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Formulation, Optimization and Evaluation of Extended Release Tablet of Pregabalin for the Treatment of Diabetic Neuropathy

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ABSTRACT:

The present study is aimed to develop extended release tablet of Pregabalin using hot melt granulation method which will include hydrophobic polymer that will form hydrophobic matrices which will retard release of drug for extended period of time. Different concentration of Compritol ATO 888 and Hydrogenated Castor Oil were utilized for desired criteria of optimized batch. A 32 full factorial design was employed for optimizing the concentration of hydrophobic polymer. The tablets were evaluated in terms of average weight, friability, hardness and in vitro drug release profile. Optimized batch was also evaluated for in vitro drug release profile in presence of alcohol and short term stability study. The kinetic model fitting of the optimized batch was carried out to find out the mechanism of drug release from the tablet and Korsmeyer and Peppas model fits best for the release of the drug from the tablet. The n value was determined using korsmeyer and peppas model and mechanism of drug release was found to be non fickian diffusion. The optimized batch shows satisfactory results with respect to theoretical drug release profile.

Key words: Extended release tablet, Pregabalin, Compritol ATO 888, Hydrogenated Castor Oil.

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INTRODUCTION:

Diabetic neuropathies are nerve damaging disorders associated with diabetes mellitus patients. (Figure: 1.) These conditions are result from diabetic micro vascular injury involving small blood vessels that supply blood (vasa nervorum), in addition to macro vascular conditions that can culminate in diabetic neuropathy. Mainly common conditions to the patients having diabetes due to decrease in blood flow. Neuropathic pain can be very severe and disabling, common treatment goals are to decrease pain and/or improve function. Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance.¹ Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has been the predominant route for drug delivery.^{2,3} It does not pose the sterility problem and minimal risk of damage at the site of administration.⁴ In the past few decades, significant advances have been made in the area of drug delivery system with the development of novel dosage forms. The designed extended release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the delivery rate of drug to the target sites. Moreover, there is a rising need for the controlled and or continuous delivery of such therapeutic agents due to several biopharmaceutical, safety

and patient compliance issues related with these therapies. Matrix type drug delivery systems are one of the reliable options in the development of an oral extended release drug delivery system. The European Federation of Neurological Society recommends Pregabalin as first line agent for the treatment of Diabetic Neuropathy. It has low potential for abuse and limited dependence liability if misused. Pregabalin has shorter half-life (5-6 hours) and dose of Pregabalin is 50mg three times a day so it is an ideal candidate for the preparation of once daily dosage form using hydrophobic polymer.⁵ Melt granulation (thermoplastic granulation) is a process in which the granules is obtained through the addition of binder, which melts or softens at relatively low temperature. After melting, a binder acts like a binding liquid. It is solvent free process. The present study is aimed to develop extended release tablet of Pregabalin using hot melt granulation method which include hydrophobic polymer that will form hydrophobic matrices which will retard release of drug for extended period of time.

MATERIALS AND METHODS:

Pregabalin and Compritol ATO 888 were provided by Emcure Pharmaceutical Ltd., Ahmedabad. Hydrogenated castor oil was obtained by Astrone Research Ltd., Ahmedabad. All other excipients were purchased by local vendors and were of analytical grade.

Method of Preparation:

The drug can be present in crystalline form for sustain release applications. The polymer is first heated and melted into porcelain dish in water bath. Then Drug powder is added step by step and lump is prepared. Lump is screened by sieve no. 25 and lubricant and diluent are added, later final material is compressed into tablet.

Evaluation of Pre compression Parameters of granules:⁶

Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It is expressed in g/ml or g/cm³. It is given by

$$D_b = M / V_b$$

Where, M = mass of powder

V_b = bulk volume of the powder.

Tapped Density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume is

measured by tapping the powder for 500 times (in a bulk density apparatus). It is expressed in g/ml or g/cm³. And is given by

$$D_t = M / V_t$$

Where, M = mass of powder

V_t = tapped volume of the powder.

Carr's Index (CI) or Carr's Compressibility Index: It indicates powder flow properties. It is expressed in percentage.

$$CI = (D_t - D_b) / D_t \times 100$$

Where, D_t = tapped density of the powder

D_b = bulk density of the powder.

Angle of Repose: The angle of repose or critical angle of repose of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. At this angle, the material on the slope face is on the verge of sliding. The angle of repose can range from 0° to 90°. The angle of repose was determined using fixed funnel method. Radius of the heap (r) is measured and the angle of repose is calculated using below formula.

$$\tan \theta = h / r$$

Therefore $\theta = \tan^{-1} h/r$

Where,

θ = Angle of repose

h = height of pile

r = radius of the heap

Hausner's Ratio: Hausner's ratio is an indirect index of ease of powder flow. The Hausner's ratio is not an absolute property of a material; its value can vary depending on the methodology which is used to determine it. It is calculated by the following formula,

$$\text{Hausner's ratio} = D_t / D_b$$

Where,

D_t = tapped density

D_b = bulk density.

Evaluation of Post Compression Parameters of Tablets⁶:

Weight Variation: 20 tablets are selected randomly from the lot and weighted individually to check for weight variation.

Tablet Hardness (Crushing Strength): Hardness of tablet is defined as the force applied across the diameter of the

tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation shall be determined using Monsanto hardness tester or Pfizer hardness tester.

Thickness: Thickness of tablet of each batch will be checked using Vernier Calipers and it is measured in mm.

Friability (Mechanical Strength): Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator will be used for the Purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a Plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of tablets was placed in the friabilator, which will then operate for 100 revolutions. Tablets shall be dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

$$F = \frac{Wt\ initial - Wt\ final}{Wt\ initial} \times 100$$

In vitro drug release study:⁷

Acid Stage: Place 1000 ml of 0.1 M hydrochloric acid in the vessel and assemble the apparatus. Warm the dissolution medium to 36.5 to 37.5 °C. Place one unit dosage in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in the acid medium, withdraw an aliquot of the liquid and proceed immediately as directed under buffer stage. Perform the analysis of the aliquot using suitable assay method.

Buffer stage: Use buffer that has previously been warmed to 36.5 to 37.5° C. Drain the acid from the vessel and add 1000 ml of pH 6.8 phosphate buffer, prepared by mixing 3 volumes of 0.1 M HCl with 1 volume of 0.2 M solution of trisodium phosphate dodecahydrate and adjusting if necessary, with 2 M HCl or 2M NaOH to a pH of 6.8 ±0.05.

Theoretical Release Profile of Pregabalin Extended Release Tablet:⁸

The total dose of Pregabalin for once-daily sustained release formulation was calculated by using the following equation

$$D_t = \text{Dose} (1 + 0.693 \cdot t / t_{1/2})$$

Where,

D_t = Total dose of drug,

Dose = Dose of immediate release,

t = Time during which sustained release is desired i.e. 24 hours, and

$t_{1/2}$ = Half-life of the drug

Hence,

$$150 = \text{Dose} (1 + 0.693 \cdot 24 / 5)$$

$$\text{Dose} = 34.67 \text{ mg}$$

Hence, the formulation should release 34.67 mg in 1 hour like and 5.01 mg per hour up to 24 hours thereafter.

Drug Excipient Compatibility:⁹

Drug - excipient interactions is investigated by: Fourier Transmit Infra-Red Spectroscopy. Drug Excipient mixtures were recorded by FTIR spectrometer in the range of 4000-400 cm^{-1} . Study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients.

Optimization of variable using 3² Full Factorial Design:

A 3² full factorial design was used in present research work. In this design 2 factors was evaluated, each at 3 levels and experimental trials has been performed. The concentration of both the polymers Compritol ATO 888(X_1) and Hydrogenated Castor Oil (X_2) were selected as independent variables, while selected dependent variables were, Y_1 = % Drug Release in 1 hour (21.95 < Y_1 < 24.25), Y_2 = % Drug Release in 8 hour (44.17 < Y_2 < 48.81), Y_3 = % Drug Release in 16 hour (69.54 < Y_3 < 76.87), Y_4 = % Drug release in 24 hour (95 < Y_4 < 99.99). The polynomial terms were used to evaluate the responses. Where Y is the dependent variable. B_0 is the arithmetic mean response of 9 runs and B is estimated coefficient for the respective factor. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high values. 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.

$$Y = B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_{11}X_1^2 + B_{22}X_2^2$$

In Vitro Drug Release Study in Presence of Alcohol:

United States statistical data showed that around 50% of the American population routinely

consumes alcoholic beverages. The potential effect of alcoholic drinks in significantly accelerating drug release from Extended Release oral formulations has been of some concern in recent past. If the total amount of drugs is suddenly released from modified release dosage forms in the body, untoward effects may be seen. In-vitro dissolution profile of optimized formulation was taken in presence of 40% v/v of ethanol.

Kinetic Analysis of the Drug Release of Optimized Batch¹⁰:

The mechanism of drug release from the prepared extended release tablets during dissolution tests in 0.1 N HCl and phosphate buffer pH 6.8 was determined using different kinetic model like zero order, first order, Higuchi and Korsmeyer–Peppas.

$$(Mt/M_{\infty}) = kt^n$$

Where,

K = constant for the structural and geometric characteristics of the tablets,

n = release exponent, indicative of the drug release mechanism and

(Mt/M_1) = drug dissolved fraction at time t. Based on various kinetic models, the magnitude of the release exponent “n” indicates the release mechanism of tablet.

RESULT AND DISCUSSION:

From the FTIR Spectroscopy, the drug and excipient interactions were checked. But no interactions were found in the spectra. So they are compatible with each other. As concentration of lipophilic binders increase, release from matrix decreases, due to slower penetration of dissolution media into waxy matrices. Combination of both the polymers has been studied with different concentration of Compritol ATO 888 and Hydrogenated Castor Oil.

$$Y_1 = 19.52 + (-1.56) X_1 + (-1.26) X_2 + (-2.73) X_1 X_2 + 1.73 X_1^2 + (-5.44) X_2^2 \dots\dots\dots (1)$$

$$Y_2 = 44.40 + (-3.82) X_1 + (-13.50) X_2 + 2.76 X_1 X_2 + (-0.81) X_1^2 + 0.40 X_2^2 \dots\dots\dots (2)$$

$$Y_3 = 66.03 + (-0.11) X_1 + (-19.04) X_2 + (-1.78) X_1 X_2 + 4.6 X_1^2 + 2.82 X_2^2 \dots\dots\dots (3)$$

$$Y_4 = 94.90 + (-4.46) X_1 + (-10.40) X_2 + (-4.68) X_1 X_2 + (-0.69) X_1^2 + (-6.19) X_2^2 \dots\dots\dots (4)$$

In all case of Responses, It was anticipated that both matrix forming polymer collective effect on release retardation. In case of Y_1 , the result of multiple regression analysis had shown that both coefficient B_1 and B_2 bear a negative sign which indicates a release retarding effect (Figure: 5, 6). It can be stated that both polymer (X_1 and X_2) were responsible for obtaining value of Y_1 but X_1 has more pronounced effect on drug release retardation. In case of Y_2 , X_2 has more prominent effect on drug release retardation than X_1 (Figure: 7, 8). In case of Y_3 and Y_4 , X_2 has overall effect on drug release retardation because penetration of solvent molecule is hindered due to hydrophobic coating of hydrogenated castor oil on the drug particle which leads to slow down release of drug for prolonged period of time (Figure: 9, 10, 11, 12). Contour curve and three dimensional (3-D) response surface plots were constructed based on the model polynomial function using Design Expert 10. These plots are very useful to see interaction effect on the factor of the response. In the overlay plot, responses generated the optimized area as per requirement (Figure: 13). Response Y_1 (% Drug Release at 1 hour) was set in the range of 21.99 to 24.25, Response Y_2 (% Drug Release at 8 hour) was set in the range of 44.17 to 48.81, Response Y_3 (% Drug Release at 16 hour) was set in the range of 69.54 to 76.87, Response Y_4 (% Drug Release at 24 hour) was set in the range of 95 to 99.99. These requirements are satisfactory for the extended release tablet in terms of theoretical release profile shown in overlay plot. The optimized batch shows similar results as compared to predicted release and so the validity of developed model is confirmed. Comparing the % Drug Release of Predicted and Experimental values of responses, the f_2 value- Similarity factor was found to be 97.65, which indicates that there is no significant change in drug release profile. Figure 14, shows that the cumulative drug release of optimized batch has almost identical in dissolution media containing up to 40% v/v alcohol. Hence, dose dumping was not observed even when the dosage form was taken with alcohol. By comparing the dissolution profile of optimized Batch at initial stage and after four weeks (figure 15), there is no significant difference in *in vitro* release profile. The f_2 value was found to be 83.07. The result indicates that there is no change found in physical appearance and other parameters. So it can be concluded that the formulated tablets are stable at defined storage condition.

CONCLUSION:

Pregabalin extended release tablet containing 30% of Compritol ATO 888 and 25% of Hydrogenated castor oil of a total weight of tablet hold good promise for drug release retardation.

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Table: 1. Composition of Batches of 3² Factorial Design

Excipients (mg)	P1	P2	P3	P4	P5	P6	P7	P8	P9
Pregabalin	15	15	15	15	15	15	15	15	15
n	0	0	0	0	0	0	0	0	0
Compritol ATO 888	30	35	40	30	35	40	30	35	40
(% of Total Weight)	%	%	%	%	%	%	%	%	%
Hydrogenated Castor Oil	20	20	20	25	25	35	30	30	30
Di	%	%	%	%	%	%	%	%	%
Calcium Phosphate	82	52	22	52	22	-	22	-	-
Lactose	50	50	50	50	50	50	50	50	50
Talc	6	6	6	6	6	6	6	6	6
Magnesium Stearate	12	12	12	12	12	12	12	12	12
Total Weight	60	60	60	60	60	66	60	60	63
	0	0	0	0	0	8	0	8	8

Table: 2. Pre compression parameters of Batch P1 to P9

Batch	Angle of repose	Carr's Index	Hausner's Ratio	Flowability
P1	25.1±0.03	1.06±0.20	7±0.006	Excellent
P2	36±1.03	1.19±0.06	16.2±1.00	Fair
P3	39±0.0012	1.25±0.04	19±2.007	Fair
P4	26.3±0.005	1.10±0.023	8.6±0.8	Excellent
P5	37.6±0.006	1.21±0.009	16.8±0.004	Fair
P6	40.2±0.055	1.25±0.007	19.7±0.005	Fair
P7	31.2±0.01	1.13±0.001	10±0.011	Good
P8	38.7±0.10	1.23±0.83	18±.33	Fair
P9	43.6±.004	1.32±.0039	22.3±0.009	Passable

Table: 3. Post Compression Parameters of Batch P1 to P9

Parameters	P1	P2	P3	P4	P5	P6	P7	P8	P9
Average Weight (mg)	60	60	60	60	60	66	60	60	63
Weight (mg)	0±	2±	1±	0.5	0±	8±	2±	7±	8±
Thickness (mm)	0.0	0.0	0.0	±	0.0	0.0	0.0	0.1	0.1
	1	15	12	0.0	10	13	2		5
				36					
Thickness (mm)	4.3	4.3	4.3	4.3	4.3	4.5	4.3	4.3	4.4
	±	2±	1±	±	1±	±	2±	3±	±
	0.0	0.0	0.1	0.0	0.1	0.0	0.1	0.1	0.2
	02	1	4	49	7	4	0	8	

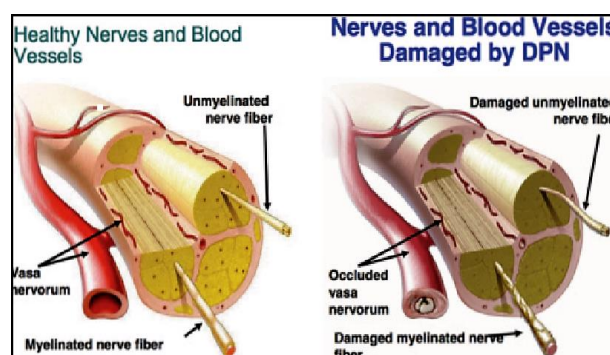
Diameter (mm)	13.65 ± 0.049	13.69 ± 0.017	13.64 ± 0.01	13.65 ± 0.021	13.66 ± 0.019	13.63 ± 0.014	13.68 ± 0.011	13.65 ± 0.016	13.65 ± 0.014
Hardness	5.0 ± 0.0	5.0 ± 0.0	4.8 ± 0.0	5.0 ± 0.0	4.9 ± 0.0	5.1 ± 0.0	5.1 ± 0.0	5.1 ± 0.0	5.2 ± 0.0
(kg/cm ²)	7	9	0.1	5	0.0	0.0	0.0	0.0	0.0
Friability	0.75 ± 0.11	0.73 ± 0.10	0.76 ± 0.07	0.55 ± 0.08	0.69 ± 0.09	0.70 ± 0.05	0.50 ± 0.06	0.50 ± 0.08	0.52 ± 0.11

Table: 4. Comparative % Drug Release of Batch P1 to P9

Time hour	Theoretical Release	P1	P2	P3	P4	P5	P6	P7	P8	P9
0	0	0	0	0	0	0	0	0	0	0
1	23.11	20.73	15.36	18.23	22.98	19.18	19.89	18.89	13.15	10.08
2	26.45	23.08	23.74	29.32	25.1	25.1	22.17	23.50	21.64	14.45
4	33.13	34.45	31.70	39.60	31.95	31.95	28.33	26.26	24.51	20.12
6	39.81	44.14	42.98	45.81	38.44	38.44	33.26	29.52	29.68	24.76
8	46.49	65.55	55.21	52.54	47.11	45.36	39.11	30.39	33.45	28.44
10	53.17	68.01	58.66	65.26	52.07	52.07	49.06	36.14	35.64	33.71
12	59.85	72.57	63.04	71.34	57.13	57.13	55.09	43.26	37.07	39.52
14	66.53	82.43	76.22	83.10	66.16	66.16	63.25	50.08	45.73	45.48
16	73.21	90.23	87.62	95.38	72.9	65.64	69.08	55.23	50.49	53.24
20	86.57	92.02	97.11	98.26	87.66	87.66	83.17	80.44	68.49	61.23
24	99.93	99.37	99.23	98.38	99.23	90.98	93.13	85.06	83.13	65.35

Table: 5. *In vitro* dissolution profile of Optimized Batch in Presence of 40% v/v Alcohol

Time (Hour)	% Drug Release			
	Set 1	Set 2	Set 3	Average ± Standard Deviation
0	0	0	0	0 ± 0
1	24.5	23.16	24.12	23.92 ± 0.56
2	26.23	26.8	24.12	25.71 ± 1.15
4	33.89	34.82	34.33	34.34 ± 0.37
6	41.53	40.46	40.88	40.95 ± 0.44
8	47.36	46.57	47.72	47.21 ± 0.48
10	53.41	54.36	54.68	54.15 ± 0.53
12	57.59	56.62	56.98	57.06 ± 0.40
14	68.75	70.14	68.93	69.27 ± 0.61
16	72.86	72.99	74.15	73.33 ± 0.57
20	86.44	88.19	88.03	87.55 ± 0.78
24	96.94	98.23	99.28	98.15 ± 0.95

**Figure: 1. Nerves and Blood Vessels damaged by Diabetic Neuropathy**

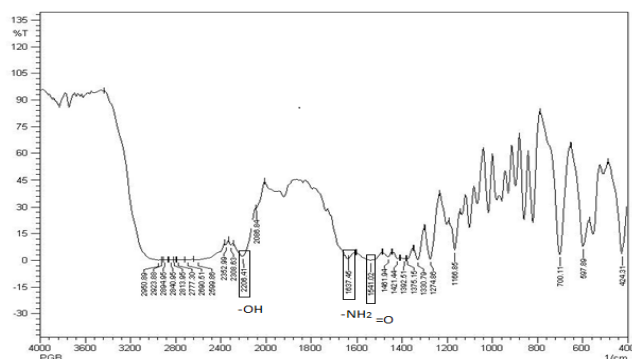


Figure 2. FTIR of Pregabalin

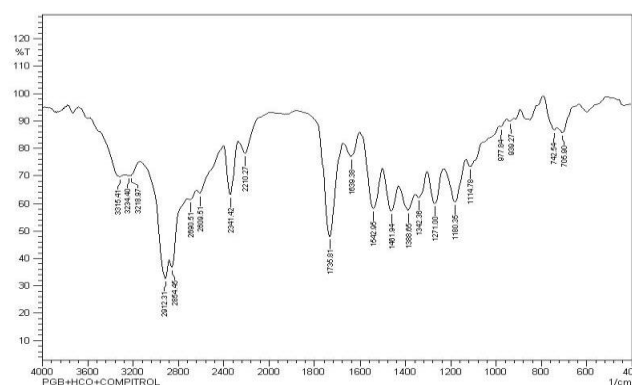


Figure 3. FTIR of Pregabalin with Compritol ATO 888 and Hydrogenated Castor Oil

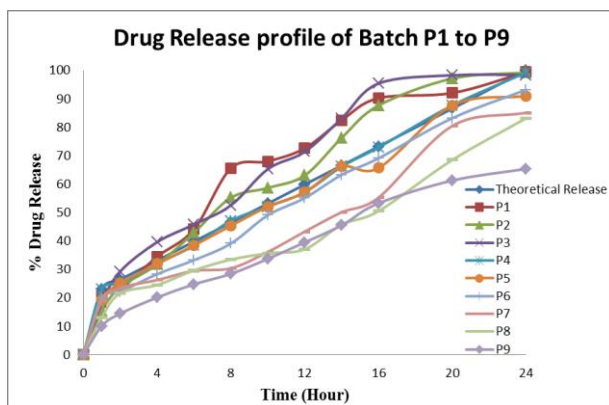


Figure 4. Comparative Drug Release profile of Batch P1 to P9

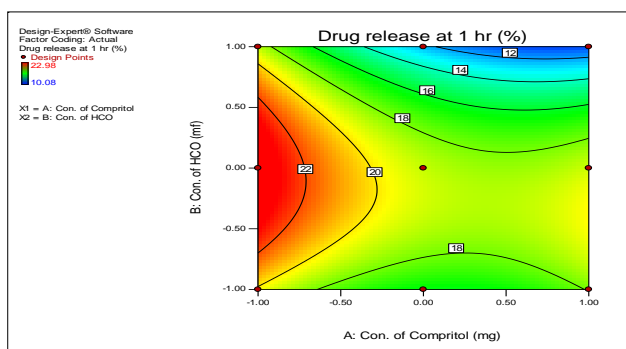


Figure 5. Contour Plot of Response Y1

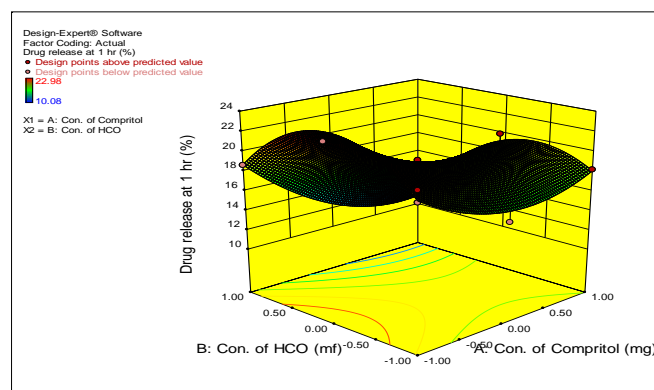


Figure 6. Response Surface Curve of Response Y1

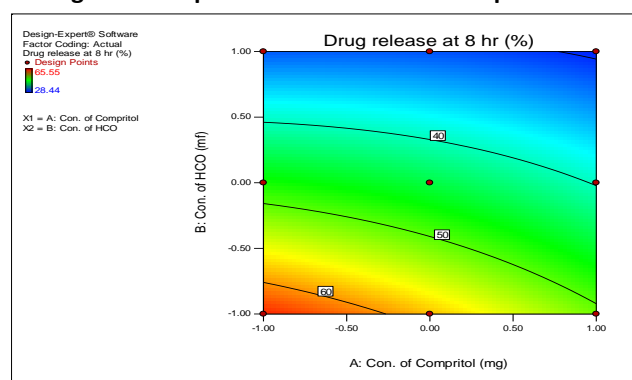


Figure 7. Contour Curve of Response Y2

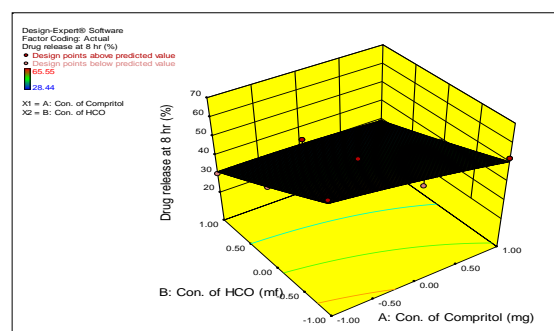


Figure 8. Response Surface Curve of Response Y

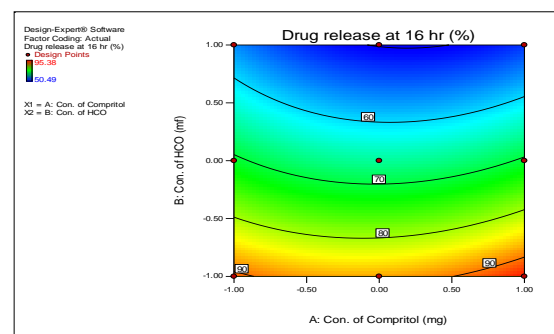


Figure 9. Contour Curve of the Response Y3

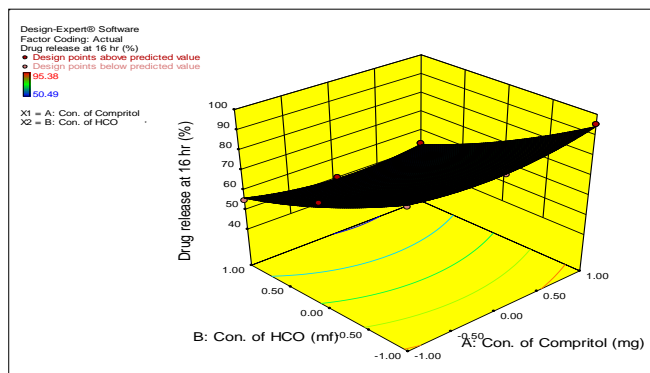


Figure 10. Response Surface curve of Response Y3

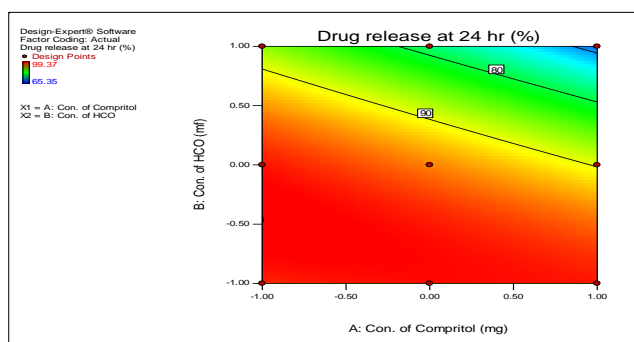


Figure 11. Contour Curve of Response Y4

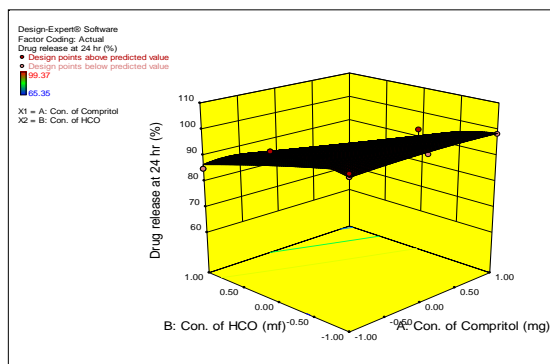


Figure 12. Response Surface Curve of Response Y4

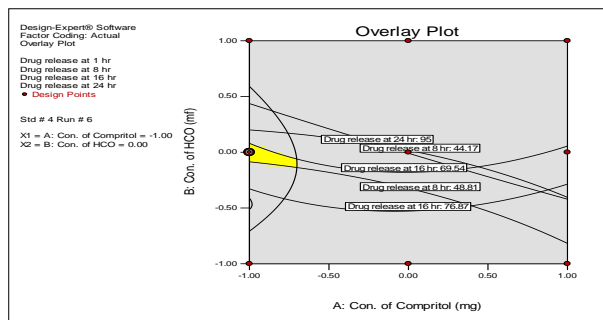


Figure 13. Overlay Plot of Response Variables

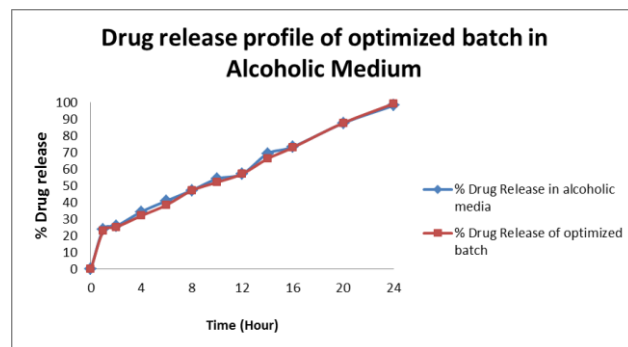


Figure 14. Drug Release Profile of Optimized Batch in Presence of Alcohol

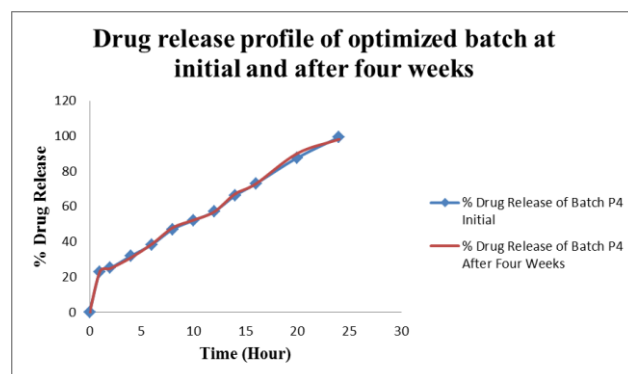


Figure 15. Drug Release Profile of Optimized Batch at Initial and after Four Weeks

