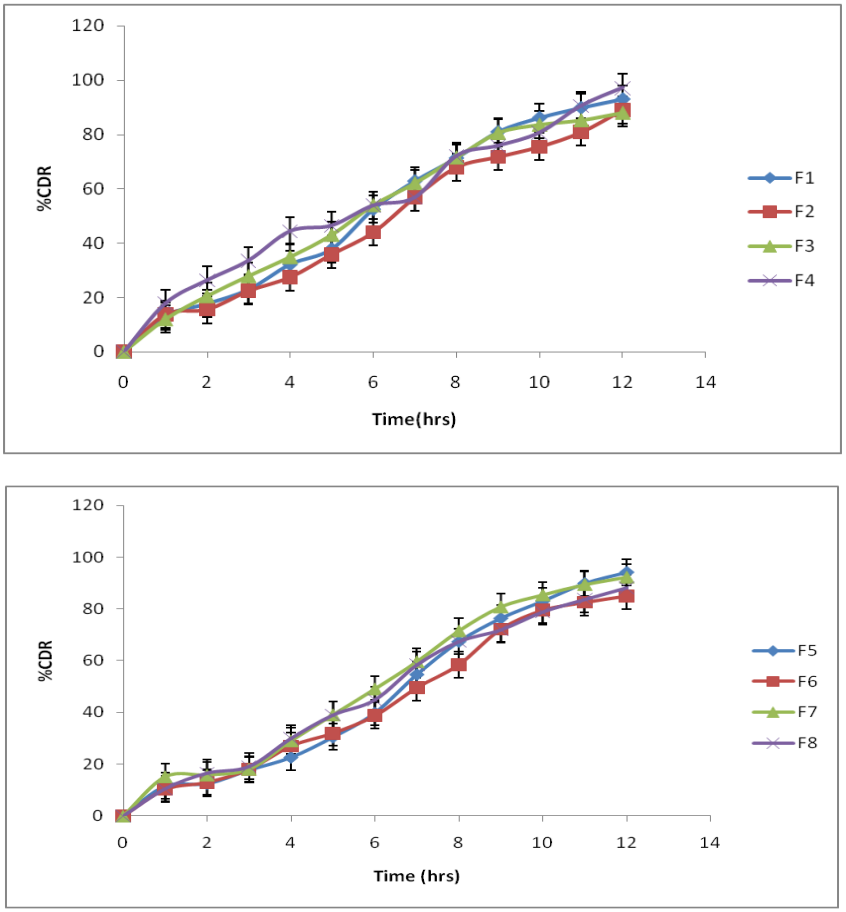

Figure 4: Comparative In-Vitro Dissolution Study of F1 – F8 Formulations:

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Table 5: Summary of ANOVA Grades In Analysing Residual And Cor Total:

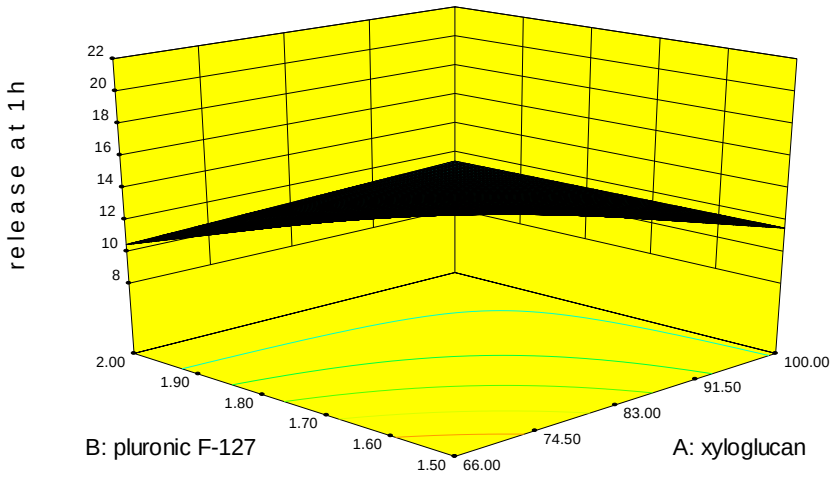
Source	Sum square	DF	Mean square	F value	Probability
Gelation temperature					
Model	32.37	3	10.79	7.85	0.0376*
Residual	5.50	4	1.38	-	
Cor Total	37.88	7	-	-	
Gel strength					
Model	507.66	5	101.53	112.03	0.0089*
Residual	1.81	2	0.91	-	
CorTotal	509.47	7	-	-	
%CDR at 1st hr					
Model	65.91	3	21.97	8.04	0.0361*
Residual	10.93	4	2.73	-	
CorTotal	76.84	7	-	-	
%CDR at 8th hr					
Model	159.22	3	53.07	6.92	0.0462*
Residual	30.66	4	7.67	-	
Cor Total	189.89	7	-	-	
%CDR at 12th hr					
Model	35.25	2	17.98	1.81	0.2560*
Residual	27.64	4	6.91	-	
Cor Total	85.57	7	-	-	

Release at 1 hr, 8hr, and 12hr:

Amount of Metformin HCl released from all formulations at 1hr. ranges from 10.28 % to 17.835 %, at 8th hr. ranges from 58.44% to 72.08% and at 12th hr. ranges from 84.93% to 94.17%. Decreased rate of drug release was observed with increased concentration of polymers.

Drug release at 1hr = + 12.81 -1.31 *A -1.84 *B
Drug release at 8hr = + 65.02 -2.77 *A -2.10 *B
Drug release at 12hr = +90.00 -1.80375*A -1.11375 *B

The linear model is selected for the 1hr with Model F-value 31.8 and p value is 0.0500, 8 hr with Model F-value 6.92 and p value is less than 0.0500, 12hr with Model F-value 4.79 and p value is less than 0.0500 which indicates the models is significant The factors A (Xyloglucan) and B (Pluronic F127) showing negative effect at 1hr,8hr and 12hr. Which indicates that as the factors (A,B) increases the drug release found to be decreased shown in the Fig.5,6,7.



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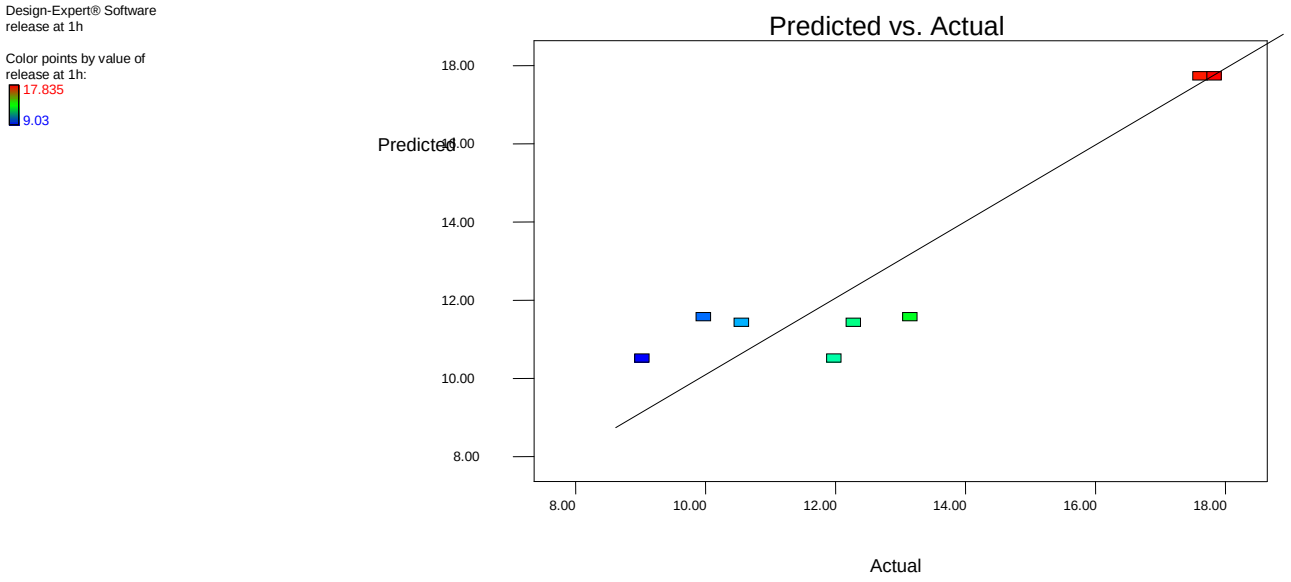
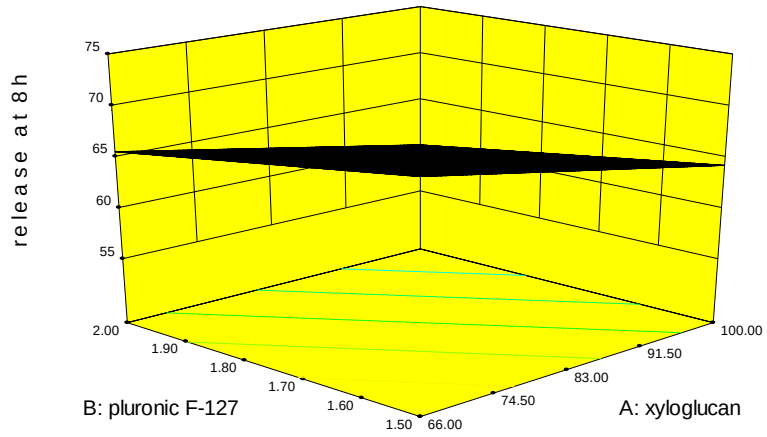


Figure 5: 3D Graph Showing Effect Of Xyloglucan And Pluronic F127 And Actual And Predicted Values For Drug Release At 1st Hour (R_3)



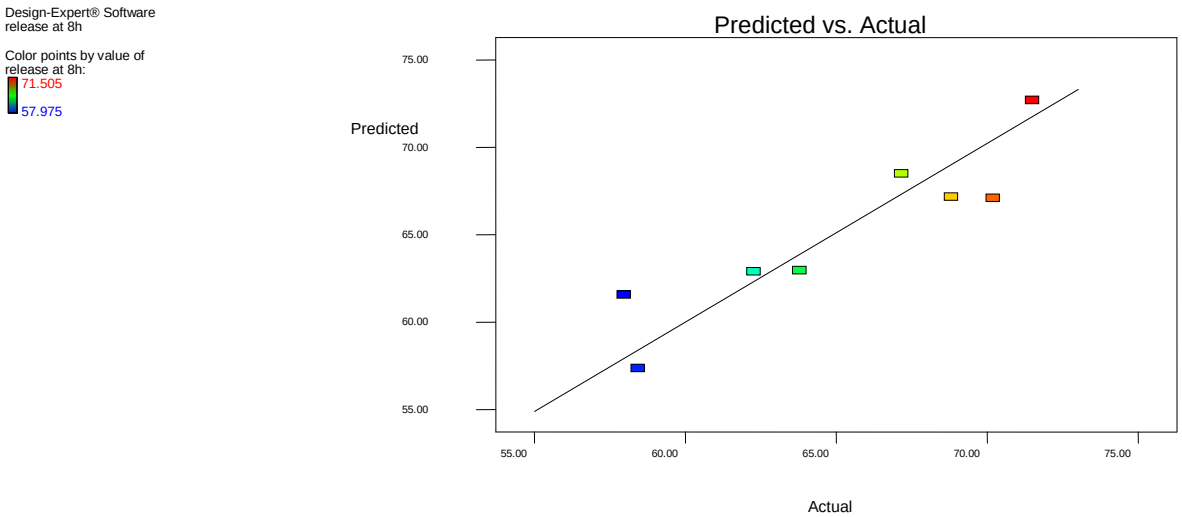


Figure 6: 3D Graph Showing Effect of Xyloglucan And Pluronic F127 And Actual And Predicted Values For Drug Release At 8th Hour (R4)

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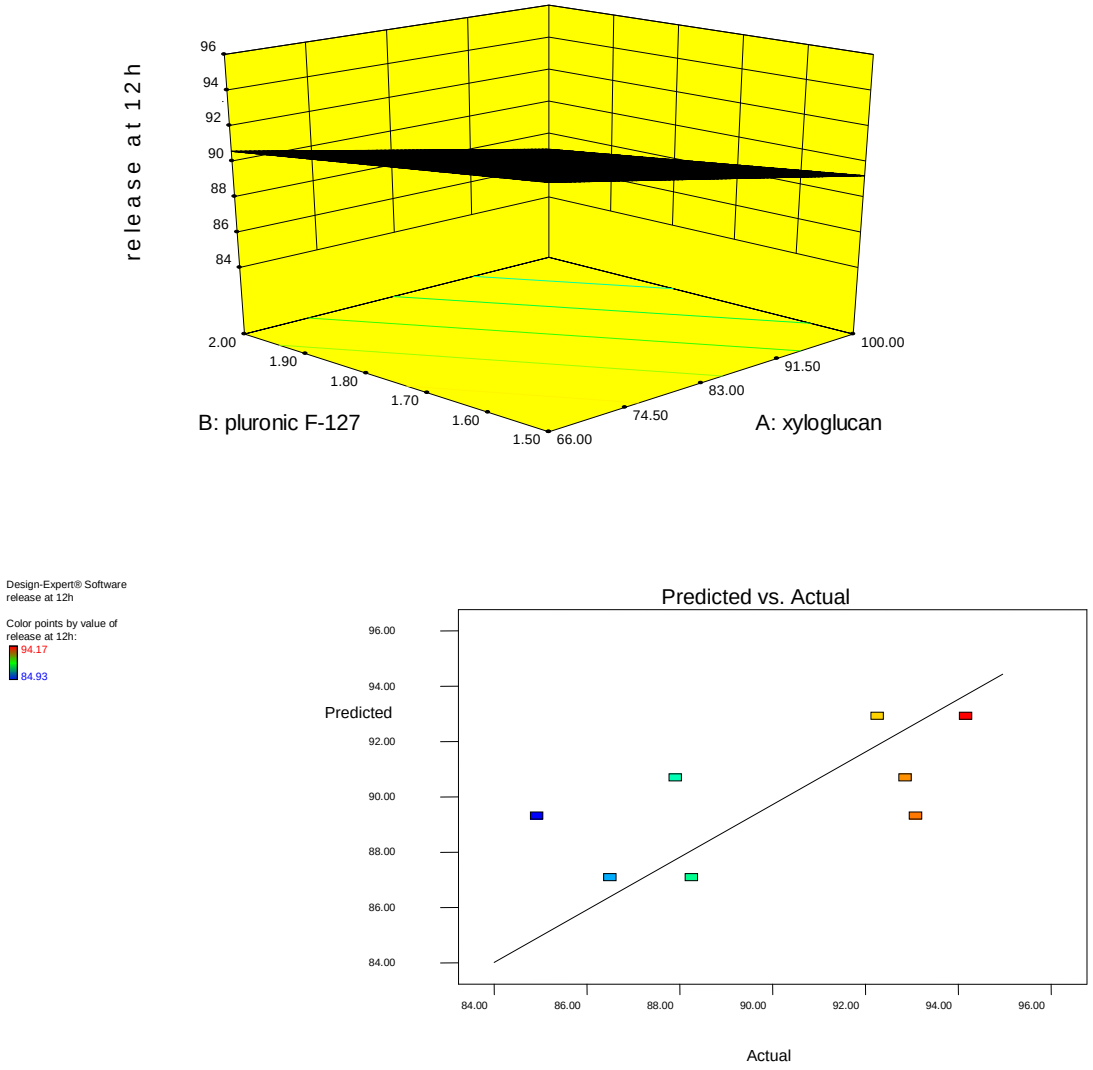

Figure 7: 3D Graph Showing Effect Of Xyloglucan And Pluronic F127 And Actual And Predicted Values For Drug Release At 12th Hour (R_5)

The result of ANOVA demostrate that the model was singnificant for all dependent variables shown in table-4. Regression analysis was carried out to determine the regression coefficients. All the independent variables (Factors) were found to be significant for all R1, R2, R3, R4 and R5 response variables shown in table-5. The linear model was found to be significant for all responses. So,above result indicate that both the factors play an important role in the formulation of in-situ gels containing metformin HCl.

For the optimized formulation, gelation temperature, gel strength, the drug release at 1sthr, 8th hr and 12th hr was kept at maximize.The composition of optimized formula is Metformin HCl (1gm), Xyloglucan (0.066 gm), Pluronic F-127 (1.56 gms) and Sorbitol (25 mg). The optimized formulation was prepared according to predicted model and evaluted for responses.

CONCLUSION

In conclusion the *in-situ* gels containing Metformin Hydrochloride were successfully prepared by simple mixing method and capable of exhibiting controlled release. The result of Two level Factorial Design revealed that the Xyloglucan and Pluronic F-127 have a significant effect on the gelation temperature, gel strength, the drug release at 1 hour, 8 hour, and at 12 hour. The n value range of the Peppas equation is 0.678, which indicates non-fickian diffusion mechanism.

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