

STATISTICAL OPTIMIZATION AND QUALITY BY DESIGN (QBD) APPROACH FOR THE DEVELOPMENT OF METHOCARBAMOL DELAYED-RELEASE TABLETS USING POLYMER BLENDS

Hemant H. Gangurde^{1*}, Nayana S. Baste², Vandana R. Daga², Charulata T. Nemade², Anita S. Wagh³, Manisha Bihani⁴, Sandip S. Khandagale¹, Shankar P. Chavan¹

¹ NMSM's Abasaheb Kakade Institute of Pharmacy and Research, Bodhegaon-414503, Ahilyanagar, Maharashtra, India.

² SNJB's SSDJ College of Pharmacy, Chandwad-423101, Nashik, Maharashtra, India.

³ Srinath College of Pharmacy, Chhatrapati Sambhaji Nagar, Maharashtra, India.

⁴ Krupanidhi College of Pharmacy, Bengaluru-560035, Karnataka, India

*Corresponding Author: Hemant H. Gangurde, Email ID: drswatipathakmch@gmail.com

ABSTRACT

The present study utilizes the principle of rheological synergism between hydrophilic polymers in development of pharmaceutical formulations, more specifically to develop and evaluate delayed release matrix tablet using polymer blends. Methocarbamol is an FDA approved centrally acting skeletal muscle relaxant. It works by calming overactive nerves in body, which helps muscles to get relaxed but its mechanism of action is not well defined and its effects are measured mainly by subjective responses. Half-life of Methocarbamol is short so it is necessary to prolong drug action, hence it was decided to develop matrix tablets as desired dosage form. HPMC, SCMC, its blends and marketed Instamodol 41 and 49 polymer blends were used for the study. Further Instamodol 41 was selected and matrix tablets were further coated with Instacoat EEN to protect drug release in upper GIT. Preliminary trial batches were studied for pre and post compression evaluation test. Formulation showed desirable lag time and dissolution profile were further optimized by applying 3² full factorial design to study the effect of extent of coating (% w/w) Instacoat EEN and Instamodol 41 matrix tablet were selected as independent variables X1 and X2 respectively and two responses as lag time and Cumulative % drug release at 18 hours as Y1 and Y2 respectively. Various kinetic models were applied to the all optimized batches. All F1-F9 and optimized solution batch M results complied with IP standards. The regression equation generated for Lag Time = $9.35 - 3.76 A + 0.7533B$ and for % CDR = $+93.93 - 0.9717 A - 4.27 B$. The drug release data of optimized formulation were close to that predicted by the model. The formulation M with 5.903 %w/w Instacoat EEN and 125 mg w/w Instamodol 41 was found to be optimum. The present study demonstrates that Methocarbamol enteric coated matrix tablet could be successfully released in lower GIT with delayed action.

KEYWORDS: Statistical optimization, Methocarbamol, delayed release, matrix tablet, Instacoat EEN, Instamodol 41.

INTRODUCTION:

The intrinsic characteristic of GIT like physiology, pharmacokinetics and pharmacodynamics are essential in formulation design to achieve a systemic application. Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug through several pharmaceutical dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration trust for drug absorption [1]

The rationale for controlled drug delivery is to alter pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and pharmacological parameters inherent in the selected route of administration. It is appropriate that the drug action duration becomes most desirable property of rate controlling dosage form and less or no property of drug molecule inherent kinetics properties. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs. [2-4]

Methocarbamol is a musculoskeletal relaxant for the relief of acute pain. It acts by mechanism by obstructing pain sensations by blocking nerve impulse that is sent to brain. The plasma protein binding of methocarbamol ranges between 46% and 50%. In healthy volunteers, the plasma clearance of Methocarbamol ranges between 0.20 and 0.80 L/h/kg, the mean plasma elimination half-life ranges between 1 and 2 hours, and administered several times near about three to four times in a day. It is rapidly and fully absorbed from the GIT and undergoes extensive metabolism in liver.

It may develop prominent adverse effects like dizziness, drowsiness, and headache associated with its use. So, it was chosen as model drug.

Mixture of at least two macromolecular substances, polymers or copolymers, in which the API content is above 2%. Polymer alteration or modification processes based on simple physical mixtures of two or more polymers originates new class of materials called polymer blends. The performance of polymer blends depends on the properties of each polymer in the blend, their content, and morphology. Polymer blends can be classified into the following categories immiscible polymer blends, miscible polymer blends and compatible polymer blends. Polymer blends can be achieved by using different types of machinery like single or multishaft mixers, and extruders, such as single or twin-screw extruders. [5,6]

Polymers of varying physico-chemical properties when blended, they may not interact in the same way with water and drug, resulting in different mobility of water and drug within the polymeric networks. Polymer blends sensitive to the surrounding environment may be of particular interest for many applications. The application of polymers to sustain drug release is increasingly becoming popular and the use of polymer blends offers a good alternative method to develop new pharmaceutical raw excipient. This work aims to study the effect of polymer blends of HPMC with SCMC and marketed polymer blend Instamodel 41 on the mechanical properties and release rate of delayed release tablet. [7-13]

EXPERIMENTAL WORK

Materials

Methocarbamol was a kind gift from Athena Pharma Pvt. Ltd. (Mumbai, India). Instamodel 41, Instamodel 49 and Instacoat EEN were also a kind gift sample from Ideal Cures pvt. ltd Pvt. Ltd. (Mumbai, India). HPMC, SCMC, IPA etc. were purchased from Thermosil Chemicals (Pune, India).

Methods

Preformulation and Characterization [6, 14,15]

A thorough understanding of physicochemical properties may help in providing a rational for formulation design of dosage form, supporting need for molecular modification and checking if there are no barriers to compounds development. So, the Preformulation studies and characterization of selected drug sample for their physicochemical properties were studied like UV spectroscopy, IR spectroscopy and DSC.

U.V Spectroscopy

An accurately weighed 10 mg of Methocarbamol was dissolved in 10 ml methanol in 10 ml volumetric flask which produced 1000 µg/ml solution. The aliquot of 1 ml pipette out from this 1000 µg/ml solution and was diluted to 10 ml methanol in 10 ml volumetric flask, which produced 100 µg/ml solution and after that by using UV spectrophotometer, the λ_{max} was found by scanning between 400 to 200 nm.

IR Spectroscopy

Infrared spectrophotometer is a useful analytical technique utilizes to check the conformation drug functional group. Methocarbamol (1 mg) powdered was kept in a sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400 cm⁻¹ using IR spectrophotometer.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry equipped with an intra- cooler and a refrigerated cooling system was used to analyze the thermal behavior of Methocarbamol in the range of 35 to 300°C. Indian standard was use to calibrate the DSC temperature and Nitrogen was purged 50 ml/min and 100ml/min through cooling unit.

Formulation of Preliminary trial Methocarbamol delayed release tablet using polymer blends [16-22]

Initial trial batches using various polymers blends of HPMC, SCMC and marketed polymer blend like Instamodel 41 and 49 were tested, finally it was confirmed to use Instamodel 41 blend 150 mg to develop delayed release tablets by wet granulation method each tablet containing 500mg of Methocarbamol. On performing pre and post compression quality test specifically *in vitro* dissolution test to control drug release in upper GIT it was decided to coat tablet with Instacoat EEN between 1-5 % coating weight gain shown in Table 1.

Table No. 1: Composition of preliminary trial batches C1 to C5

Sr. No.	Ingredients	C1	C2	C3	C4	C5
A	Matrix Tablet Formulation					
1	Methocarbamol	500	500	500	500	500
2	Instamodel 41	150	150	150	150	150
3	PVP K30	50	50	50	50	50
4	Magnesium stearate	10	10	10	10	10
5	Aerosil	10	10	10	10	10
6	MCC	50	50	50	50	50
7	Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
B	Coating Formulation					

1	Instacoat EEN (% weight gain)	1	2	3	4	5
2	IPA Purified Water (70:30)	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of Methocarbamol delayed release matrix tablet [23-27]

a. Pre-compression parameter

Granules were characterized for their physical parameter such as bulk density, tapped density, compressibility index Hausner's ratio.

b. Post compression parameter

1. Uniformity of weight

Uniformity of weight test select the 20 tablets randomly and weigh a separately each tablet after average weight and standard deviation is calculate as per IP guidelines.

2. Hardness

Tablet hardness was determined using Monsanto Hardness Tester. Five tablets from each batch were selected and evaluated, and the average value was recorded.

3. Friability

Friability of tablets was performed using Roche Friabilator. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions. The tablets were then de-dusted and re-weighed.

4. *In vitro* Dissolution studies

In vitro dissolution study of Methocarbamol was performed using USP dissolution test apparatus-II (paddle assembly). The dissolution was performed using 900 ml of pH 1.2 HCL 2 hr. and then it replace by phosphate buffer solution (pH 6.8) for 12 hrs. as dissolution media maintained at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. 5ml aliquots were withdrawn at regular intervals and volume was replaced with fresh dissolution medium to maintain sink condition. % drug release concentration was measured at given wavelength by UV spectrophotometer.

5. Drug release models:

To describe the kinetics of the drug release from the controlled release tablet, the release data were evaluated with the help of mathematical models such as zero-order, first-order, Higuchi and Koresmeyer-Peppas model.

Experimental design [21,28-30]

Batch C5 was selected from preliminary experimental batch, and 3^2 randomized full factorial design was implemented. The independent variables were weight gain of Enteric coating polymer (X1) and Instamodel 41 as release retardant polymer blend (X2) were selected as independent variables. The dependent variables (responses) Y1 = Lag time and Y2 = Cumulative % drug release at 18 hrs. Coded levels and full factorial design layout with experimental runs and their combinations are given in Table 2.

Table No. 2: Translation of the Coded Levels in Actual Units

Factors (independent variables)	Levels used			Responses (dependent variables)
	-1	0	+1	
X1= Concentration of coating polymer (% w/w)	4	5	6	Y1= Q2 (lag time)
X2= Concentration of Instamodel 41 polymer blend (% w/w)	125	150	175	Y2= Q18 (Cumulative % drug release)

Preparation of Formulation Batches (F1 to F9) as per Factorial Design

Instamodel 41 was used for preparation of tablet and their concentration in the formulation ranging 125, 150 and 175 mg respectively of total weight of tablet. Matrix tablet of Methocarbamol in were prepared by wet granulation method as their 9 batches F1 to F9 Batches containing different at coating weight gain of Instacoat EEN 4, 5 and 6% respectively shown in Table 3. Post compression parameters were carried out as shown earlier.

Table No. 3: Composition of Formulation Batches (F1 to F9) as per Factorial Design

Ingredients	Quantity per tablet (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Methocarbamol	500	500	500	500	500	500	500	500	500
Instamodel 41	125	150	175	125	150	175	125	150	175
PVP K30	50	50	50	50	50	50	50	50	50
Magnesium stearate	10	10	10	10	10	10	10	10	10
Aerosil	10	10	10	10	10	10	10	10	10

MCC	175	150	125	175	150	125	175	150	125
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight	874	874	874	874	874	874	874	874	874
Instacoat EEN (%weight gain)	4	4	4	5	5	5	6	6	6
IPA: Water (70:30)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

RESULT AND ANALYSIS

Preformulation studies and characterization for physicochemical properties of selected drug, excipient and its combination were studied by UV spectroscopy, IR spectroscopy and DSC.[21]

Fourier Transform Infrared Spectroscopy: (FTIR)

FTIR spectrum of Methocarbamol pure drug and with polymer blends like HPMC K100 and SCMC, Instamodel 49 and Instamodel 41 respectively at ratio (1:1) are shown in Figure 1. From the IR spectrum of drug and physical mixture no significant change in peak pattern was observed. Hence it can be concluded that there was no any interaction of drug with excipients and it was compatible with excipients used in present work.

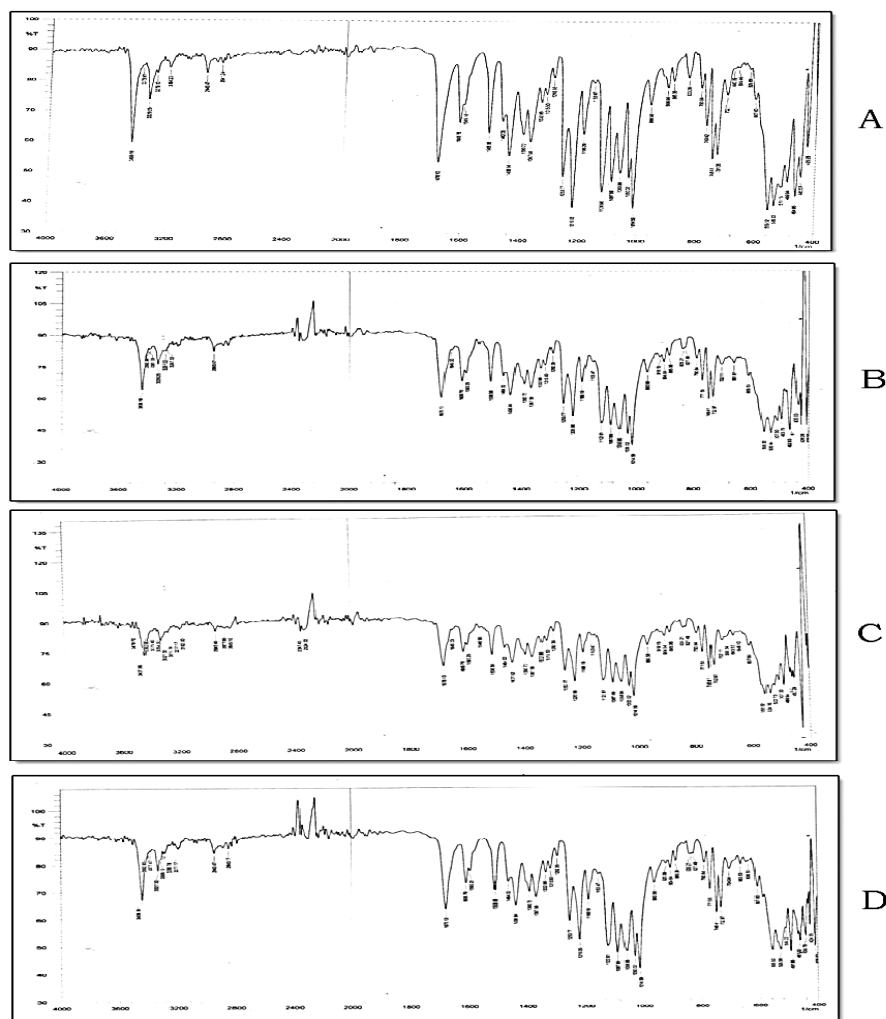


Figure No.1: FTIR spectrum of A: Methocarbamol, B: mixture of Methocarbamol, HPMC and SCMC (1:1:1), C: Methocarbamol and Instamodel 49 (1:1), D: Methocarbamol and Instamodel 41 (1:1).

Differential scanning Calorimetry (DSC)

The DSC thermogram shows a sharp endothermic peak at 95.11°C for Methocarbamol. While in drug with HPMC and SCMC blend and drug with Instamodel 41 endothermic peak was observed at 94.47°C and 94.71°C respectively, which was as same as close to pure drug shown in Figure 2. Evaluation and interpretation of the thermogram revealed no interaction between the drug and polymer in the optimized formulation.

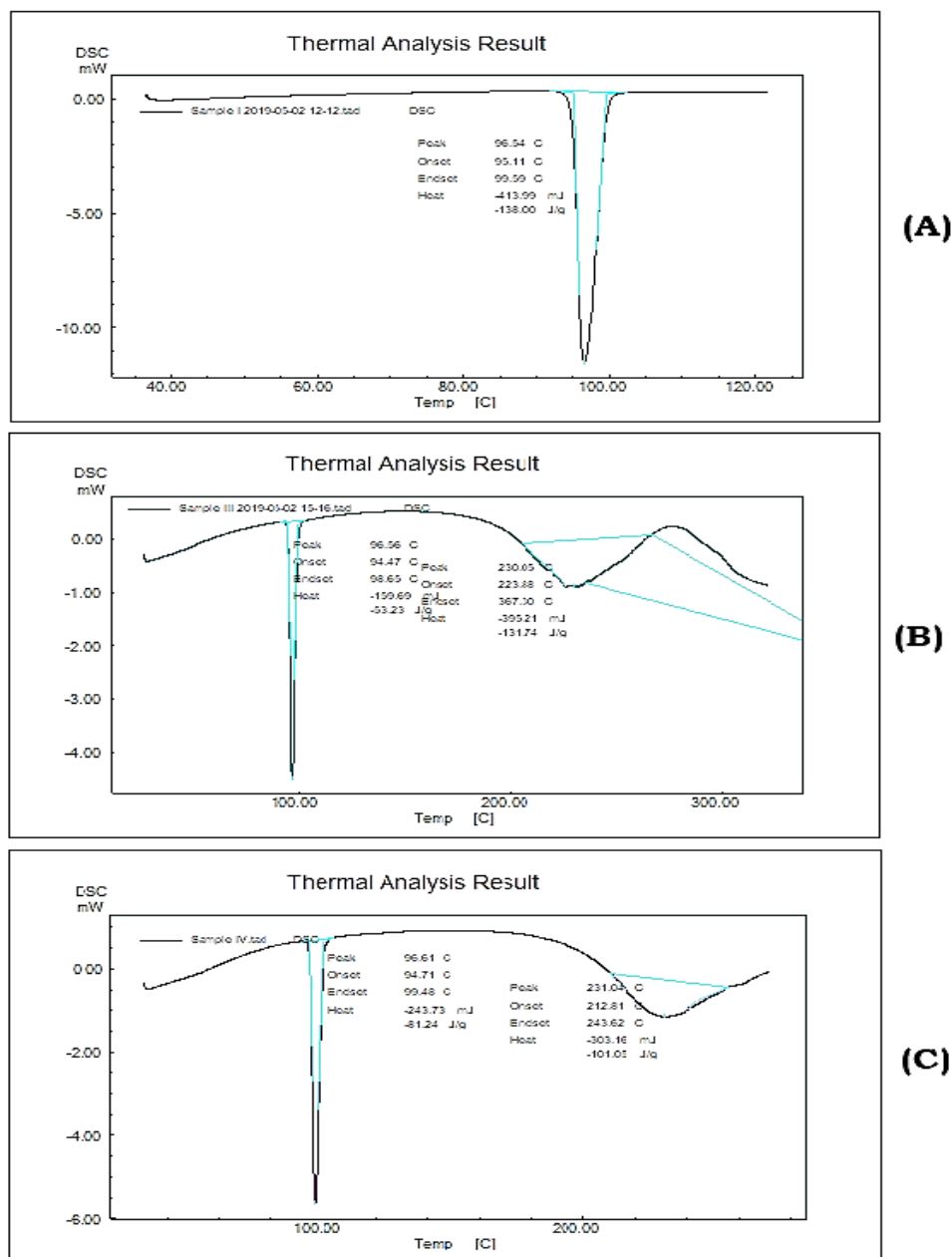


Figure No. 2: DSC thermogram of A: Methocarbamol, B: Methocarbamol and HPMC: SCMC blend and C: Methocarbamol and Instamod 41.

Preliminary trial Methocarbamol delayed release tablet using polymer blends

In vitro release depends upon several factors such as manufacturing process, type of excipients and amount of drug. In this work effect of polymer blends on Methocarbamol release was studied and drug release pattern observed for formulation C1 to C5. Formulation C1 to C3 which contain instamod41 150 mg and coating weight gain of 1, 2 and 3 % respectively showed drug release up to 14 hr. Formulation C4 indicating 94% drug release up to 16 hrs. at 4% coating and formulation C5 indicating 97 % drug release at 18 hrs., batch contained 5% coating as seen in Figure 3.

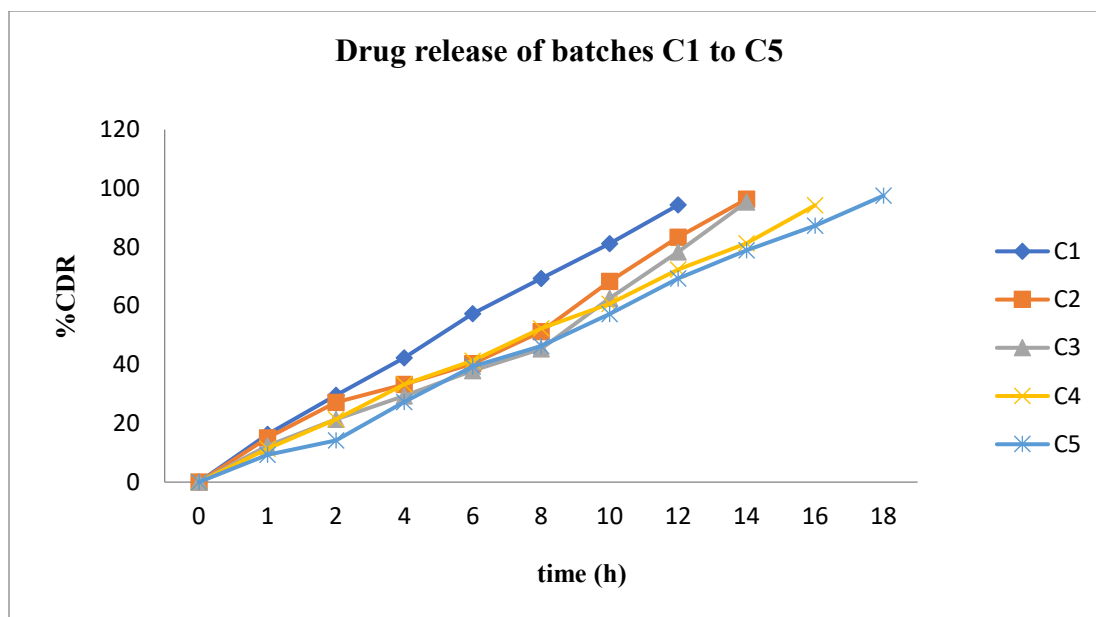


Figure No.3: % drug release of Tablet batch C1 to C5

Methocarbamol delayed release formulation of optimization batches.

Actual value% obtained from C5 Batch Translation of the Coded Levels in Actual Units. % coating of Instacoat EEN there 9 batches F1 to F9 the polymer Instamol41 (14-20%) and Batches containing different % coating of Instacoat EEN. Granules prepared using blend of Instamodel 41 (14-20%) respectively of drug weight at various combinations was evaluated for the micromeritic parameter like bulk density, tapped density, Carr's index and Hausner's ratio. Table 4 gives the result of evaluation parameter with their standard deviation values

Table No. 4: Precompression parameter result of batches F1 to F9.

Formulation code	Angle repose of	Bulk density (gm/cm ³)	Tapped density (gm/cm ³)	Hausner's ratio(HR)	Carr's index (%)
F1	19.30±0.13	0.356±0.009	0.470±0.009	1.32±0.057	24.25±7.40
F2	23.68±0.012	0.418±0.004	0.559±0.018	1.33±0.056	25.22±5.68
F3	25.7±0.13	0.371±0.005	0.471±0.010	1.26±0.047	21.23±2.68
F4	15.87±0.68	0.375±0.044	0.496±0.001	1.04±0.032	24.39±13.5
F5	16.04±0.19	0.417±0.004	0.438±0.013	1.39±0.085	4.79±2.66
F6	17.18±0.77	0.384±0.062	0.470±0.018	1.28±0.015	18.29±8.47
F7	27.41±0.21	0.433±0.001	0.486±0.041	1.12±0.11	10.90±3.90
F8	21.6±0.34	0.358±0.012	0.500±0.024	1.39±0.11	28.4±2.64
F9	13.11±0.41	0.383±0.004	0.430±0.018	1.12±0.020	10.93±2.80

M± S.D., n=3

Tablet Prepared with Instamodel 41 (14-20%) of drug weight was evaluated for the various parameters like Uniformity of Weight, thickness, hardness friability and drug content. Table 5 gives the result of evaluation parameter with their standard deviation values.

Table No. 5: Post compression parameter result of batches F1 to F9

Formulation code	Hardness* (kg/cm ²)	Thickness* (mm)	Uniformity of Weight#(mg)	Friability* (%)	Drug* content (%)
F1	11.2±1.03	7.21±0.14	872±5.43	0.34±0.02	95.99±1.45
F2	12.4±1.17	6.34±0.41	870±15.9	0.24±0.09	96.68±1.48
F3	14.7±0.93	6.79±0.28	877±8.28	0.30±0.06	94.66±0.68

F4	13.2±0.87	7.11±0.32	871±5.43	0.34±0.02	96.42±1.71
F5	12.4±1.23	5.29±0.48	874±15.9	0.24±0.02	93.12±0.87
F6	14.7±1.41	6.49±0.18	877±8.28	0.30±0.06	97.78±0.94
F7	13.2±0.56	7.11±0.17	876±5.43	0.34±0.09	94.72±0.84
F8	12.4±1.12	6.19±0.25	8.75±15.9	0.24±0.05	92.78±0.86
F9	14.7±0.72	5.79±0.33	875±8.28	0.30±0.08	99.12±1.68

#M± S.D., n=20

*M± S.D., n=3

The total amount of release from the formulation F5, F6 up to 14 hrs. ranged between 95 to 98%. And F1, F2, F3 F5, F6 F8 and F9 up to 18 hrs. ranged between 92-97%. As the total percent of matrix system increase in the formulation, more delayed release effect was observed shown in Figure 4, from this we can concluded that Instamodell41 is the release controlling agent.

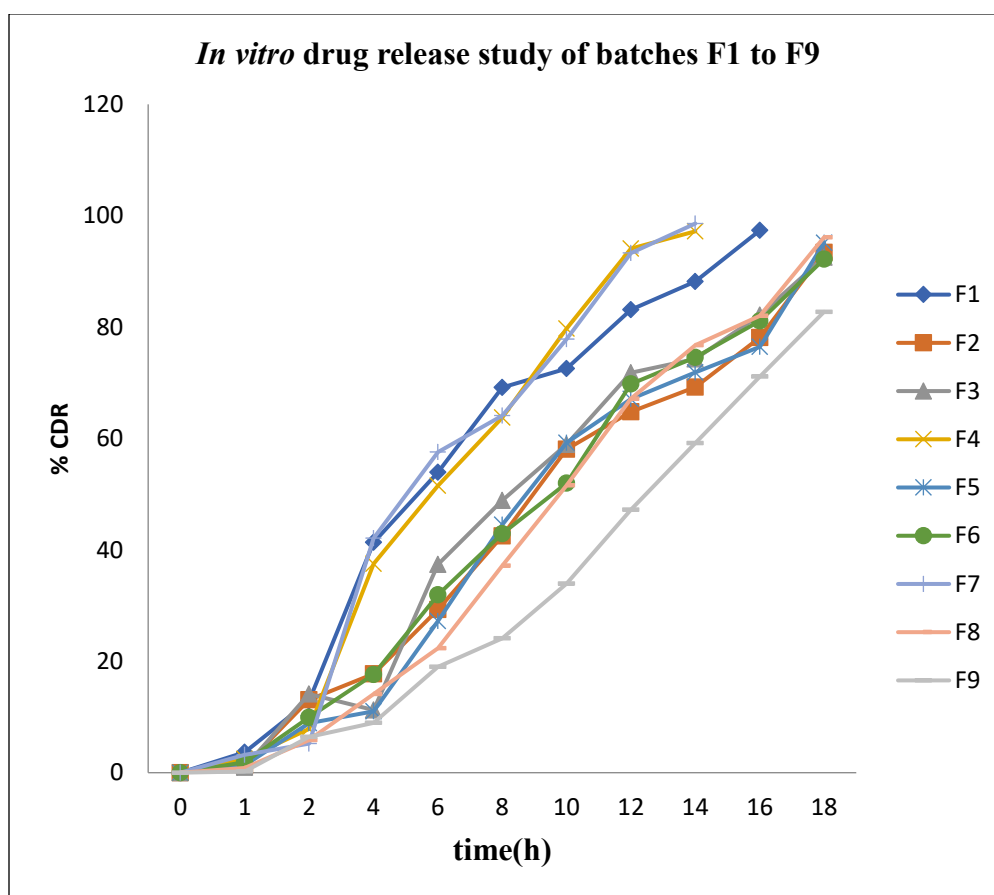


Figure No. 4: Cumulative % drug release of optimization batches (F1 to F9).

Drug Kinetic release

The drug release pattern was investigated by the different kinetic equations like Zero order, First order, and Higuchi's, Hixon-Crowell and Korsmeyer-Peppas equation. The release mechanism was understood fitting the obtained data to Korsmeyer-Peppas model. Figure no. 5 shows different release kinetics pattern, release mechanism from the different formulations as well as best fit release pattern. The best fit model representing the mechanism of drug release from matrices was Korsmeyer-Peppas and Higuchi. This release mechanism is not purely diffusion-controlled but involves a combination of diffusion and from matrix. The combination of both can lead to control of drug release producing greater therapeutic effects with minimum side effects

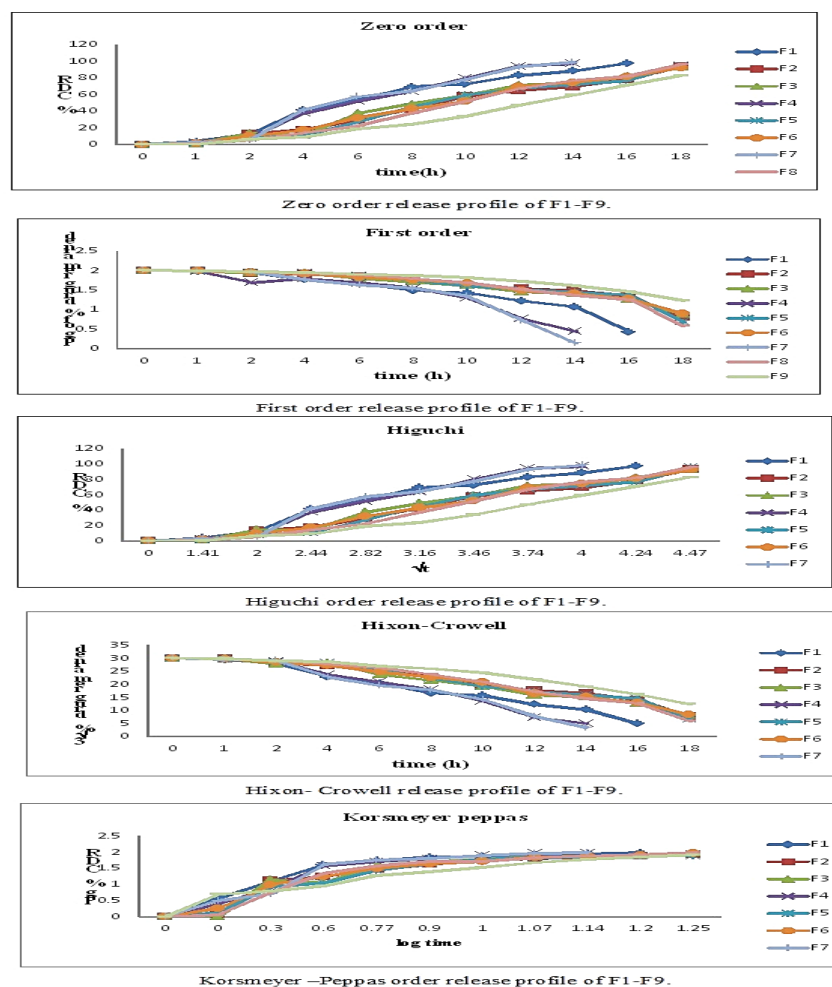


Figure No. 5: Drug release kinetic profile of F1-F9.

Optimization data analysis

Various computations for the current optimization study were performed using Design Expert® software version 11.1.2. Stat-Ease Inc., USA. A two factor three level full factorial design was used for systemic study of combination of natural polymer and channeling agent. A 3^2 full factorial design was constructed where the amounts of Instamodell 41 (X_1) and Instacoat EEN (X_2) were selected as the independent variables. The levels of these factors were selected on the basis of initial studies and observations. All the other formulation aspects and processing variables were kept invariant throughout the study period. Polynomial models including interaction and quadratic terms were generated for the entire response variables using multiple linear regression analysis (MLRA) approach is represented in the Equation

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \dots\dots\dots (1)$$

Where Y is the dependent variable; b_0 is the arithmetic average of all the quantitative outcomes of nine runs. b_1 , b_2 , b_{12} are the estimated coefficients computed from the observed experimental response values of Y and X_1 and X_2 are the coded levels of the independent variables. The interaction term (X_1X_2) shows how the response values change when two factors are simultaneously changed. The polynomial terms (X_1^2 , X_2^2) are included to investigate nonlinearity. Statistical validity of the polynomials was established on the basis of analysis of variance (ANOVA) provision in the Design Expert software. Level of significance was considered at $p < 0.05$. The best-fitting mathematical model was selected based on the comparison of several statistical parameters, including the coefficient of variation (CV), multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2), and predicted residual sum of squares (PRESS), provided by the software.

Table No.6: Layout of Design Actual.

		Factor 1	Factor 2	Response 1	Response 2
Std	Run	A:Instacoat EEN	B:Instamodell 41	Lag Time	% CDR
		%	mg	Hrs.	Hrs.
1	1	4	125	12.84	97.35
3	2	6	125	5.2	98.6

5	3	5	150	8.88	95.14
8	4	5	175	9.91	92.21
4	5	4	150	13.09	93.41
2	6	5	125	7.87	97.2
6	7	6	150	5.87	96.13
9	8	6	175	6.4	82.75
7	9	4	175	14.12	92.55

The 3² factorial experimental design was selected and as per required 9 batches were prepared. The ranges of the Lag Time (Y1) and % CDR (Y2) are 82.75- 98.60% and 5.2-14.12 hrs respectively. The all responses observed for a 9 formulations prepared were simultaneously fitted to the linear, 2FI, quadratic and cubic models by using Design Expert® software version 11.1.2.Stat-Ease Inc. It was observed that best-fitted model were quadratic and linear for the Lag time and the % CDR. It was evident two independent variables, namely the concentration of Coating EEN (A), and Concentration of Instamodel 41 blend (B), respectively have the interactive effects on the two responses, Y1 and Y2. The positive value represents an effect that favors optimization, while the negative value indicates inverse relationship between the factor and response. Hence, goals were set for the responses Y1 and Y2 in a Design Expert® software version 11.1.2 Stat-Ease Inc. After the analysis of a both independent and dependent variables the Design Expert® software gave almost 4 solutions with the various desirability but only one batch was selected with high desirability near to the one. The values of R², adjusted R², predicted R², SD and %CV Table 7, along with regression equation generated for each response.

Table No. 7: Summary of results of regression analysis for responses Y1 and Y2.

Models	Std. Dev	Mean	C. V. %	R ²	Adjusted R ²	Predicted R ²	Adeq Precision
Response (Y1) Linear model	0.4654	9.35	4.98	0.9855	0.6316	0.9676	33.6177
Response (Y2) Linear model	3.30	93.93	3.51	0.6380	0.5173	-0.0117	5.5035

Full and Reduced Model assessment for the dependent variables:

A) Model for Q2: Final Equation in Terms of Coded Factors

$$\text{Lag time} +9.35-3.76+0.7533$$

(2)

Final Equation in Terms of Actual Factors

$$\text{Lag time} +23.6500-3.7633\text{Instacoat EEN}+0.030133 \text{ Instamodel 41}$$

Where, Y1 is Lag Time, A is the Instacoat EEN, and B is the Instamodel 41 blend. The **Model F-value** of 204.01 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 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms, model reduction may improve your model.

Model for Q18:

Final Equation in Terms of Coded Factors

$$\% \text{CDR} = +93.93-0.9717\text{A}-4.27\text{B}$$

(4)

Final Equation in Terms of Actual Factors

$$\% \text{CDR} = +124.425-0.971667 \text{ Instacoat EEN}-0.170933 \text{ Instamodel 41}$$

(5)

Where, Y2 is % CDR, A is the concentration of Instacoat EEN, and B is the concentration of Instamodel 41 blend. The **Model F-value** of 5.29 implies the model is significant. There is only a 4.75% 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, model reduction may improve your model. ANOVA data shown in Table 8.

Table No 8. Analysis of variance (ANOVA) of dependent variables.

Source	Sum of Squares	Degree of freedom	Mean Square	F Value	p-value	Prob>F
Analysis of Variance for Y1 (lag time)						
Model	88.38	2	44.19	204.01	< 0.0001	Significant
A-Instacoat EEN	84.98	1	84.98	392.30	< 0.0001	
B-Instamodel 41 blend	3.41	1	3.41	15.72	0.0074	

Residual	1.30	6	0.2166	-	-	
Cor Total	89.68	8	-		-	
Analysis of Variance for Y2 (% CDR)						
Model	115.23	2	57.62	5.29	0.0475	Significant
A- Instacoat EEN	5.66	1	5.66	0.5197	0.4981	
B- Instamodel 41 blend	109.57	1	109.57	10.05	0.0193	
Residual	65.39	6	10.90	-	-	
Cor Total	180.63	8				

The two dimensional contour plots, response surface analysis and predicted Vs actual were prepared for the Y1 response they are as shown in Figure 6. These plots are known to the study interaction effects of the factors on the responses

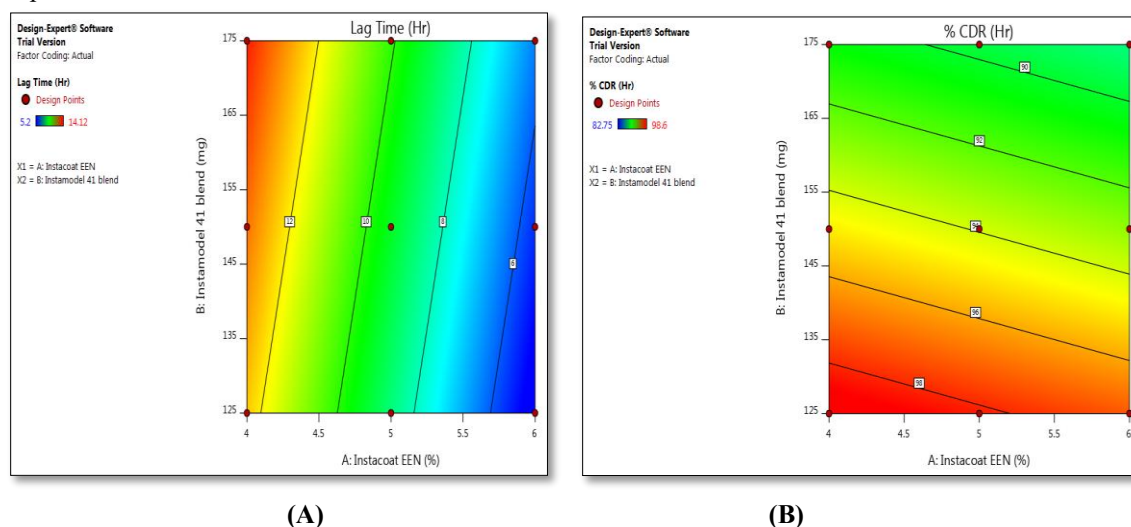


Figure No. 6: 2D Contour plot of Lag time (A) and % CDR (B)

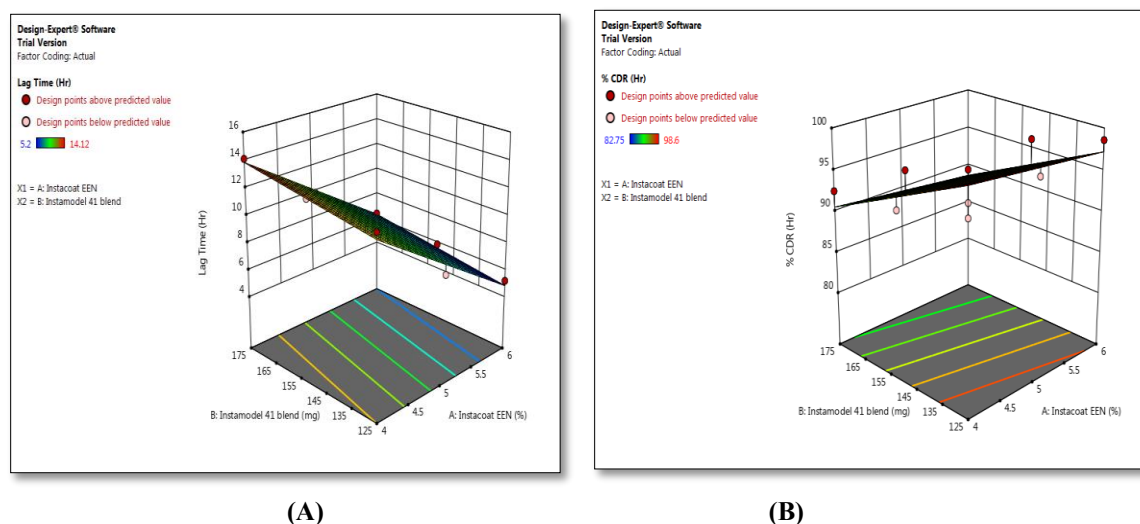
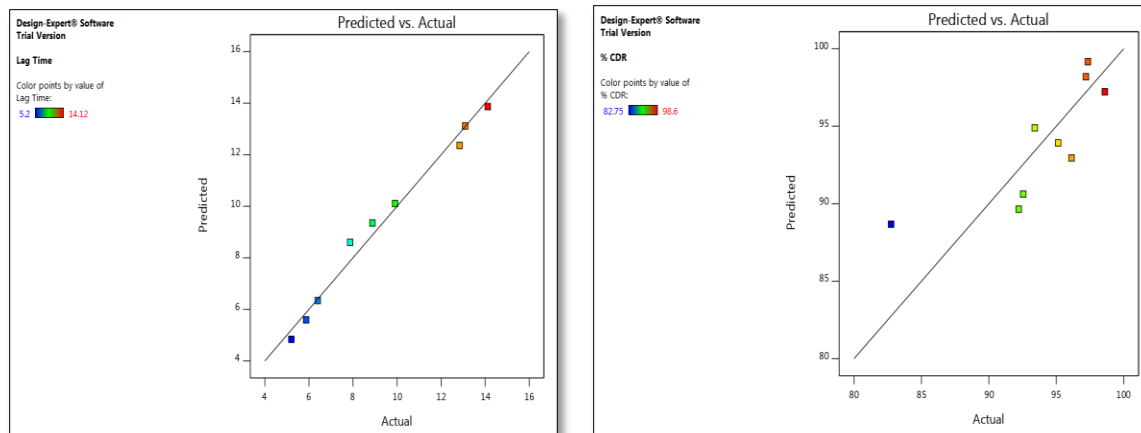


Figure No. 7: 3D Surface plot of Lag time (A) and % CDR (B)

Validation of optimum formulations:

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent (response) variables Y_1 and Y_2 . The optimum formulation was selected based on the criteria of attaining the maximum value of Q_2 and minimum value of Q_{18} . Y_1 and Y_2 are lag time and cumulative % drug release in 18 hrs. respectively. The result in Figure 8 illustrates the comparison between the actual and predicted values of both the responses Y_1 and Y_2 for all the formulations presented. It can be seen that in all cases there was a reasonable agreement between the predicted and the experimental values. It can be concluded that equations describe adequately influence of the selected independent variables on responses under study. This indicates that the optimization technique was appropriate for optimizing matrix tablet formulation. The linear correlation plots

drawn between the predicted and experimental values for all the batches of the tablets are shown in Figure 8, which demonstrated high values of R^2 (0.926 and 0.938). Thus, the low magnitudes of error as well as the values of R^2 in the present investigation prove the high prognostic ability of the optimization technique by factorial design.



(A) (B)
Figure No. 8: Predicted vs Actual graph of Lag time (A) and % CDR (B)

Desirability

The two dimensional contour plots, response surface analysis and predicted Vs actual were prepared for the desirability they are as shown in Figure 9. These plots are known to the study interaction effects of the factors on the desirability. The solution batches suggested by software based on high desirability close to 1 shown in Table 9.

Table No. 9: Solution batches suggested by Software

Number	Instacoat EEN	Instamodel 41 blend	Lag Time	% CDR	Desirability
1	5.903	125.00	5.200	97.322	0.959 Selected
2	5.945	125.00	5.045	97.282	0.958
3	5.987	125.00	4.885	97.241	0.956
4	5.854	125.00	5.387	97.370	0.950

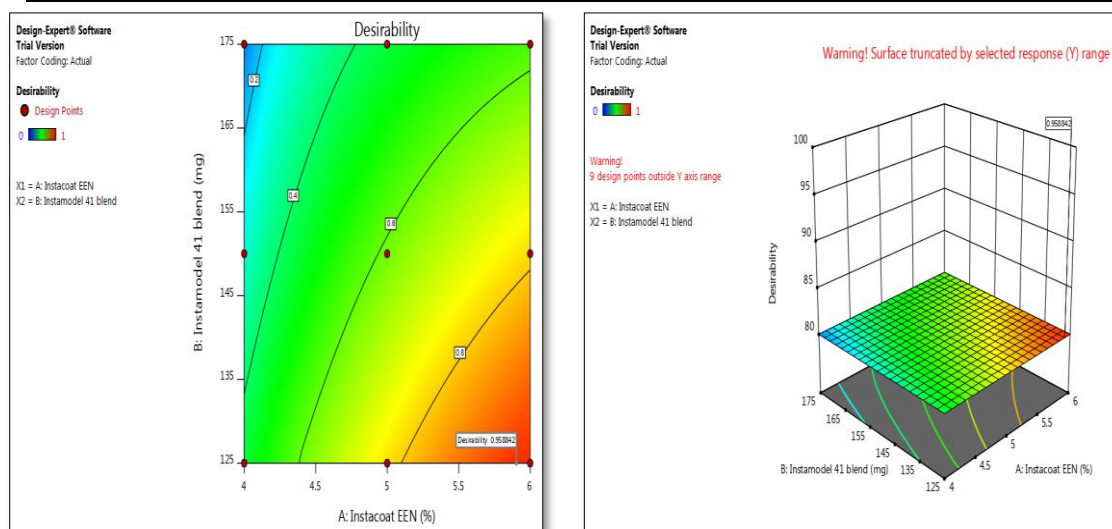


Figure No. 9: 2D Contour and 3D Surface plot of desirability

Determination of optimized formulation

After analyzing independent variables (i.e. factors) and dependent variables (i.e. responses), Design Expert® software has provided number of solutions. One batch with highest desirability of 0.959 from the solutions provided by software was selected as an optimized batch M. The optimized batch containing 125mg of Instamodel 41 polymer and 5.903 % Instacoat EEN as coating polymer was evaluated for various pre and post compression QC test and the results are depicted in Table 10. The *In vitro* drug release profiles of optimized batch M is shown in Figure 10. The optimized

batch was identified to provide desired values lag time of about 2 hours and 97.63% cumulative drug release in 18 hrs.

Table No. 10: Pre and Post compression evaluation of optimized batch (M)

Sr. No.	Precompression evaluation parameters	Optimized batch	Post compression evaluation parameters	Optimized batch
1.	Bulk density (g/cm ³)	0.353±0.016	Average weight (mg)	872±5.43
2.	Tapped density (g/cm ³)	0.473±0.016	Hardness (kg/cm ²)	13.2±1.22
3.	Carr's Index (%)	25.36±3.11	Friability (%)	0.34±0.02
4.	Hausner's ratio	1.33±0.19	Drug content(mg/tab)	97.29±2.27
5.	Angle of repose (°)	26.43±6.29	Thickness (mm)	7.11±0.12

M± S.D., n=3

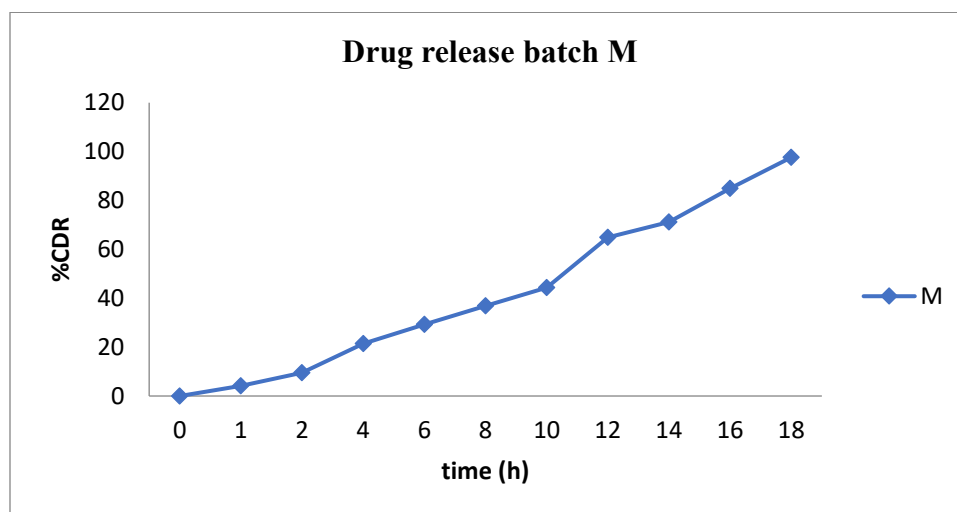


Figure No. 10: In vitro drug release graph of Optimized batch M

CONCLUSION

The aim of the present study was to optimize and evaluate delayed release matrix tablets of Methocarbamol using polymer blend, in view to improve patient compliance by reducing dosing frequency and prolonged therapeutic action. The delayed release matrix tablets of Methocarbamol was formulated by using Instamodell 41 polymer blend and coating with Instacoat EEN used at different concentration levels and optimized by using Design expert software. Instacoat EEN role in the formulation was to protect drug in stomach and not to release more than 15% in 2 hrs. and Instamodell 41 to form matrix and control drug release till 18 hrs. The results of all the tests carried out, were found to be satisfactory. The above result suggested that it was promising Methocarbamol delayed release tablets with above mentioned excipients can be effective in the treatment of muscle sprain with improved bioavailability and with good patient compliance.

REFERENCES

- Chien Y. W., Novel Drug Delivery System 2nd ed, Revised and expanded, 1992, 1-140.
- Bankers G.S. and Rhodes C.T., Modern Pharmaceutical, 3rded. Marcel Dekker, New York, 1995, 1-580.
- Kamboj S, Gupta G.D, Jagmohan Oberai, Matrix Tablets-An Important tool for Oral controlled release dosage forms, Vol 7, Pharmainfo.net, 2009, 5.
- Qui Y., Zhang G., Research and development aspects of oral controlled release dosage forms. In: Wise D.L., editor. Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker, New York, 465-99.
- Ramalakshmi N, Savita, and S. Arunkumar, Method Development and Validation of Combination of Methocarbamol and Ibuprofen Using RP-HPLC, *Journal of Chemical, Biological and Physical Sciences*, 2017, 7(4); 919-29.
- Nagamani M, Ramana H, Bhadrar B and Vasanthi R, method development and validation of methocarbamol in bulk and its formulation by UV spectroscopy, *International journal of pharmaceutical, chemical and biological sciences*, 2015, 5(1), 258-61.
- Gangurde HH. Co-Excipient: Future of Formulation Industry, *Academ J Polym Sci*. 2019; 3 (3), 54-59.
- Nasser N. Nyamweya. Applications of polymer blends in drug delivery. *Future Journal of Pharmaceutical Sciences*, 2021, 7(18):1-15.

9. Bakre L. G, Osunsanyabef Y, Bamiro A, The Effect of Polymer Blends on the Formulation of Sustained Release Ciprofloxacin Matrix Tablets, *Nig.J.Pharm. Res.* 2018, 14 (1):35-42.
10. Gandhi KJ, Deshmane SV, Biyani KR, Polymers in Pharmaceutical drug delivery system: A Review, *International Journal of Pharmaceutical Sciences Review and Research*, 2012; 14(2), 57-66.
11. Baste NS, Basarkar GD, Upasani CD, Gangurde HH. Design and Development of Oral Mucoadhesive Drug Delivery System Based on Natural Polymer. *ECS Transactions*, 2022; 107 (1) :11239-59.
12. Vandana R. Daga, Ganesh Basarkar, Hemant Gangurde. Development of Directly Compressible Co Processed Excipient By Spray Drying For Extended-Release Tablets. *IJCSPUB* 2023; 13(3):447-64.
13. Gangurde HH, Chavan NV, Mundada AS, Derle DV, Tamizharasi S. Biodegradable Chitosan Based Ambroxol Hydrochloride Microspheres: Effect of Cross-Linking Agents. *Journal of Young Pharmacists*, 2011; 3 :9-14
14. Gangurde HH, Kadam KA, Davkhar SS, Baste NS. Formulation, Optimization and Evaluation of Novel Biomaterial as a Sustained Release Excipient. *JPRT*, 2025; (2), 62-84.
15. Sanikommu Charishma L, Surendra P, CH. Ajay Babu L, formulation development and evaluation of Pantaprazole delayed release tablets, *Asian Journal of Research in Pharmaceutical Sciences and Biotechnology*. 2013, 1(2), 70 - 79.
16. Suresh Kumar P, Navaneetha Krishnan S, Pavani S, Formulation and evaluation of Rabeprazole sodium delayed release tablets, *Scholars Research Library*, 2012, 4 (1):287-296.
17. Deore PT, Kothawade PD, Gangurde HH. To Study Effect of Different Polymer Ratio On Drug Release Of Bilayer Floating Drug Delivery System. *WJPR*, 2016; 5: 1484-1503
18. Chordiya MA, Gangurde HH, Senthilkumaran K. Formulation and In Vitro Evaluation of Effervescent Floating Matrix Tablet of Propafenone HCl. *WJPPS*, 2013; 2: 5348-62.
19. Hemant H. Gangurde, Kamlesh A. Kadam, Somnath S. Davkhar, Nayana S. Baste. Formulation, Optimization and Evaluation of Novel Biomaterial as a Sustained Release Excipient. *JPRT*, 2025; (2), 62-84.
20. David A., Ajaz Husain, Delayed Release Tablet Dissolution Related to Coating Thickness by Terahertz Pulsed Image Mapping, *Journal of Pharmaceutical Sciences*, 2008, 97(4) 1543–1550.
21. Gangurde H.H., Chordiya M.A., S. Tamizharasi and T. Sivakumar., Statistical optimization of mesalamine pulsatile release pH dependent coated pellets for possible ileo-cecal targeting, *Thai J. Pharm. Sci.*, 2013, 37, 39-55.
22. Chang R.K. Robinson J. R., Sustained drug release from tablets and particles through coating, In: Liberman H.A., Lachman L.S., Chwartz J.B., *Pharmaceutical Dosage Forms: Tablets, Vol 3, 2nd end.* 2005.
23. Indian Pharmacopoeia Commission. Tablets. Indian Pharmacopoeia, vol. 2. Ghaziabad: Indian Pharmacopoeia Commission, Govt. of India, Ministry of Health and Family Welfare; 2007. 662–5.
24. Martins E, Lucy John, Yetunde isimi, Olobayo kunle, sabinus ofoefule Eudraginated polymer blends: A potential oral controlled drug delivery system for theophylline, *Acta Pharm.* 62 (2012) PP-71–82.
25. Damodharan N, Manimaran V, Sravanthi B, formulation development and evaluation of delayed release doxycycline tablets, *International Journal of Pharmacy and Pharmaceutical Sciences Vol 2*, 2010.
26. Kalyani Chithaluru L, Ramarao tadikonda, K.kalyan kumar kandula3, formulation and *In vitro* evaluation of sustained release matrix tablets of losartan potassium, *Asian Journal of Pharmaceutical and Clinical Research Vol. 4*, Issue 3, 2011, 1822.
27. Hina Kouser Shaikh, Kshirsagar R V, Patil S G, mathematical models for drug release characterization: a review, *World Journal of Pharmacy and Pharmaceutical sciences*, 4 (4), 324-338.
28. Biswas R, Basak SC, Shaikh S A, Formulation Development and Polymer Optimization for Once-Daily Sustained Release Matrix Tablets of Domperidone, *Journal of Pharma Sci Tech* 2011; 1(1):28-34.
29. Yilma Z , Belete A. and Gebre-Mariam T., formulation and optimization of sustained release floating matrix tablets of salbutamol sulphate using xanthan gum and Hydroxypropyl methylcellulose polymer blend, *International Journal of Pharmaceutical Sciences and Research*, 2015; Vol. 6(5): 1877-1892.
30. Manjurul K, and Jiben Roy .B, The development of cracks on delayed release film of hygroscopic cores: A review of the tablet and coating formulations, coating processes and storage conditions, *J. Excipients and Food Chem.* 6 (3) 2015, 83 – 93.